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M Terzolo Italy
M Theodoropoulou Germany
H Timmers Netherlands
J Tomlinson UK
M Toth Hungary
P Touraine France
R Trifanescu Romania
A Tsapas Greece
E Tsourdi Germany
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CONTENTS

e-ECE 2021
23rd European Congress of Endocrinology

PRIZE LECTURES AND BIOLOGRAPHICAL NOTES

The Geoffrey Harris Prize Lecture AP1.1–AP1.2
The *European Journal of Endocrinology* Prize Lecture AP2
European Hormone Medal Lecture AP3
Clinical Endocrinology Trust Lecture AP4
Jens Sandahl Christiansen Award JSC1

PLENARY LECTURES

Plenary 1: The hard road to new therapies against diabetes and obesity PL1
Plenary 2: Light, body clocks and sleep: Biology to new therapeutics PL2
Plenary 3: 1 Year in Pituitary PL3.1–PL3.2
Plenary 4: Neuroendocrine stress response at single cell resolution PL4
Plenary 5: 1 Year in Bone PL5.1–PL5.2
Plenary 6: New advances in novel targets for thyroid cancer and thyroid cancer theragnostics PL6
Plenary 7: Central and Eastern European heritage in genetics of hypopituitarism - how the prevalent ancestral PROP 1 gene variants spread overseas PL7

SYMPOSIA

Symposium 1: The new technology in the clinical management of thyroid nodules S1.1–S1.3
Symposium 2: Adrenal incidentalomas S2.1–S2.3
Symposium 3: Expanding the benefits of GLP-1R agonists S3.1–S3.3
Symposium 4: Peripheral neuroendocrinology S4.1–S4.3
Symposium 5: Human foetal exposure to environmental endocrine disruptors S5.1–S5.3
Symposium 6: COVID: The sequelae of the virus S6.1–S6.3
Symposium 7: Inheritable metabolism S7.1–S7.3
Symposium 8: Lessons from MDT in MEN1 patients S8.1–S8.3
Symposium 9: Large ambitious and inspiring European prevention programs S9.1–S9.3
Symposium 10: New approaches in pituitary pathologies from a multidisciplinary team S10.1–S10.3
Symposium 11: Thyroid hormones, regulation of metabolism and energy balance S11.1–S11.3
Symposium 12: What's new in cardiovascular protection and function S12.1–S12.3
Symposium 13: TGF-β signalling in ovaries in women with PCOS S13.1–S13.3
Symposium 14: Complex clinical cases S14.1–S14.3
Symposium 15: Nutrition intervention: Not just to lose weight S15.1–S15.3
Symposium 16: Splicing in endocrine-related cancers S16.1–S16.3
Symposium 17: New advances in the managements of hypophosphatemia S17.1–S17.3
Symposium 18: The future of endocrinology Artificial Intelligence (AI) and big data! S18.1–S18.3
Symposium 19: Emerging concerns in reproduction S19.1–S19.3
Symposium 20: Diabetes and bone S20.1–S20.3
Symposium 21: Hot topics in neuroendocrine tumours S21.1–S21.3
Symposium 22: From adrenal stem cells to ACC S22.1–S22.3
Symposium 23: Novel targets in diabesity S23.1–S23.3
Symposium 24: Intermediate thyroid cancer soft or aggressive approach S24.1–S24.4
Symposium 25: Parathyroid disorders S25.1–S25.3

JOINT SESSIONS

ESE/EASD Joint Session: Diabetes and growth hormone JS1.1–JS1.3
ESE/ESPE Joint Session: Transition – A step into the unknown JS2.1–JS2.3
ESE/Endocrine Society Joint Session: Emerging endocrine abnormalities and COVID-19 outcomes JS3.1–JS3.5
ESE/SBEM, FASEN and SMNE Joint Session: Pituitary conditions and COVID-19 ..... JS4.1–JS4.3
ESE/KES Joint Session: COVID-19 and endocrine disorders JS5.1–JS5.3
ESE/EndoERN Joint Session: Rare endocrine disorders. Improving diagnosis, management and awareness by strengthening patients and physician collaboration JS6.1–JS6.4
ESE/EASO Joint Session: Endocrine lab findings in people with obesity and their therapeutic consequences JS7.1–JS7.4
ESE/Clinical Guidelines of the European Academy of Andrology: Male specific endocrine conditions JS8.1–JS8.3

NEW SCIENTIFIC APPROACHES

New Scientific Approaches 1: 3D adrenal models for the study of adrenal tumors NSA1
New Scientific Approaches 2: Regeneration or replacement of beta cells NSA2
New Scientific Approaches 3: Cutting-edge scientific advances NSA3
New Scientific Approaches 4: Multiplex analysis platform for endocrine disruption prediction using zebrafish NSA4
New Scientific Approaches 5: Whole genome sequencing in cancer care, lessons from the 100,000 Genomes Project and opportunities for NEN NSA5

DEBATE SESSIONS

Debate 1: Should the biochemical spectrum primary aldosteronism be expanded? D1.1–D1.2
Debate 2: CGM for all people with diabetes? D2.1–D2.2
Debate 3: Selenium for autoimmune thyroid disorders: necessary or unnecessary? D3.1–D3.2
Debate 4: Endocrine disruptors harmonisation in EU: The new EU Chemicals Strategy will speed up efficient reduction of EDC exposure for EU citizens! D4.1–D4.2
Debate 5: Treatment breaks should be mandatory in the majority of people taking oral bisphosphonates D5.1–D5.2
Debate 6: What levels of prolactin to aim for... The lower the better? D6.1–D6.2

MEET THE EXPERT BASIC SCIENTIST SESSIONS

Meet The Expert Basic Scientist 1: Histopathology of human obese adipose organ: New insights MTEBS1
Meet The Expert Basic Scientist 2: When and how to employ molecular genetic testing in thyroid pathology? MTEBS2
Meet The Expert Basic Scientist 3: Interference of EDC with thyroid hormone binding and transport impacts on neural stem cell fate: from development to ageing MTEBS3
Meet The Expert Basic Scientist 4: GWAS and mendelian randomisation studies in osteoporosis diagnosis MTEBS4

MEET THE EXPERT SESSIONS

Meet The Expert 1: New therapies in the treatment of thyroid ophthalmopathy MTE1
Meet The Expert 2: Non-contraceptive therapeutic use of combined oral contraceptives in PCOS MTE2
Meet The Expert 3: Long-term effects of testosterone replacement therapy MTE3
Meet The Expert 4: What one should know on PRRT-lessons from clinical practice MTE4
Meet The Expert 5: Craniopharyngeoma management MTE5
Meet The Expert 6: Difficult phaeochromocytoma cases MTE6
Meet The Expert 7: Do you know how to define sarcopenic obesity? MTE7
Meet The Expert 8: GH replacement in adults MTE8
Meet The Expert 9: Sequential osteoporosis treatments MTE9
Meet The Expert 10: Outlook for male fertility preservation MTE10
Meet The Expert 11: Cardiovascular risk reduction in endocrine patients MTE11
Meet The Expert 12: Pituitary surgery bites MTE12
Meet The Expert 13: Marrow adiposity and bone MTE13
Meet The Expert 14: For the use of AMH as a diagnostic tool in female reproduction MTE14
Meet The Expert 15: Challenges in genetic counseling for hereditary endocrine neoplasia syndromes MTE15

ORAL COMMUNICATIONS

Oral Communications 1: Adrenal and Cardiovascular Endocrinology OC1.1–OC1.6
Oral Communications 2: Diabetes, Obesity, Metabolism and Nutrition OC2.1–OC2.6
Oral Communications 3: Pituitary and Neuroendocrinology OC3.1–OC3.6
Oral Communications 4: Reproductive and Developmental Endocrinology OC4.1–OC4.6
Oral Communications 5: Thyroid OC5.1–OC5.6
Oral Communications 6: Calcium and Bone OC6.1–OC2.6
Oral Communications 7: Diabetes, Obesity, Metabolism and Nutrition OC7.1–OC7.6
Oral Communications 8: Pituitary and Neuroendocrinology OC8.1–OC8.6
Oral Communications 9: Endocrine-Related Cancer OC9.1–OC9.6
Oral Communications 10: Thyroid OC10.1–OC10.6
Oral Communications 11: Adrenal and Cardiovascular Endocrinology OC11.1–OC11.6
Oral Communications 12: Diabetes, Obesity, Metabolism and Nutrition OC12.1–OC12.6
Oral Communications 13: Pituitary and Neuroendocrinology OC13.1–OC13.6
Oral Communications 14: Across Endocrinology OC14.1–OC14.6
Oral Communications 15: Late Breaking OC15.1–OC15.6
Young Investigator Awards YI1–YI12

PRESENTED EPOSTERS

Presented ePosters 1: Adrenal and Cardiovascular Endocrinology PEP1.1–PEP1.8
Presented ePosters 2: Diabetes, Obesity, Metabolism and Nutrition PEP2.1–PEP2.8
Presented ePosters 3: Pituitary and Neuroendocrinology PEP3.1–PEP3.8
Presented ePosters 4: Reproductive and Developmental Endocrinology PEP4.1–PEP4.8
Presented ePosters 5: Thyroid PEP5.1–PEP5.8
Presented ePosters 6: Calcium and Bone PEP6.1–PEP6.8
Presented ePosters 7: Diabetes, Obesity, Metabolism and Nutrition PEP7.1–PEP7.8
Presented ePosters 8: Pituitary and Neuroendocrinology PEP8.1–PEP8.8
Presented ePosters 9: Endocrine-Related Cancer PEP9.1–PEP9.8
Presented ePosters 10: Thyroid PEP10.1–PEP10.8
Presented ePosters 11: Adrenal and Cardiovascular Endocrinology PEP11.1–PEP11.8
Presented ePosters 12: Diabetes, Obesity, Metabolism and Nutrition PEP12.1–PEP12.8
Presented ePosters 13: Pituitary and Neuroendocrinology PEP13.1–PEP13.8
Presented ePosters 14: COVID-19 ..... PEP14.1–PEP14.8
Presented ePosters 15: Late Breaking PEP15.1–PEP15.8

AUDIO EPOSTER PRESENTATIONS

Adrenal and Cardiovascular Endocrinology AEP1–AEP80
Calcium and Bone AEP81–AEP155
Diabetes, Obesity, Metabolism and Nutrition AEP156–AEP378
Endocrine-Related Cancer AEP379–AEP403
Environmental Endocrinology AEP404–AEP405
General Endocrinology AEP406–AEP456
Pituitary and Neuroendocrinology AEP457–AEP569
Reproductive and Developmental Endocrinology AEP570–AEP624
Thyroid AEP625–AEP781
Late Breaking AEP782–AEP895

EPOSTER PRESENTATIONS

Adrenal and Cardiovascular Endocrinology EP1–EP21
Calcium and Bone EP22–EP42
Diabetes, Obesity, Metabolism and Nutrition EP43–EP124
Endocrine-Related Cancer EP125–EP131
General Endocrinology EP132–EP142
Pituitary and Neuroendocrinology EP143–EP174
Reproductive and Developmental Endocrinology EP175–EP187
Thyroid EP188–EP230
Late Breaking EP231–EP240

AUTHOR INDEX

Prize Lectures and Biographical Notes

The Geoffrey Harris Prize Lecture
AP1.1

Complex problems often have simple solution - let's move on from Hippocrates!

John Wass
University of Oxford, Oxford, United Kingdom

The philosophy of my research over the years has been to ask clinically relevant questions which will enhance the practice of decision making in endocrinology, based on scientific assessment of reasonable cohorts. In hitherto unpublished data, we have done work on the assessment of somatostatin responsive headaches in acromegaly and show that they persist over many years, may respond to radiotherapy and may also remain problematic even if acromegaly is cured. We have also looked at a cohort of giants to see whether they present differently and have different complications. Lastly in as yet unpublished data, we have looked at disparate growth hormone and IGF-I in a cohort of patients taken from the UK Acromegaly Database to see whether this group has increased mortality and morbidity. In other work, we have shown the importance of pituitary surgical experience in improving outcome, the importance of debulking growth hormone secreting macroadenomas to improve long-term control with medical therapy, the natural history of non-operated non-functioning pituitary tumours and the indications for further treatment based upon post-operative scans in non-functioning tumours. In prolactinoma we have looked at pituitary functional recovery after treatment. We have done work on apoplexy showing the predictive factors for recovery and lastly shown the importance of various degrees of removal and likelihood of recurrence long-term. Research is accomplished with energy and enthusiasm. Good results are helped, as above, as well with warmth and lack of enmity.

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AP1.2

Complex problems often have simple solution - let's move on from Hippocrates!

Vera Popovic-Brkic
Professor of Medicine, University of Belgrade, Belgrade, Serbia

Why should we be suspicious of simple explanations in complex problems? The past decades have seen critical advances in understanding the regulation of growth hormone (GH) secretion. I spent many fruitful years studying the actions of synthetic GH secretagogue , the GH releasing peptide-6 (GHRP-6), on human GH secretion. GHRP-6 mimicked GH releasing hormone (GHRH) but did not bind to GHRH receptor. Powerful joint action (synergism) of GHS/ GHRH was blocked in patients with hypothalamic-pituitary disorders. Amongst our many findings was a safe and reliable test for diagnosing adult GH deficiency. Our special interest was in testing with GHRH/GHS in patients with traumatic brain injury and after cranial irradiation in whom the primary damage is in the hypothalamus causing GH deficiency. Identification of ghrelin , the natural ligand for GH secretagogue receptor, with abundant literature which accumulated over 20 years, showed the complexity of ghrelin's actions: from GH releasing peptide to hunger hormone to glucose regulation. It was a long route to clinical utility of highly selective oral ghrelin mimetic (macimorelin) recently approved of its use in diagnosing GH deficiency in adults. Remarkable progress in collaboration with clinician investigators (investigating medical genetics) have borne fruit. We found families with genes associated with predisposition to early- onset pituitary tumors. We also hypothesized that shared genetic susceptibility may predispose a patient with a strong family history of malignancy to an early-onset pituitary tumor (in a clinical observational study). We better understood the intriguing clinical presentation of polycythaemia/ duodenal somatostatinoma with multiple paragangliomas, by discovering a mutation of the HIF-2A gene (the Pacak–Zhuang syndrome).Science is embedded in case stories.

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The *European Journal of Endocrinology* Prize Lecture
AP2

Communication between the hypothalamus and peripheral organs in energy balance

Rubén Nogueiras
University of Santiago de Compostela, Spain

Obesity pandemic has a tremendous impact on economic and healthcare systems. Our group investigates molecular mechanisms involved in obesity and its associated diseases such as type 2 diabetes and non-alcoholic fatty liver disease. We are particularly interested in studying the actions and mechanisms by which the central nervous system, and more precisely the hypothalamus, controls energy homeostasis. We have provided evidence that different gastrointestinal hormones such as GLP-1, ghrelin or uroguanylin, acts through the hypothalamus to modulate not only food intake, but also peripheral metabolism. Furthermore, we have also shown that neuropeptides like melanin concentrating hormone and neurotransmitters like dopamine can differentially modulate systemic metabolism by acting on specific neuronal subsets. The effects of peripheral and central signals are tightly controlled through the autonomic nervous system. The appropriate crosstalk between peripheral organs and the brain is essential to maintain a fine-tune regulation of energy balance and understanding the complex and redundant metabolic networks are critical to find new targets to fight against metabolic syndrome.

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European Hormone Medal Lecture
AP3

Is human reproductive health sustainable in the 21st century?

Niels E. Skakkebaek
Department of Growth and Reproduction, Rigshospitalet, University of Copenhagen, Denmark

Human birth rates are decreasing in industrial countries and are now far below levels, where our populations can be sustained. Although some socio-economic analyses suggest that the trends are due to behavioral changes, adverse health factors may also be at play. In Europe, we have epidemics of infertility resulting in increasing need for assisted reproduction. In Denmark, 9 – 10 % of all children are now born after medical assistance. Female infertility due to delays in pregnancy planning causing 'oocyte aging' combined with partner's poor semen quality may often be among the etiological factors. We have been focusing on possible links between increasing trends in testicular germ cell cancer and decreasing semen quality. Our work has provided evidence of a testicular dysgenesis syndrome (TDS) of fetal origin. The symptomatology of TDS includes cryptorchidism, decreased spermatogenesis, low sperm counts and risk of testicular germ cell cancer. In patients with TDS we detected a cell pattern which gives rise to testicular cancer (seminomas and non-seminomas). These precursor cells*, germ cell neoplasia in situ (GCNIS)*, are similar to primordial germ cells of testis in first trimester (gonocytes) and express several embryonic genes, including OCT-4, in line with the theory of fetal origin of testicular cancer occurring in young adults. We hypothesize that endocrine disrupters originating from fossil fuels may play a role in the increasing trends in reproductive health problems. Perinatal exposures may be particularly harmful for normal differentiation of the embryonic gonocytes into spermatogonia in the fetal testis and thereby cause TDS, including testicular cancer in young adulthood. If the hypothesis of links between trends in male reproductive disorders and non-sustainable birth rates is confirmed, unconventional and interdisciplinary research collaborations, followed by regulatory actions, will be needed to reverse the trends.

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Clinical Endocrinology Trust Lecture
AP4

Advances on complications and therapy of cushing's syndrome

Rosario Pivonello
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In the last decade, new evidence on Cushing's syndrome (CS) complications and therapies have gradually emerged. CS is associated with well known systemic complications, mainly including metabolic syndrome,

cardiovascular disease, immune and infectious disorders, skeletal diseases, neuropsychiatric disorders, as well as impairment of gonadal function with impact on reproduction and sexuality. However, more recently several studies specifically focused on muscle and brain structure and function, as well as on the role of cortisol rhythm loss as key determing factor in development, and of glucocrticoid receptor sensitivity in the clincial manifestations of cortisol excess-related complications, offering new perspectives in the clinical management of CS and its complications. Undoubtedly, the main advance in CS management, classically based on surgical tumor removal or irradiation, is represented by medical therapy, which was historically conceived as a marginal treatment, but recently acquired an emerging role in both preoperative and postoperative settings, and as an alternative to surgery. The first advance was the introduction of pituitary-directed drugs, specifically targeting the cause of pituitary CS, namely Cushing's disease (CD), represented by cabergoline, a dopamine agonist, and pasireotide, a daily multi-ligand receptor somatostatin analogue, that showed a good efficacy on hormonal and tumour growth control, as well as an improvement in clinical picture. Although hyperglycemia was frequently reported during pasireotide treatment, european guidelines were provided for its safety management. More recently, a long-acting release pasireotide formulation showed similar efficacy and safety as compared to the daily formulation, with a potential better compliance. New advances appeared also on adrenal-directed drugs, with the introduction of osilodrostat and levoketoconazole, which showed a good efficacy on hormonal control and improvement in clinical picture, with a good safety profile. Compared to the classic steroidogenesis inhibitors metyrapone, also acting on 11β-hydroxylase, osilodrostat may allow higher efficacy at lower doses, due to its higher potency, and a twice-daily administration, due to its higher half-life. Similarly, compared to the classical ketoconazole, levoketoconazole, its 2S,4R enantiomer, might allow higher efficacy at lower doses, due to its higher potency, and decreased hepatotoxicity, due to its diminished CYP7A activity. However, comparative studies are needed to confirm this hypothesis. Lastly, in recent years, new advances appeared on glucocorticoid receptor (GR)-antagonists, with the introduction of relacorilant, a selective GR-antagonist, able to improve glucose metabolism and blood pressure in patients with impairment of glucose metabolism and hypertension, respectively. Compared to the classic GR-antagonist mifepristone, relacorilant was not associated with endometrial thickening and vaginal bleeding, due to its lack of affinity for the progesteron receptor. Although these new medical therapies may offer promising therapeutic options for CS management, further researches and advances are required to allow a more personalized and tailored approach.

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Jens Sandahl Christiansen Award
JSC1

Cardiovascular disease – menopause

Panagiostis Anagnostis
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Transition to menopause is associated with increased cardiovascular disease (CVD) risk, mainly attributed to acquisition of a more atherogenic lipid profile, including an increase in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and apolipoprotein B concentrations, and a decrease in high-density lipoprotein cholesterol (HDL-C) concentrations, mostly due to the HDL_2-C subfraction. Derangement in glucose metabolism, visceral adiposity and development of metabolic syndrome also contribute to the menopause-related CVD risk. Inconsistent data exist with regard to blood pressure and lipoprotein (a) [Lp(a)]. Whether the aforementioned changes are translated into an increased risk of CVD events and mortality, irrespective of age, remains to be established. However, this association is evident in cases with early age at menopause (i.e. < 45 years) or premature ovarian insufficiency (POI), which demonstrate a 1.5-2-fold increased CVD risk, compared with women of normal age at menopause. Oestrogen administration ameliorates most of the CVD risk factors to a various extent depending on the regimen, dose, duration and route of administration. In particular, it decreases TC, LDL-C and Lp(a), whereas it increases HDL-C concentrations. The effect on TG depends on the route of administration (i.e. increase with oral and decrease or neutral effect with transdermal oestrogen). Oestrogen also improves insulin resistance and reduces the risk of type 2 diabetes. These effects are dissipated after withdrawal. Menopausal hormone therapy (MHT) is recommended in cases with early menopause or POI, irrespective of the presence of menopausal symptoms. It may be also considered in symptomatic postmenopausal women <60 years old or <10 years since menopause, starting at the lowest effective dose. CVD and breast cancer risk should be assessed prior to MHT. Transdermal oestrogen and micronized progesterone or dydrogesterone are the preferred regimen. In any case, tailoring the MHT regimen according to women's risk profile and preference, constitute the wisest strategy.

DOI: 10.1530/endoabs.73.JSC1

Plenary Lectures

Plenary 1: The hard road to new therapies against diabetes and obesity

PL1

Abstract unavailable

Plenary 2: Light, body clocks and sleep: Biology to new therapeutics

PL2

Light, body clocks and sleep: Biology to new therapeutics

Eve Van Cauter
Department of Medicine, University of Chicago, United States

Circadian rhythms are a ubiquitous feature in living organisms. They are not just a passive response to daily cyclic fluctuations in the environment, but are instead driven by endogenous and self-sustained clocks. More than 40 years ago, the suprachiasmatic nucleus (SCN) of the hypothalamus was identified as the location of an endogenous circadian clock driving internal rhythmicity and this SCN oscillator was long thought to be the only mammalian clock, functioning as a master pacemaker. It is now well recognized that peripheral circadian oscillators are present in virtually every organ and cell of the body and that optimal functioning of the circadian system is dependent on the tight synchronization of the central and peripheral pacemakers. The tempo between central and peripheral clocks is transmitted by multiple pathways, including the hard-wired autonomous nervous system, the release of hormonal signals in the peripheral circulation (notably glucocorticoids and melatonin) and behaviors such as sleeping and eating. Circadian misalignment refers to abnormal timing between SCN rhythms, peripheral rhythms and behavior (e.g. sleeping during the biological day, eating during the biological night) and the environment (e.g. exposure to light during the biological night). Conditions of circadian misalignment abound in modern society and are invariably associated with metabolic and sleep disturbances. In the present talk, we will review the impact of impaired light perception (as occurs in diabetic retinopathy) and abnormal rhythmicity of circulating corticosteroids (as occurs in adrenal insufficiency) on endocrine and metabolic function. Novel therapeutic approaches, including timed melatonin administration and chronophysiological delivery of exogenous glucocorticoids will be discussed.

DOI: 10.1530/endoabs.73.PL2

Plenary 3: 1 Year in Pituitary

PL3.1

1 Year in Pituitary

Clara V Alvarez

Neoplasia and Endocrine Differentiation Research Group. Center for Research in Molecular Medicine and Chronic Diseases (CIMUS). University of Santiago de Compostela. Santiago de Compostela, Spain. This has been an extraordinary year, where scientists have not been able to get close to the laboratory in many months. However, in the pituitary/hypothalamus we have outstanding contributions. Being at home does not mean stopping thinking, as highlighted by interesting reviews on the novelties in therapeutic peptides targeting GPCRs, new causes of hypopituitarism, DNA damage or pituitary stem cells. In pituitary tumours, use of several omics (mutations, genome alterations, mRNA expression, miRNA clustering, and methylation patterns) in a pangenomic study is a superb contribution, followed by other confirmatory studies allowing understanding of their cellular origin and pre-selection of patients responding better to analogs. At a functional level, we will highlight how the continued activation of the cAMP pathway increases the probability of DNA damage, how hypoxia activates PKA after repressing its regulatory subunits, and what is the molecular protein surface when GHRH activates its GHRHR receptor, obtained through cryo-EM studies. The GPR101 receptor mouse model explaining human pathology but also raising intriguing questions has been one of the milestones of this year. Single-cell RNA sequencing in normal tissue identifies the most abundant genes expressed in an individualized cell; collecting a sufficient number of unique cells it is possible to characterize the different populations of an organ. We have contributions in the changing populations during embryonic development of human pituitary, and several in populations of the mice hypothalamus. At a functional level, we have the role of histone H3 methyl-transferase in the development of GHRH neurons, a new relationship between lysosomes and primary cilium in the early stages of life with consequences in adiposity, or precocious puberty induction by protein signals or ceramides in animal models relevant to the human situation. New and surprising hypothalamic neural circuits in mice controlling metabolism, open exciting possibilities about its existence in humans.

DOI: 10.1530/endoabs.73.PL3.1

PL3.2

Abstract unavailable

Plenary 4: Neuroendocrine stress response at single cell resolution

PL4

Abstract unavailable

Plenary 5: 1 Year in Bone

PL5.1

One year in osteoporosis

Cyrus Cooper
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Osteoporosis constitutes a major public health problem through its association with age-related fractures. These fractures typically occur at the hip, spine and wrist. Our research into osteoporosis at the MRC Lifecourse Epidemiology Unit over three decades has characterised the epidemiology of these fractures, and contributed to the generation of preventive strategies against them throughout the lifecourse. Around 1 in 2 women and 1 in 5 men in the UK will sustain an osteoporotic fracture from age 50 years onwards. Incidence rates rise with age, and rates in women are around double those in men above age 50 years (in large part due to the accelerated bone loss after the menopause among women). Rates are generally higher in Caucasian than in Asian and Afro-Caribbean populations. Life expectancy is increasing around the globe and the number of elderly individuals is rising in every geographic region. Assuming constant age-specific incidence rates for fracture, the number of hip fractures occurring worldwide among people aged 65 years and over will rise from 1.7 million in 1990 to 6.3 million in 2050. In this review of major research findings in the last twelve months, we shall review: (a) key developments in risk assessment of future fracture risk, including approaches to estimating "very high" or "imminent" fracture risk; (b) risks and benefits of currently available antiresorptive and formation stimulating osteoporosis therapies; (c) effectiveness of primary and secondary preventive strategies against fracture; (d) developmental contributors to fracture risk and the role of interventions during intrauterine and early postnatal life; and (e) characterisation of the osteoporosis treatment gap, and measures to try and close this.

DOI: 10.1530/endoabs.73.PL5.1

PL5.2

1 year of basic research in bone

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The last year has definitely not been the most easy one for research in general as the COVID-19 pandemic resulted in limitations on how basic research could be performed. Despite this, it is definitely worthwhile to look back on the data that has been published over the last year. During this presentation, I will highlight some publications that, for one or another reason, can be considered of major importance for or impact on the bone field. This selection was made by searching high impact journals with terms including bone, osteoblast, osteoclast and osteocyte. Obviously this resulted in a large number of publications. Making a balanced selection on what can be considered as most breaking is difficult and clearly personal. Without doubt, the selection made can be debated and, also because of time restraints, unfortunately a lot of papers of high value will not make it to the presentation.

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Plenary 6: New advances in novel targets for thyroid cancer and thyroid cancer theragnostics

PL6

New advances in novel targets for thyroid cancer and thyroid cancer theragnostics

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Thyroid cancer derived from follicular cells is the most frequently endocrine malignancy with an increasing rate of incidence. The identification of new molecules involved in the pathogenesis of these tumors is necessary in order to use it as a novel targets for a better diagnostic and therapy. Recently, the RNA networks emerge as fundamental in the control of gene expression, achieving a strong interest the microRNAs (miRNAs). Our RNA-Seq study together with the analysis of The Cancer Genome Atlas (TCGA) identified novel RNA regulatory mechanism in papillary thyroid carcinomas. We show that miRNA dysregulation involves not only individual changes in the expression of miRNAs, but also disruption of the biogenesis machinery and/or modifications of miRNA sequences by RNA editing. We explored the role of the oncogenic miR-146b, the most upregulated miRNA in thyroid cancer, identifying novel targets that help explain miR-146b-induced cell aggressiveness. Among them, DICER1, the enzyme involved in miRNA biogenesis, is downregulated in thyroid tumor cells overexpressing miR-146b. The decrease in DICER1 levels was associated with a worse clinical outcome of thyroid tumors. Restoration of DICER1 by different treatment reduced tumor aggressiveness both *in vitro* and *in vivo*. Currently, RNA editing is getting great relevance in cancer biology. Thus, we investigated the role of adenosine-to-inosine (A-to-I) RNA editing, a process governed by the enzyme ADAR1. We demonstrate that ADAR1 induces thyroid tumorigenesis by a mechanism dependent on the over-editing of the tumor-suppressor miR-200b, impairing its ability to inhibit the epithelial mesenchymal transition factor ZEB1. Altogether our results highlight potential therapeutic approaches based on miRNA inhibition, restoring global miRNA levels *via* the DICER1 pathway, and suppressing RNA editing, providing a basis for new thyroid cancer treatments.

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Plenary 7: Central and Eastern European heritage in genetics of hypopituitarism - how the prevalent ancestral PROP 1 gene variants spread overseas

PL7

Central and Eastern European heritage in genetics of hypopituitarism – how the prevalent ancestral *PROP1* gene variants spread overseas

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Pituitary development is governed by activation of a cascade of transcription factors that orchestrate both pituitary morphogenesis and differentiation. Among them, loss of function of PROP1 is the most common genetic cause of combined pituitary hormone deficiency (CPHD) with two *PROP1* gene variants (c.[301_302delAG];[301_302delAG] and c.[150delA];[150delA]) being most prevalent. We identified the homozygous c.[301_302delAG] variant in 70% out of 67 Lithuanian subjects with CPHD, suggesting a founder effect and precised their auxological and hormonal phenotype - normal birth lengths/weights, testicular retention in 31% of boys, and a progressive decline of median height SDS over years 1 – 5: –1.56, –2.34, –3.43, –3.52 and –3.70. Deficiencies of GH, TSH, ACTH and FSH/LH were diagnosed in 44/44, 44/44, 19/44 and 22/44 subjects at median age 5.5, 5.6, 13.1 and 15.0 years, respectively. In addition, we aimed to elucidate the origin of the two prevalent *PROP1* variants. We studied 237 patients originating from 21 different countries worldwide. We genotyped 21 single-nucleotide variant markers flanking the 9.6-Mb region around the *PROP1* gene. Haplotypes were reconstructed by Phase and Haploview software. We demonstrated the ancestral origin of both variants – c.[301_302delAG] originated in Lithuania ~ 101 generations ago (confidence interval 90.1 – 116.4). Patients from the Iberian Peninsula displayed a different haplotype, which was estimated to have emerged 23.3 (20.1 – 29.1) generations ago. Subsequently, the data indicated that both the haplotypes were transmitted to Latin American patients ~ 13.8 (12.2 – 17.0) and 16.4 (14.4 – 20.1) generations ago, respectively. The c.[150delA] variant that was carried on a haplotype spanning about 0.3 Mb was estimated to appear 43.7 (38.4 – 52.7) generations ago at the territory of current Byelorussia. We confirmed that the most frequent variants in the *PROP1* gene are founder variants that spread from Eastern/Central Europe overseas. That explains their unequal distribution among various populations.

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Symposia

Symposium 1: The new technology in the clinical management of thyroid nodules

S1.1

Novel approaches beyond cytology

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Background
The traditional cytology-based management of thyroid nodules often leads those with indeterminate cytology to unnecessary resection for diagnostic purposes. In an attempt to improve presurgical diagnosis, several molecular marker tests have been developed in the last decade.
Methods
The benefits and limitations of prospectively validated molecular marker tests in cytologically indeterminate thyroid nodules; and other risk stratification strategies that allow the individualization of management will be discussed.
Results
A selective use of molecular marker tests could be useful in the identification of low-risk nodules; but long-term follow-up of molecularly-benign/negative nodules is currently necessary. Furthermore, their predictive values need to be validated in specific clinical scenarios. Meanwhile, the sonographic pattern and some cytological features enable risk-stratification and can be used to individualize management in cytologically indeterminate thyroid nodules.
Conclusion
An individualized approach for cytologically indeterminate thyroid nodules is not only desirable but also possible through the integration of clinical, sonographic, and cytological features. Current molecular marker tests could be of use selectively; but their role in the evaluation of cytologically indeterminate thyroid nodules needs to be better defined.

DOI: 10.1530/endoabs.73.S1.1

S1.2

Can sonoelastography and artificial intelligence improve the diagnostics of thyroid nodules?

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Thyroid nodules (TN) are the most common endocrine disorder present in 10 – 67% of adults, with a malignancy risk of 3 – 15%. Sonoelastography (SE) is a novel ultrasound technique providing information on elasticity of TN. Decreased elasticity proved to be a useful predictor of malignancy. SE cannot be regarded as a substitute for fine-needle aspiration biopsy (FNAB), but should rather be considered as a complementary tool facilitating estimation of TN malignancy risk and selection of the region for FNAB. SE is particularly useful as a rule-out technique, thanks to its high negative predictive value, thus might help to reduce the number of FNABs. However, certain limitations of SE must be considered during interpretation of the results (TN size and localization, follicular lesions, calcified or cystic TN, multinodular goiter, subacute/acute thyroiditis, obesity, acromegaly, operator-dependence, lack of standardized method for data reporting and clearly defined cut-off values). The use of semi-quantitative methods is recommended. The TIRADS classification system corrected by SE is more accurate in TN diagnosis. Recently computer-aided diagnosis (CAD) systems based on artificial intelligence algorithms allowing for an automated ultrasound image analysis have been developed to obtain accurate, reproducible and more objective diagnosis of TN. In clinical settings CAD performed similarly or worse than experienced sonographists, but still markedly better than a physician with basic ultrasound skills. It may assist in decision-making and has a potential to be used as a screening device for less-experienced physicians. Future improvements of the technique would increase its diagnostic efficiency. Our research demonstrated that CAD characterizes with high sensitivity and good specificity. The EU-TIRADS classification used by an experienced sonographist allows to identify suspected lesions with high sensitivity but rather low specificity. The best diagnostic performance in estimation of malignancy risk of TN was obtained for the combined model of CAD and EU-TIRADS scale.

DOI: 10.1530/endoabs.73.S1.2

S1.3

Abstract unavailable

Symposium 2: Adrenal incidentalomas

S2.1

Abstract unavailable

S2.2

Abstract unavailable

S2.3

Abstract unavailable

Symposium 3: Expanding the benefits of GLP-1R agonists

S3.1

Abstract unavailable

S3.2

Novel biological targets for GLP-1R agonists

Darleen Sandoval
Department of Pediatrics, University of Colorado

The preproglucagon gene (Gcg), expressed in the intestine, the pancreas, and a small cluster of neurons in the hindbrain, encodes multiple peptides in a tissue-specific manner. One of these peptides, glucagon like peptide-1 (GLP-1) increases following meals, functions to stimulate insulin secretion, and is essential for normal glucose tolerance. The dogma is that intestinally-derived GLP-1 acts as a hormone binding to pancreatic GLP-1 receptors (GLP-1r) to stimulate insulin secretion. However, limited by rapid intravascular metabolism, the plasma concentrations of GLP-1 are relatively low and are only modestly elevated during meal ingestion. We have developed several mouse models that all tissue-specific gain- or loss-of-function manipulation of the GLP-1 system. We used these models to advance our understanding of the physiology and pharmacology of the GLP-1 system. An alternative to the endocrine model of GLP-1 physiology in regulation of glucose homeostasis is a paracrine model within the islet. To explore this hypothesis we administered a GLP-1r antagonist to our gain-of-function mouse targeted to Gcg. This work suggests that it is pancreatic, and not intestinal-derived GLP-1 that mediates the physiological regulation of glucose homeostasis. Thus, we hypothesize that the acute insulinotropic effects of endogenous GLP-1 are paracrine rather than endocrine, derived from islet ńcells and acting on β-cell GLP-1r to stimulate insulin secretion. Pharmacologically, while pancreatic but not central nervous system GLP-1r are necessary to regulate improvements in glucose homeostasis by long-

acting GLP-1r agonists, central but not peripheral nervous system GLP-1r are necessary for these agonists to induce weight loss.

DOI: 10.1530/endoabs.73.S3.2

S3.3

Abstract unavailable

Symposium 4: Peripheral neuroendocrinology

S4.1

Serotonergic regulation of insulin release – Hormone secretion, beta cell mass and metabolic status.

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Lund University Diabetes Centre (LUDC), Unit for Molecular Metabolism, Clinical Research Centre, Malmö, Sweden

The neurotransmitter Serotonin (5-hydroxytrympatmine (5-HT), influences hormone secretion from human and rodent islets of Langerhans. Given its confirmed local production in the insulin producing beta (β)-cells, this monoamine has been shown to modulate insulin secretion by both intra- and extracellular mechanisms. However, the precise mechanisms by which 5-HT its effects on insulin release and whole-body glucose metabolism is yet to be fully understood. Fourteen different 5-HT receptors are present in human islets, localized in the different hormone-secreting cell types (e.g., α-and β-cells). The receptors activate a number of intracellular signaling pathways. In fact, both stimulatory and inhibitory actions on insulin release by 5-HT have been observed. Recent advances have pinpointed specific receptors as being crucial for regulation of β-cell mass and compensatory insulin release during pregnancy. Under such circumstances, changes in metabolic status appear to alter both the synthesis of β-cell 5-HT as well as expression of specific 5-HT receptors. Whether actions of 5-HT are implicated in β-cell dysfunction in Type 2 Diabetes is yet to be clarified, but cannot be excluded. Indeed, 5-HT may be an important modulator that fine tunes the release of insulin both and glucagon, the two main hormones that control glucose and lipid homoeostasis.

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S4.2

Abstract unavailable

S4.3

Abstract unavailable

Symposium 5: Human foetal exposure to environmental endocrine disruptors

S5.1

Nutritional programming of cardio-metabolic health: The role of maternal and fetal hyperinsulinaemia

Susan Ozanne
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Strong evidence from studies in humans and animal models suggests that the nutritional environment to which a developing fetus is exposed impacts on long-term cardio-metabolic health. This concept has been termed nutritional programming. Although initial focus was on the detrimental consequences of fetal under-nutrition, the growing prevalence of obesity across the globe has focussed attention towards fetal over-nutrition. Obesity prevalence is increasing in all age groups, including women of childbearing age. In many populations over half of women are now either overweight or obese during pregnancy and this is accompanied by an increased prevalence of gestational diabetes. This is of major concern as evidence suggests that developing *in utero* in an obesogenic/diabetic environment has both immediate and long-term impacts on the health of the mother and child. The strongest evidence from humans to suggest that development *in utero* in an obesogenic environment "programmes" increased risk of obesity and cardio-metabolic disease comes from the study of siblings born before and after maternal bariatric surgery. These revealed that the sibling born post-surgery had reduced adiposity, lower blood pressure and increased insulin sensitivity compared to their sibling born prior to maternal weight-reducing surgery. We have used a mouse model of maternal diet-induced obesity to define the mechanisms by which obesity/impaired glucose tolerance during pregnancy impacts on the long-term cardio-metabolic health of the offspring. These studies show that the offspring of obese dams develop insulin resistance, cardiac dysfunction, hypertension and fatty liver even when the offspring are lean. We have identified maternal hyperinsulinaemia as a key 'programming" factor and shown that insulin resistance in some tissues can occur *in utero*. These findings highlight maternal hyperinsulinaemia as an important target of intervention studies such as those involving increased maternal physical activity to reduce the transmission of poor cardio-metabolic health between mother and child.

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S5.2

Abstract unavailable

S5.3

Pubertal urinary phthalate metabolite concentrations and semen quality among young Russian men: exploring potential windows of susceptibility

Lidia Minguez-Alarcon
Harvard School of Public Health, United States

Aim
To prospectively investigate the associations of urinary phthalate metabolite concentrations measured during four peri-pubertal windows with semen parameters in Russian men.
Methods
516 boys were enrolled at ages 8 – 9 years (2003 – 2005). Urine samples were collected annually and pooled into four pubertal exposure windows based on physician assessed Tanner stages and testicular volume (prepuberty, early puberty, late puberty and sexual maturity). 15 phthalate metabolites were quantified using isotope dilution HPLC-MS/MS at Moscow State University. We calculated molar sums (∑) of di-2-ethylhexyl phthalate (DEHP), non-DEHP, di-isononyl phthalate (DiNP) and di-isodecyl phthalate (DiDP) metabolites. At sexual maturity (18 – 19 years), men provided 1 – 2 semen samples for analysis. We estimated the associations between quintiles of ∑phthalate metabolites and semen parameters for each pubertal window by fitting generalized linear mixed models with random intercepts to account for repeated semen samples, adjusting for abstinence time, body mass index, and specific gravity. We also modelled the probability of having a semen sample below any WHO cut-offs measured as < 15 mil/ml for concentration, < 39 mil for count, or < 32% progressive motility.
Results
Higher urinary concentrations of ∑DiNP in the late pubertal samples were associated with poorer semen quality; men with the highest versus lowest quintile of ∑DiNP had 32% lower sperm concentration, 34% lower count and 33% lower progressive motile count. Also, men with the highest versus lowest quintile of ∑DiNP had 15% higher probability of having a semen parameter below WHO cut-offs. ∑DiNP measured in the other three peri-pubertal windows was not associated with semen quality. No

associations of ∑DEHP, ∑non-DEHP and ∑DiDP with semen quality parameters were observed.
Conclusions
∑DiNP metabolites in late puberty was associated with poorer semen quality, highlighting the importance of considering specific windows of exposure when investigating chemical exposures in relation to fertility in men.
Funding
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Symposium 6: COVID: The sequelae of the virus

S6.1

Abstract unavailable

S6.2

Abstract unavailable

S6.3

Abstract unavailable

Symposium 7: Inheritable metabolism

S7.1

Abstract unavailable

S7.2

Abstract unavailable

S7.3

Transgenerational influences of AMH and the pathogenesis of PCOS
Paolo Giacobini
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Polycystic ovary syndrome (PCOS) is the major reproductive and metabolic disorder affecting 10 – 15% of women in reproductive age. Up to 70 percent of daughters of women with PCOS also develop the disease, but genetic variation doesn't fully explain the high incidence within families and the mechanisms underpinning its transmission remain to be elucidated. We have previously shown that prenatal anti-Müllerian hormone (AMH) exposure leads to the manifestation of PCOS-like traits in the female offspring (PAMH mice). More recently we utilized this animal model to show that the transmission of reproductive and metabolic PCOS-like traits occurs across three generations. We next performed RNA sequencing and genome-wide DNA methylation profiling of ovarian tissue from control and third-generation PCOS-like mice. We found that DNA hypomethylation regulates key genes associated with inflammation and metabolic related pathways in PCOS and that several of the differentially methylated genes are also altered in blood samples from women with PCOS compared with healthy controls. We further explored the epigenomic basis for this transgenerational transmission of PCOS-like phenotypic expression by reversing many of its traits through supplementation with the universal methyl donor, S-adenosylmethione (SAM). These findings show that the transmission of PCOS reproductive and metabolic dysfunctions to multiple generations occurs via altered landscapes of DNA methylation and highlight a roadmap to new diagnostic and therapeutic avenues of the disease.
DOI: 10.1530/endoabs.73.S7.3

Symposium 8: Lessons from MDT in MEN1 patients

S8.1

Abstract unavailable

S8.2

Abstract unavailable

S8.3

Abstract unavailable

Symposium 9: Large ambitious and inspiring European prevention programs

S9.1

Abstract unavailable

S9.2

Prevention program for male health
Daniele Gianfrilli
Department of Experimental Medicine, Section of Medical Pathophysiology, Food Science and Endocrinology, Sapienza, University of Rome, Rome, Italy

Context
Although in the past andrological health has been a poorly addressed topic due to historical and cultural reasons, in recent times male reproductive and sexual health has emerged as a main healthcare issue. Young male subjects could suffer from various andrological problems, as cryptorchidism, varicocele, sexual dysfunctions, sexually transmitted infections, testicular

cancers. Early finding and treatment are fundamental, especially because if some conditions are not promptly recognized, they are managed later with greater complexity. The identification of early risk factors, including modifiable ones, involved in the development of andrological disorders is extremely important and adolescence is a key time. Despite all this, there is still a clear gender gap in research and prevention programs for reproductive health and sexuality.
Objective
It is essential to provide health programs aiming to: 1) inform and educate young people about andrological prevention; 2) early detection of andrological pathologies.
Methods
In Italy, some information campaigns and programs focusing on andrological prevention have been made. An example is the national andrological health surveillance project named "Amico-Andrologo (AA)", which is conducted by the Sapienza, University of Rome and the Italian Society of Andrology and Sexual Medicine in the final year of high school. During the onsite visit, all subjects are invited to complete an anonymous, self-administered questionnaire and, if willing, to undergo a voluntary andrological examination performed by trained clinicians, who also provide all students informative material about andrological prevention issues.
Results
During the AA survey, abnormal andrological clinical examination was found in one third of students, showing high percentage of varicocele (27.1%), testicular hypotrophy (14%) and phimosis (7.1%). Unprotected sex was quite common and heavy alcohol or drug use were associated with testicular hypotrophy.
Conclusions
Prevention program for sexual and reproductive male health are effective and needed.
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1. Gianfrilli D. et al. Risk behaviours and alcohol in adolescence are negatively associated with testicular volume: results from the Amico-Andrologo survey. *Andrology*. 2019 Nov; **7(6)**:769–777.

DOI: 10.1530/endoabs.73.S9.2

S9.3

Abstract unavailable

Symposium 10: New approaches in pituitary pathologies from a multidisciplinary team

S10.1

Abstract unavailable

S10.2

Tumor or not tumor and what's new in pituitary pathology

Jacqueline Trouillas
Faculté de Médecine Lyon Est, Lyon, France

Pituitary adenohypophyseal tumors are considered benign and termed "adenomas" but can also be invasive, "aggressive" and malignant with metastases (carcinoma). Taking into account this variability in behavior and the oncological definition, pathologists have proposed changing the term adenoma to tumor. Indeed, "tumor designates a neoplasm which is benign or malignant". The invasion of the surrounding tissues is a criterion of malignancy. For this reason, the terms "invasive adenoma or aggressive adenoma" are inappropriate pathologically. Recently, a Workshop of Endocrinologists (PANOMEN) recommended that the term adenoma be retained, arguing that "tumor may have a sinister tone and may adversely affect patients". What is your opinion? These tumors are classified into seven morphofunctional types and three lineages identified by transcription factors: lactotroph, somatotroph and thyrotroph (PIT1 lineage), corticotroph (TPIT lineage) or gonadotroph (SF1 lineage), null cell or immunonegative tumors and plurihormonal tumors. The WHO 2017 classification suggested that subtypes, such as male lactotroph, silent and "Crooke cell" corticotroph, sparsely granulated somatotroph, and silent plurihormonal PIT1 tumors, should be considered as "high risk" tumors. However, the prognostic impact of these subtypes remains controversial. In contrast, the French five-tiered classification, taking into account invasion (MRI), the immunohistochemical type, and proliferative markers (Ki-67 index, mitotic count, p53 positivity), has prognostic value for recurrence/progression, that has been independently validated by statistical analysis on around 2000 patients. In the European Society of Endocrinology (ESE) cohort of "aggressive" tumors (125 APC) and carcinomas with metastases (40 PC), the clinical and pathological features were similar. This cohort (APT+PC) differed greatly from a reference surgical cohort, especially in the percentage of tumors with Ki67 $\geq$ 10%. We suggest that these clinically aggressive, invasive and highly proliferative tumors represent tumors with malignant potential. Pathological diagnosis may help clinicians to adapt post-operative management, including appropriate follow-up and early recognition and treatment of potentially malignant tumors.

DOI: 10.1530/endoabs.73.S10.2

S10.3

Abstract unavailable

Symposium 11: Thyroid hormones, regulation of metabolism and energy balance

S11.1

Abstract unavailable

S11.2

The cross talk between thyroid hormones and the central nervous system in thermoregulation

Jens Mittag
Internal Medicine I, Molecular Endocrinology, Center of Brain, Behavior and Metabolism, University of Lübeck, Lübeck, Germany

Thyroid hormone is long known for its profound effect on body temperature regulation. Patients suffering from hyperthyroidism display elevated body temperature and are sensitive to heat, while hypothyroid patients are cold sensitive. The precise regulation of body temperature by thyroid hormone, however, has been incompletely understood. In our recent studies, we have studied the thermogenic effects of the hormone in a mouse model in detail. We observed that the body temperature increase induced by the hormone persisted independent of the environmental temperature, demonstrating that it constituted an upregulation of the central set point comparable to fever. However, there was a parallel increase in peripheral thermogenesis, which at room temperature even exceeded the elevated set point, causing a hyperthermia response. Using mice lacking the thermogenic uncoupling protein 1, we subsequently demonstrated that this hyperthermia was not caused by brown or beige fat thermogenesis, but likely originated in muscle. To test the central set point hypothesis further, we studied mice lacking the thyroid hormone transporters MCT8 and OATP1C1. Consequently, these animals display a severely hypothyroid brain in the presence of systemically elevated T3 levels. Interestingly, the double knockout mice did not present with an elevated body temperature, demonstrating that the central actions of the hormone are required for the fever phenotype observed in hyperthyroidism. Taken together, our work shows that thyroid hormone

simultaneously acts thermogenic in the periphery and pyrexic in the brain, which is of particular interest for the role this hormone may have played in the evolutionary development of endothermy.

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S11.3

Chronic glucocorticoid treatment causes metabolic abnormalities: The role of hypothalamic glucocorticoids and DIO2

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Synthetic glucocorticoids (GCs) are widely used in clinical practise to treat various inflammatory disorders including rheumatoid arthritis, asthma and some malignancies. Although generally well tolerated, long-term, especially high dose use can lead to metabolic side effects. We have developed a mouse model of GC treatment in drinking water, using corticosterone (Cort, the endogenous GC in rodents), which recapitulates many of the side-effects in patients treated with GCs. After 24 h treatment we observe hyperphagia, leading to increased body weight from day 10 of treatment. There are changes in gene expression consistent with insulin resistance from day 2 of Cort treatment and hyperglycaemia develops by day 21. Although GCs signal peripherally, there is growing evidence that peripheral metabolic effects can be mediated by GCs acting on the neurons of the arcuate nucleus of the hypothalamus (ARC). To investigate these potential central effects, we treated with Cort for 2 days and then carried out global transcriptomic analysis of the ARC, to identify novel GC target genes. Genes which were altered included well known target genes, such as *Fkbp5* and *Agrp*. However, we also identified novel GC target genes and interestingly, GCs upregulated type II iodothyronine deiodinase (*Dio2*), suggesting that GCs might increase the conversion of T4 to T3. *Dio2* was of particular interest, due to its discreet localisation in the tanycytes and astrocytes of the ARC, and because elevated T3, like glucocorticoids, can influence hyperphagia and energy balance, potentially by activating AgRP neurons. Therefore, we knocked down *Dio2* by injecting AAV-CRISPR-Cas9 guide RNAs bilaterally into the ARC. In these knockdown mice, we found little effect on the GC-induced metabolic phenotype. However, we observed a reduction in GC-induced *Agrp* expression, indicating that GC effects in the hypothalamus may be mediated in part by their actions on *Dio2*.

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Symposium 12: What's new in cardiovascular protection and function

S12.1

Abstract unavailable

S12.2

Abstract unavailable

S12.3

Role of inflammation in the therapy of cardiometabolic diseases

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Morphological and therapeutic interventions have uncovered an inflammatory process in patients with type 2 diabetes. This inflammation is due to a pathological activation of the innate immune system by metabolic stress and is largely governed by IL-1 signaling. Initially, the inflammatory response is probably deployed to promote adaptation and regeneration. Indeed, we identified a role for IL-1β and insulin in the regulation of both metabolism and immunity in response to feeding. Yet, as it becomes chronic, activation of auto-inflammatory processes may then become deleterious. It follows that modulation of inflammatory mediators may present as a possible causal therapy. This is supported by clinical studies showing that IL-1 antagonism decreases glycated hemoglobin. Furthermore, IL-1 antagonism prevents heart failure and cardiovascular diseases, the major complication of diabetes.

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TGF-β signalling in ovaries in women with PCOS

S13.1

Interplay between androgens and TGF-β signalling in the ovary

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Theca cells are indispensable for female reproduction being the source of androgens required for follicular oestrogen synthesis and also for interacting with androgen receptors in the ovary and other somatic tissues. Differentiated theca interna cells acquire responsiveness to LH and other endocrine signals, including insulin, that upregulate the steroidogenic pathway leading to androgen biosynthesis. In addition, numerous intraovarian factors of thecal, granulosal and/or oocyte origin modulate thecal androgen production, mostly in an inhibitory manner; many of these are members of the TGF-β family. These ligands bind to different combinations of type-I and -II signalling receptors expressed by theca cells; ligand-receptor interaction is regulated by various extracellular binding proteins, co-receptors and likely by competition amongst cross-reactive ligands for common receptors. In vitro studies in the author's and other laboratories indicate functional redundancy amongst TGF-β family ligands in that activins and various BMPs (including BMP2,4,6,7) suppress thecal androgen production in an inhibin-reversible manner. Follistatins neutralize activin action while other binding proteins (e.g. noggin, gremlin) selectively neutralize different BMPs. Other ligands including TGF-$\beta_{1,2,3}$ also strongly inhibit thecal androgen production while AMH and GDF9 appear to have limited effect. Recent evidence indicates that myostatin (GDF8) is expressed within human and bovine follicles and suppresses thecal androgen production in a manner opposed by follistatin. It has also emerged that bovine theca cells express free inhibin-α subunit and that its knockdown suppresses androgen output although the significance of this finding requires further investigation. With regard to ovarian hyperandrogenaemia commonly associated with polycystic ovarian syndrome, it is hypothesised that this could be due to compromised intraovarian signalling by one or more TGF-β family ligands that tonically suppress thecal androgen synthesis. This could arise from altered expression or processing of ligands, antagonists (i.e. inhibins), extracellular binding proteins, signalling receptors, co-receptors and/or intracellular signal transduction components.

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S13.2

LH-receptor activity and interaction with TGF-β family members in women with PCOS

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The luteinising hormone/chorionic gonadotropin receptor (LHCGR) plays an essential role in ovarian follicular function, mediating the action of LH on theca cell steroidogenesis and, in the preovulatory follicle, on granulosa cell (GC) steroid production and the ovulatory cascade. Following ovulation, LH (and CG) are responsible for maintenance and function of the corpus luteum. Arrested antral follicle development in PCOS is characterised by premature responsiveness of GCs to LH and recent studies in our laboratory have indicated that LHCGR mRNA is increased in GCs of small, human antral follicles (hSAFs). A similarly increased gene expression of LHCGR was observed in granulosa-lutein cells (GLCs) from PCOS women. Several previous studies point to the interaction of LH with members of the TGF-β

family. TGF-β's, activin, inhibins and AMH have all been implicated in modulating LH action in both theca and granulosa cells. In our recent study we found that aberrant expression of LHCGR in GCs of hSAFs in PCOS, was associated with increased expression of inhibin A, but not of inhibin B, AMH, AMH receptor 2 (AMHR2) or follistatin. Nevertheless, there are functional studies that implicate AMH in abnormalities of gonadotropin-induced steroidogenesis in women with PCOS and there remains considerable scope for further investigation in attempting to understand what role the interaction between gonadotropins and members of the TGF-β family has to play in the mechanism of anovulation in PCOS.

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S13.3

Cell-specific expression of TGF-β family members in follicles of women with and without PCOS

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Polycystic ovary syndrome (PCOS) is a common endocrine disorder, affecting 5 – 10% of women of reproductive age, and is the major cause of anovulatory infertility. The mechanisms of reproductive dysfunction in PCOS remain to be clarified. Members of the TGF-β and IGF signalling pathway have been suggested to be involved in aberrant follicle development in women with PCOS. This talk will focus on previous and ongoing research that we carried out in Denmark and the United Kingdom, which imply differences in follicular TGF-β and IGF signalling between women with and without polycystic ovaries (PCO). The results in this talk are based on materials obtained from follicle fluids (FFs), granulosa cells (GCs), and fixed human small antral follicles (hSAFs) collected from women with and without PCO undergoing ovarian tissue cryopreservation as well as granulosa lutein cells (GLCs) collected from women undergoing IVF. Protein levels of inhibin-A and inhibin-B were significantly lower in FFs from women with PCO (hSAFs < 8 mm). *AMH* and *AMHR2* gene expression and AMH FF-levels in hSAFs < 8 mm did not differ between the groups, however, FF-levels of AMH remained high in hSAFs > 8 mm from women with PCO. FF-levels of GDF9 were higher, whereas levels of BMP15 were reduced in PCO women (follicles > 6 mm). Gene expression levels of inhibitors (stanniocalcins) of the IGF signalling were downregulated in GLCs of women with PCOS. Further, FF-levels of PAPP-A (enhances IGF signalling) in hSAFs were reduced in women with PCO. AMH, PAPP-A, and stanniocalcin proteins were identified and localised by immunohistochemistry in ovaries of both PCO and non-PCO subjects. In conclusion, aberrant levels of TGF-β and IGF members in ovaries from women with PCO(S) highlight dysregulated growth factor signalling as a contributory mechanism in follicle arrest and anovulation in PCOS.

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Symposium 14: Complex clinical cases

S14.1

GH: too much, too early

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According to the WHO classification and to clinical practice most pituitary tumors are benign, although invasion and aggressive behavior, as well as resistance to somatostatin/dopamine (SS/DA) analogs, occur in 25 – 50% of cases. In particular, genetic forms of acrogigantism (X-linked acrogigantism - X-LAG) are characterized by a very precocious and resistant phenotype associated with microduplications in the Xq26.3 region involving the GPR101 gene. The GPR101 gene encodes an orphan G protein-coupled receptor strongly expressed in the human normal pituitary during fetal development as well as in adolescence but not in adult pituitary. The molecular mechanism of pituitary tumorigenesis involves cAMP pathway activation. Indeed, GPR101 is constitutively coupled with stimulatory G proteins, leading to intracellular cAMP accumulation, with direct effects on somatotroph cells proliferation and GH secretion. The pathogenic mechanism may also involve the ability of GPR101 to increase GHRH secretion by hypothalamus, accordingly to the elevated circulating GHRH levels described in some XLAG patients. A young woman, now 24 years-old, has been followed at our Institution since she was 2. At that time, gigantism due to an endo and suprasellar GH-secreting pituitary macroadenoma was diagnosed and she underwent a first trans-sfenoidal neurosurgery at the age of 3. Because of persistent disease, she was treated with first-generation somatostatin analogues associated with cabergoline and then with pegvisomant. At the age of 18 she was operated for the second time but pharmacological treatment was again necessary after surgery. Since then, she was treated with octreotide, cabergoline, pasireotide and pegvisomant. The diagnosis of acrogigantism due to a microduplication in the Xq26.3 region was finally made when she was 18. The talk will describe in detail her clinical history focusing on the multimodal approach. It will also summarize the current knowledge on the clinical presentation and evolution of this rare disease.

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S14.2

Abstract unavailable

S14.3

Abstract unavailable

Symposium 15: Nutrition intervention: Not just to lose weight

S15.1

Abstract unavailable

S15.2

Abstract unavailable

S15.3

Abstract unavailable

Symposium 16: Splicing in endocrine-related cancers

S16.1

Abstract unavailable

S16.2

Alternative splicing in breast cancer

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The dysregulation of the splicing process has emerged as a novel hallmark of metabolic and tumor pathologies. Specifically, in breast cancer (BCa), which represents the most diagnosed cancer type among women worldwide, several oncogenic splicing variants have been reported to have a relevant pathophysiological role. This is the case of the splicing variants of HER2 gene, or the In1-ghrelin and SST5TMD4 isoforms, which exhibit oncogenic roles, increasing the malignancy, poor prognosis and resistance to treatment of BCa. However, the implication and putative dysregulation of the elements belonging to the macromolecular machinery that regulate the splicing process [spliceosome components (SCs) and the associated splicing factors (SFs)] have not been systematically explored in BCa. Similarly, the impact of the metabolic status (i.e. obesity) of the patients on the regulation of the splicing machinery in the context of BCa has not been explored. A recent study from our group has characterized the expression pattern of key SCs (n = 17) and associated SFs (n = 28) in the tissue of 69 patients with BCa and 50 non-tumoral controls, demonstrating a profound dysregulation of the splicing machinery in BCa samples (i.e. upregulation of ESRP1 or SRSF10 and downregulation of CELF4, NOVA1 or PTBP1). These alterations have been found in other external cohorts (TCGA, Curtis) and correlate with the expression of oncogenic splicing variants, poor prognosis and reduced survival of the patients. Interestingly, the obesity and post-menopausal status clearly influenced the expression levels of certain splicing machinery components (i.e. SRSF3 or SRSF9) under normal and/or tumoral (BCa) conditions. In addition, the experimental modulation of these altered factors impacted the aggressiveness and tumorigenic potential of different BCa cell lines. In conclusion, there are growing evidence indicating that splicing machinery is deeply dysregulated in BCa samples, finely influenced by obesity and menopausal status and implicated in the tumorigenic potential of BCa cells.

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S16.3

Abstract unavailable

Symposium 17: New advances in the managements of hypophosphatemia

S17.1

Pathogenesis and pathophysiology of hypophosphatemia

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The maintenance of a phosphate level within the normal range in the body is essential for an optimal function of several vital processes. Phosphate is an important component of bone and teeth, cell membranes, phospholipids, nucleic acids, enzyme systems, the energy carrier adenosine triphosphate (ATP) among others. Thus, the state of hypophosphatemia potentially disturbs many processes in the body. Hypophosphatemia may be mild, moderate or severe and may develop in acute or chronic disease processes. Examples of diseases characterised by acute hypophosphatemia are refeeding syndrome, diabetic ketoacidosis, and respiratory alkalosis in severe, acute diseases. Most often, chronic hypophosphatemia arises due to increased renal phosphate excretion. X-linked hypophosphatemia (XLH) is an inborn disease where a mutation in *PHEX* leads to an increased level of fibroblast growth-factor 23 (FGF23), being the main regulatory hormone for the phosphate homeostasis. Increased levels of FGF23 leads to increased renal phosphate excretion in addition to inappropriately low levels of active vitamin D, 1,25-dihydroxyvitamin D. During periods of skeletal growth, hypophosphatemia causes rickets and osteomalacia, leading to dysproportionate short stature and often bowing of weight bearing long bones. In addition, dental abscesses may occur. Adults with XLH experience osteomalacia, arthrosis, muscle fatigue, and increasing number of dental abscesses by age. A rare achieved phosphate disorder is tumour induced osteomalacia, TIO. An often very little tumour with excess production of FGF23 may lead to invalidating symptoms due to severe hypophosphatemia. In addition, the state of i.v. iron induced, FGF23 mediated hypophosphatemic osteomalacia is a rare complication to medical treatment. These are important differential diagnoses as they are potentially curative.

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S17.2

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S17.3

Abstract unavailable

Symposium 18: The future of endocrinology Artificial Intelligence (AI) and big data!

S18.1

AI in the clinical setting

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There are different activities related to health care that are currently generating a large amount of data. Real-world evidence studies are becoming an important source of information that complements the one produced through other sources of evidence. On top of this, current knowledge in the field of massive data analysis allows processing of these data to produce relevant information that will eventually help clinicians in many aspects of their daily practice, especially regarding decision making. The aim of this talk is to provide the non-expert view on the applicability of the information produced from big data and its innovative analytical methodology. Several examples on the applicability of this approach in the field of endocrine and metabolic diseases will be provided during this presentation: endocrine imaging, thyroid disease, diabetes mellitus, obesity, and other endocrine conditions. Examples will include the application of AI in key areas like prevention, diagnosis, monitoring, therapeutics, and prognosis. The use of information obtained from big data through newer analytical approaches (e.g., artificial intelligence) will the basis of a changing scenario in the clinical practice of endocrinologists in the forthcoming years. Further, improved data management and newer tools derived from more precise information will contribute a better implementation of individualized endocrinology.

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S18.2

Abstract unavailable

S18.3

AI in endocrine learning

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Artificial intelligence (A.I.) impacts patient care but it is also evolving our educational system. Several experts have pointed out the benefits and limitations associated with its use in medicine, however the applications of A.I. in an educational context requires further discussion. The rising popularity of A.I. for medical solutions is evident from the increasing amount of research conducted on this subject, and Endocrine Education should not be an exception. Researchers have proposed that A.I. could be used to analyze data to identify struggling students, similarly it can be used to assist teachers in creating personalized methods for said students increasing the chances of success. On the other hand, future endocrinologists should be able to utilize the expansive databases and other appropriate tools, resulting in a massive volume of information that can overwhelm students. In this context mentorship on data management should be provided by main endocrine societies. Furthermore, electronic health records highlight the impact of natural language processing and affect medical education. Endocrinologists in the future could learn about the natural history of chronic diseases and better identify endocrine pathologies, greatly reducing the diagnosis timeframe. There is also an opportunity to develop Endocrine Healthcare Leaders with expertise in Big Data and A.I., this newly trained professional could be the bridge between clinicians and data specialists to develop A.I. Projects. Therefore, A.I. and its applications should be taught within Endocrine Societies and needs to be formalized to train the next generations of endocrinologists with a new set of skills that will directly impact not only our education system but patient care as well.

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Symposium 19: Emerging concerns in reproduction

S19.1

Influence of the pre- and post-natal environment upon metabolic physiology of the offspring

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Our health and wellbeing are influenced by numerous factors, including our early developmental hormonal and nutritional environments. Indeed, modifications of hormones and nutrition during specific developmental periods can have long-lasting effects on fundamental functions such as metabolism and reproduction, with these long-term changes often being sex dependent. Moreover, modifications in one neuroendocrine system can have an important impact on other neuroendocrine axes, as well as on the propensity to suffer specific diseases later in life. Understanding how these processes interact throughout life is of great importance to improve health and wellbeing. We have employed various experimental models in attempt to understand how modifications in the fetal and neonatal environments can affect pubertal onset and metabolism in adulthood. For example, maternal separation can dramatically modify levels of hormones (e.g., leptin) implicated in the development of metabolic circuits, resulting in changes in the response to later dietary challenges and in the onset of puberty. Neonatal overnutrition also impacts on pubertal development and metabolic health in adulthood, with these effects being different between males and females. Likewise, maternal diet has been shown to modify metabolic wellbeing in adult offspring, and we have recently found that maternal intake of the polyphenol, resveratrol, impacts on the offspring's metabolic health in a sex specific manner, and more surprisingly, the response depends on whether the maternal diet is high fat or low fat. This talk will summarize the findings of the different models employed to support the hypothesis that our early developmental experiences have long-lasting effects on puberty and metabolism, as well as on our susceptibility to other diseases.

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S19.2

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S19.3

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Symposium 20: Diabetes and bone

S20.1

Abstract unavailable

S20.2

Abstract unavailable

S20.3

Abstract unavailable

Symposium 21: Hot topics in neuroendocrine tumours

S21.1

Epigenetics in NENs – lessons from MEN1-NENs models

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Epigenetic mechanisms are gaining increasing interest in oncology, both as drivers of tumourigenesis and as potential novel therapeutic targets. This is particularly relevant in neuroendocrine neoplasms (NENs), as a key tumour suppressor gene involved in NEN development, multiple endocrine neoplasia type 1 (*MEN1*), plays a critical role in epigenetic regulation of gene expression through micro RNA (miRNA) and histone modification pathways. *MEN1* mutations can give rise to sporadic NENs, or those occurring as part of the MEN1 syndrome in which patients predominately develop parathyroid adenomas, and NENs of the pancreas, and pituitary. Investigation of these tumours in MEN1 models has revealed insights in to the utility of epigenetics in NENs for modulating cell proliferation. For example, menin (encoded by *MEN1*) knockout results in reduced expression of the miRNA's miR-15a and miR-16-1 with a concomitant increase in the

cell cycle regulator cyclin D1 expression, which promotes cell proliferation. In addition, menin is an essential component of histone methyltransferase and deacetylation complexes, interacting with proteins including mixed lineage leukaemia 1 (MLL1), MLL2 and protein arginine methyltransferase 5 (PRMT5). Current medical treatments for NENs have limited efficacy, therefore epigenetic inhibitors targeting these specific histone modification complexes offer a promising new class of drugs for NENs. Thus, JQ1, an inhibitor of the bromo and extra-terminal (BET) protein family that bind acetylated histones, can reduce proliferation and increase apoptosis of both pancreatic NEN cell lines and pancreatic NENs occurring in a conditional *MEN1* knockout mouse model. Furthermore, JQ1 can decrease proliferation and increase apoptosis of the pituitary tumour cell line AtT20, as well as downregulate expression of the *Pomc* gene, and subsequently reduce adrenocorticotropic hormone (ACTH) secretion. Therefore, advancing our knowledge of epigenetic mechanisms may provide a novel therapeutic approach for the control of NEN growth, and hormone secretion.

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S21.2

Abstract unavailable

S21.3

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Symposium 22: From adrenal stem cells to ACC

S22.1

Adrenal cortex ageing and cancer

Katie Basham
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The adrenal cortex functions to produce steroid hormones that are essential for life and regulate key biological processes, such as control of blood pressure, metabolism, reproduction, stress, and the immune response. In order to achieve both a rapid and precise response, the adrenal cortex employs hormonal feedforward-feedback systems that function in the context of histologically distinct adrenocortical zones. These layers, the outer zona glomerulosa (zG), intermediate zona fasciculata (zF), and inner zona reticularis (zR), produce mineralocorticoids, glucocorticoids, and androgens, respectively. Functional zonation within the adrenal cortex is established by centripetal differentiation, where multipotent progenitor cells in the mesenchymal capsule and outer zG give rise to concentric layers of differentiated cortex. Previous studies have shown that the Wnt/b-catenin signaling pathway is essential for maintaining adrenal progenitor cells and allowing for proper homeostatic renewal. This presentation will focus on more recent studies examining (1) how varying levels of Wnt/b-catenin signaling are regulated during adrenal homeostasis, (2) premature ageing and cellular senescence that result from Wnt-driven hyperproliferation, and (3) the potential role of cellular senescence in adrenal cancer and its therapeutic implications.

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S22.2

Abstract unavailable

S22.3

Abstract unavailable

Symposium 23: Novel targets in diabesity

S23.1

Abstract unavailable

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S23.3

Abstract unavailable

Symposium 24: Intermediate thyroid cancer soft or aggressive approach

S24.1

Clinical Case: Papillary thyroid cancer: A surgical disease

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Case history
A 27 year-old woman presents with a right 3 cm. papillary thyroid cancer (PTC) with lateral cervical lymph node metastasis. Her past history is irrelevant. Treatment consists of total thyroidectomy plus lymphadenectomy of compartments II-III-IV-VI. iPTH and s-Ca concentrations at 24 h were 6 pg/ml and 7 mg/dl respectively. Replacement therapy (calcium + calcitriol) was required for three months (protracted hypoparathyroidism). Pathology reveals a 27 mm. non-encapsulated PTC of follicular variant, with 0N+/6N in the central neck and 6N+/24N in the lateral neck (T2N1bM0, skip metastasis). One ipsilateral parathyroid gland was found in the specimen (PGRIS 3). At three months postop her stimulated Tg was undetectable and iPTH 39 pg/ml. Suppressive T4 was administered for three years. No radioidine ablation was performed. The patient has been followed wit basal Tg determinations and neck ultrasound once a year for ten years and then every two years up to 20 years. She is currently disease-free.
Comment
There is no such thing as “differentiated thyroid cancer”. PTC and follicular thyroid cancer have different clinical presentation, biological behaviour and require different therapeutic approaches and risk assessment. RAI ablation is losing momentum in the treatment of PTC because specialized surgical treatment can render patients biochemically cured. Survival and recurrence rates of classical PTC completely resected and with no distant metastasis, are not influenced by RAI ablation. Thorough surgery including total thyroidectomy, routine central neck dissection plus elective lateral dissection based on preoperative ultrasound, and a bland follow-up is all

that is needed for most patients with PTC. Permanent hypoparathyroidism remains the main postoperative complication, but it can be minimized (< 5%) by avoiding accidental parathyroidectomy and autotransplantation, and referring patients to high-volume centres. Routine postoperative scans, repeated thyroglobulin stimulations and aggressive imaging techniques to investigate minimally elevated thyroglobulin concentrations are obsolete.

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S24.2

Abstract unavailable

S24.3

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S24.4

Abstract unavailable

Symposium 25: Parathyroid disorders

S25.1

Abstract unavailable

S25.2

How to discriminate between PHPT and FHH

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Primary hyperparathyroidism (PHPT) is a common and for the most part an asymptomatic endocrine disorder, usually discovered by routine biochemical screening, in western populations; and increasingly now in other parts of the word. It is characterized by abnormal calcium-PTH dynamics, manifesting with mild hypercalcemia, with increased or inappropriately normal plasma parathyroid hormone (PTH) levels. PHPT is most commonly seen in older post-menopausal women. In countries where routine biochemical testing is lacking, patients present with symptoms of bony pain, fractures, and nephrolithiasis. Cardiovascular and neuropsychiatric abnormalities have been described, mortality is increased, and quality of life may be decreased. Parathyroidectomy is the treatment of choice in symptomatic patients, with improvement in bone density, and a decrease in stone risk. Reversibility of other above-mentioned associated conditions is less clear. PHPT may occur in the setting of heritable disorders in 10% of all cases, some syndromic (MENs) and other non-syndromic such as familial hypocalciuric hypercalcemia(FHH), presentations. The pathophysiology of non-hereditary PHPT is not totally clear. *The calcium-sensing receptor (CaSR)* is the major regulator of PTH release and plays a central role in keeping serum ionized calcium (Ca_i) within a very narrow physiologic range. Clonal somatic mutations and allelilc loss of the CaSR do not play a role in most cases of sporadic PHPT. Recent data suggest that certain SNPs of *CASR* gene may increase the risk of PHPT. Alterations in CaSR expression due to hypermethylation of the *CaSR* promoter or increased formation of heteromeric receptor complexes of the CaSR and $GABA_{B1}R$ may contribute to pathophysiology of PHPT. *FHH:* is an autosomal dominant benign condition characterized by loss of function mutations of CaSR, or distal to it. FHH is characterized by mild hypercalcemia, with inappropriately normal or slightly elevated serum PTH levels, and low urinary calcium excretion. A heterozygous germline inactivating mutation of the CASR on 3q21.1 accounts for 2/3 of cases (FHH1), while the remaining result from mutations downstream of the CaSR; in GNA11 located on 19p13.3 (FHH2), in AP2S1 on 19q13.2-q13.3 (FHH3), or from other unknown mutations. Presentation at a young age, before age 30 years, a family history of failed PTX, and the absence of end organ damage (low BMD, stones nephrolithiasis), are strong indicators of FHH. However, it has become increasingly clear that there may be overlap in the clinical presentation and biochemical phenotype of PHPT and FHH. DNA testing may be instrumental in differentiating the two entities.

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S25.3

Abstract unavailable

Joint Sessions

ESE/EASD Joint Session: Diabetes and growth hormone

JS1.1

Abstract unavailable

JS1.2

Abstract unavailable

JS1.3

Abstract unavailable

ESE/ESPE Joint Session: Transition – A step into the unknown

JS2.1

Transition of the patient with GHD

Mohamad Maghnie
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GH plays a crucial role not only for growth, but also for the acquisition of bone mass and muscle strength. This process is completed after the achievement of adult height in the phase of transition from adolescence to adulthood. Therefore, continuation of GH replacement therapy in the transition age is essential in patients with a childhood-onset diagnosis of GHD. Higher likelihood of persistence is ovserved in patients with an early age at diagnosis, anatomical, organic, or genetic causes, and MPHD. Repeating a GH stimulation test is not necessary for patients with MPHD (≥ 3 PHD) and low-serum IGF-1 concentrations (<–2.0 SDS), in patients with documented genetic defects affecting pituitary function, and in patients with hypothalamic-pituitary structural brain defects. In these cases, rhGH therapy can be continued without interruption, although the dose should be reduced to the adult age dose. Indeed, patients with idiopathic IGHD and an IGF-1 ≥ 0 SDS are not likely to have persistent GHD, and hence transition therapy may not be necessary. There is still controversy about which limit for a normal GH response should be considered for the transition age group, and the lack of strong evidence leads to variable clinical practice. According to the last Consensus of 2019, the ITT remains the gold-standard test for establishing the diagnosis of young adult GHD using a peak GH cut-point of ≤ 5.0 µg/l, while according to others the optimal GH cut-off value after adult height achievement is 6 µg/l. While recent data have suggested that combined GHRH and arginine is unreliable and may fail to recognize patients with permanent GHD of different etiologies, it should be emphasized that the validated normative data of glucagon-stimulation test and macimorelin in transition age are still lacking.

DOI: 10.1530/endoabs.73.JS2.1

JS2.2

Abstract unavailable

JS2.3

Abstract unavailable

ESE/Endocrine Society Joint Session: Emerging endocrine abnormalities and COVID-19 outcomes

JS3.1

Abstract unavailable

JS3.2

Fractures

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Osteoporotic fractures are the main clinical manifestations of skeletal fragility and are associated with decreased survival and impaired quality of life in the general population. At the beginning of COVID-19 spread in Europe, despite several studies investigated COVID-19 clinical characteristics, no data were reported on the prevalence of vertebral fractures (VFs) in patients affected and disease impact on osteoporotic patients. We performed a retrospective study at San Raffaele Hospital, a tertiary health care hospital in Italy, to assess VFs prevalence including COVID-19 patients for whom lateral chest x-rays at emergency department were available. VFs were detected using a semi-quantitative evaluation of vertebral shape. A total of 114 patients were included and thoracic VFs were detected in 41 patients (36%). Patients with VFs were older and more frequently affected by hypertension and cardiovascular disease ($P < 0.001$, $P = 0.007$, $P = 0.034$). Thirty-six (88%) patients in VFs+ group and 54 (74%) in VFs- group were hospitalized ($P = 0.08$). Patients with VFs more frequently required noninvasive mechanical ventilation compared with those without VFs ($P = 0.02$). Mortality was 22% in VFs+ group and 10% in VFs- group ($P = 0.07$). In particular, mortality was higher in patients with severe VFs compared with those with moderate and mild VFs ($P = 0.04$). Furthermore, a recent review reported COVID-19 likely an additional mortality risk factor in patients with hip fractures exceeding the previously reported mortality rate in fractured patients or COVID-19 alone. The COVID-19 hyperinflammatory response may amplify the "first-hit" inflammatory state of fracture trauma and thereby predispose to a severe thromboembolic "second-hit", whether the patient is symptomatic or not. VFs may integrate the cardiorespiratory risk of COVID-19 patients, being a useful clinical marker of fragility particularly in osteoporotic patients that are themselves at high risk of COVID-19 poor prognosis.

DOI: 10.1530/endoabs.73.JS3.2

JS3.3

Abstract unavailable

JS3.4

Abstract unavailable

JS3.5

Abstract unavailable

ESE/SBEM, FASEN and SMNE Joint Session: Pituitary conditions and COVID-19

JS4.1

Acromegaly and Covid-19

Marcello D. Bronstein
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Acromegaly is a chronic disease caused almost invariably by a pituitary GH-secreting adenoma leading to overproduction of insulin-like growth factor I (IGF-I). The long-term hypersecretion leads to many comorbidities, as diabetes mellitus, arterial hypertension, and cardiovascular and/or pulmonary disease (including sleep apnea), which are related to an increased mortality rate. In fact, uncontrolled acromegaly is associated with a three times mortality rate as compared with normal population. Treatment of acromegaly can restore mortality rate to that of normal population. Transsphenoidal pituitary surgery is considered the first treatment option for most cases, being first generation somatostatin receptor ligands (SRL-octreotide LAR or lanreotide Autogel) and second generation SRL (pasireotide LAR), among other drugs, reserved for uncontrolled patients after surgery and for those to whom surgical procedure is not indicated. Therefore, it is of note that patients with uncontrolled acromegaly harbor the same comorbitities associated with poor prognosis for COVID-19 pandemics caused by SAR-COV-2 virus. Therefore, is crucial that acromegaly should be controlled, especially regarding the COVID-19 pandemics. Concerning medical treatment, an increase of QTc interval is a possible side effect of SRL´s, the main class of drugs used to treat acromegaly. Also drugs that have been proven to be inefficacious for COVID-19 prevention/treatment but still used as chloroquine and azithromycin and its association may prolong QTc intervals. Considering that acromegaly itself can increase QTc interval and risk of arrhythmias, the use of the above mentioned drugs should be avoided or strictly monitored. Also the hyperglycemic effect of SRL´s, especially pasireotide, should be considered. The impact of COVID-19 pandemics in acromegaly care is of relevance. Pituitary surgery has been frequently postponed, either due to risk of virus transmission or to lack of hospital availability. Also the monthly visit to medical facilities to get SRL´s injections shot has been severely compromised. Therefore, patients and health care staff need to be adapted to these changes in order to keep the disease and comorbidities controlled and to prevent acute illnesses such COVID-19 by vaccination and safety measures as masks and social isolation.

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JS4.2

Hypopituitarism & Covid-19

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In December 2019, the outbreak of coronavirus disease (COVID-19) started in Wuhan, China[1], resulting in a global pandemic. A novel coronavirus (SARS-CoV-2) was identified. The virus enters the pneumocyte through the angiotensin-converting enzyme 2 (ACE2) as a receptor[2]. The enzyme is widely expressed. A relationship between COVID-19 and the endocrine system occurs at multiple levels. On autopsies, infarct, edema, and neuronal degeneration with SARS-CoV genoma have been identified in the hypothalamus. Low normal TSH and thyroid hormone levels have been described suggesting a central mechanism related to cytokines. Mortality rate is increased in hipopituitarism mainly due to cardiovascular and cerebrovascular disease, and these are risk factors for COVID-19 disease severity. Hypopituitarism impacts the course and management of COVID-19, specially in the context of adrenal insufficiency. Among the causes of hypopituitarism, pituitary apoplexy should be particularly considered. Adrenal insufficient patients seem not to be at paticular risk of COVID-19; however, they are susceptible to infections, and worse outcomes may be expected. The diagnostic approach does not differ from usual clinical practices. However, face-to-face contact with medical staff and other healthcare professionals should be limited to extremely necessary situations. Central diabetes insipidus may be at risk of more severe dysnatraemia when developing respiratory complications of COVID-19. Dose adjustment of pituitary hormone replacement can be performed by clinical assessment. And if supplies are not available, GH and gonadal replacement can be discontinued for a short time[3]. In the context of severe COVID illness, hydrocortisone should be adjusted to stress doses and desmopressin should be given parenterally. Education for AI patients is the basis for a better evolution, reminding about sick day management, and adequate supply.

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JS4.3

Abstract unavailable

ESE/KES Joint Session: COVID-19 and endocrine disorders

JS5.1

Abstract unavailable

JS5.2

Abstract unavailable

JS5.3

Abstract unavailable

ESE/EndoERN Joint Session: Rare endocrine disorders. Improving diagnosis, management and awareness by strengthening patients and physician collaboration

JS6.1

Abstract unavailable

JS6.2

Abstract unavailable

JS6.3

Living with androgen insensitivity syndrome - Multidisciplinary care team and research

Martine Cools
Ghent University Hospital and Ghent University

Men and women who have AIS face a number of challenges. Based on research insights from the past two decades, management of this pleiotropic condition during childhood has totally changed. In this presentation, we will update endocrinologists who provide care for adults living with AIS about these changes, as they will, after transition, need to further counsel their patients and coordinate multidisciplinary care and surveillance of retained gonads in adulthood. Girls with complete AIS are fully informed about the condition in all its aspects already in early childhood. Research has demonstrated that their testes can be safely retained at least until the end of puberty, and possibly beyond, provided that optimal surveillance of tumour risk can be offered. Vaginal self-dilation has become a first choice therapy for vaginal hypoplasia but requires a supporting and experienced team. Remaining uncertainties with regard to long-term outcomes of these new approaches will need to be addressed in future research. Partial AIS in many cases remains a diagnostic odyssey. Non-coding and even epigenetic changes may underlie the condition, and with the advent of cutting-edge genomic strategies and innovative functional studies, re-testing can be considered in individuals who have remained for years without a molecular genetic diagnosis. As genital surgery in childhood becomes increasingly controversial, a new generation of children with partial AIS grows up with atypical genitalia. There is an urgent need to understand how this influences psychosocial and psychosexual development and gender well-being throughout life. In addition, individuals who have partial AIS more often grow up as boys nowadays, requiring novel strategies to address short penile length and breast development, as well as surveillance of retained gonads, and sometimes fertility. As for other DSD conditions, full transparency, adequate psychosocial support and peer contacts have been associated with positive outcomes and will in this presentation be placed ad the heart of multidisciplinary care.

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JS6.4

Abstract unavailable

ESE/EASO Joint Session: Endocrine lab findings in people with obesity and their therapeutic consequences

JS7.1

Abstract unavailable

JS7.2

Abstract unavailable

JS7.3

Abstract unavailable

JS7.4

Diagnostics and treatment of post - bariatric surgery hypoglycaemia

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Department of Bariatric and Metabolic surgery, CON, Medical Center Leeuwarden, The Netherlands

Stimulation of insulin release by increased gut hormone levels after gastric bypass surgery, especially glucagonlike polypeptide-1(GLP-1), is considered to be the most important mechanism of action in diabetes remission. However, these beneficial effects can come at a price, namely the development of postprandial hyperinsulinaemic hypoglycaemia, more often called post bariatric hypoglycaemie (PBH). The exact pathophysiology of PBH is not known but GLP-1 plays an important role as blocking the receptor with exendin 9-39 can abolish the occurrence of hypoglycaemia. Altered betacel response, insulin sensitivity, FGF-19, bile acids and the gut microbioma probably also play a role. There is no established definition of PBH as it is probably part of a sliding scale of postprandial glucose values. Consequently, none of the diagnostic tools, self-measured blood glucose, provoking tests like OGTT and MMT, or CGM have established cut-off values. Most authors agree with the diagnosis of PBH in the combination of neuroglycopenic symptoms, a blood glucose level < 2.8 mmol/l with resolution of symptoms with correction of the hypoglycaemia (Whipple's triad). Treatment of PBH is not supported by well designed studies but relies mainly on clinical experience and case reports. A diet low in carbohydrates is the first step, lowering glucose excursions and thereby diminishing insulin release. Off-label medical treatment is a matter of trial and error and consists of acarbose, reducing postprandial glucose rise, somatostatin analogues, reducing GLP-1 and insulin release, diazoxide, inhibiting insulin secretion or liraglutide, a GLP-1 agonist, the mechanism of action is currently not known. Avexitide, exendin 9-39, a GLP-1r antagonist and colesevelam are promising new medications. Surgical options for PBH, resistant to medication are banding the pouch, placing a feeding tube in the native stomache, an undo operation or even pancreatectomy, all with limited success.

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ESE/Joint session: Clinical Guidelines of the European Academy of Andrology: Male specific endocrine conditions

JS8.1

Abstract unavailable

JS8.2

Investigation, treatment and monitoring of functional hypogonadism in males

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The focus of the new guidelines of the European academy of andrology is on functional hypogonadism since the diagnosis and treatment is more controversial than for organic hypogonadism. It is important to consider functional hypogonadism, only following formal exclusion of organic hypogonadism. Diagnosis should be made on basis of both clinical symptoms as well as the biochemical confirmation of serum repeatedly low morning fasting testosterone. Most specific symptoms are sexual complaints such as low libido and erectile dysfunction. Functional hypogonadism is commonly associated with overweight, metabolic syndrome and /or type 2 diabetes.

Lifestyle changes as well as weight reduction should be the first approach in obese men since functional hypogonadism may be reversible. Several drugs may also induce functional hypogonadism and withdrawal should be considered if possible in first instance. Testosterone replacement therapy (TRT) (preferably in first line via transdermal route) can be considered in order to improve sexual symptoms after exclusion of a number of absolute and relative exclusions of contraindications in shared decision with the patient. Positive effects of TRT on endpoints other than sexual symptoms are less well established. Not only improvement of sexual symptoms but also monitoring of serum hematocrit, testosterone and PSA is needed. More data, especially with respect to cardiovascular safety for long term TRT, are needed but may become available in the near future.

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JS8.3

Abstract unavailable

New Scientific Approaches

New Scientific Approaches 1: 3D adrenal models for the study of adrenal tumors
NSA1

Abstract unavailable

New Scientific Approaches 2: Regeneration or replacement of beta cells
NSA2

Regeneration or replacement of beta cells

Lorenzo Piemonti
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In patients with type 1 diabetes (T1D), pancreatic β cells are destroyed by a selective autoimmune attack and their replacement with functional insulin-producing cells is the only possible cure for this disease. The field of islet transplantation has evolved significantly from the breakthrough of the Edmonton Protocol in 2000, since significant advances in islet isolation and engraftment, together with improved immunosuppressive strategies, have been reported. The main limitations, however, remain the insufficient supply of human tissue and the need for lifelong immunosuppression therapy. Great effort is then invested in finding innovative sources of insulin-producing β cells. One old alternative with new recent perspectives is the use of non-human donor cells, in particular porcine β cells. Also the field of preexisting β cell expansion has advanced, with the development of new human β cell lines. Yet, large-scale production of human insulin-producing cells from stem cells is the most recent and promising alternative. In particular, the optimization of in vitro strategies to differentiate human embryonic stem cells into mature insulin-secreting β cells has made considerable progress and recently led to the first clinical trial of stem cell treatment for T1D. Finally, the discovery that it is possible to derive human induced pluripotent stem cells from somatic cells has raised the possibility that a sufficient amount of patient-specific β cells can be derived from patients through cell reprogramming and differentiation, suggesting that in the future there might be a cell therapy without immunosuppression.

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New Scientific Approaches 3: Cutting-edge scientific advances
NSA3

Abstract unavailable

New Scientific Approaches 4: Multiplex analysis platform for endocrine disruption prediction using zebrafish
NSA4

Multiplex analysis platform for endocrine disruption prediction using zebrafish

Sergio Jarque, Jone Ibarra, Maria Rubio-Brotons, Jessica García-Fernández, Javier Terriente
Zeclinics SL, Badalona, Spain

Small fish are excellent experimental models to screen endocrine-disrupting compounds, but current fish-based assays to detect endocrine disruption have not been standardized yet, meaning that there is not consensus on endpoints and biomarkers to be measured. Moreover, exposure conditions may vary depending on the species used as the experimental model or the endocrine pathway evaluated. Another drawback is the fact that most methods to detect endocrine disruption rely on the use of adults, falling therefore in the category of animal experimentation. If not, a battery of a wide range of assays is needed for the complete assessment of endocrine activities. With the aim of providing a simple, robust, and fast assay to assess endocrine-disrupting potencies for the three major endocrine axes, i.e., estrogens, androgens, and thyroid, we propose the use of a panel of eight gene expression biomarkers in zebrafish embryos. This includes brain aromatase (cyp19a1b) and vitellogenin 1 (vtg1) for estrogens, cytosolic sulfotransferase 2 family 2 (sult2st3) and cytochrome P450 2k22 (cyp2k22) for androgens, and thyroid peroxidase (tpo), transthyretin (ttr), thyroid receptor α (trα), and iodothyronine deiodinase 2 (dio2) for thyroid metabolism. All of them were selected according to their responses after exposure to the natural ligands 17β-estradiol, testosterone, and 3,3′,5-triiodo-L-thyronine (T3), respectively, and subsequently validated using compounds reported as endocrine disruptors in previous studies. Cross-talk effects were also evaluated. Importantly, EC50s observed in zebrafish larvae, although higher in terms of efficiency, showed strong correlation with those obtained in adults, pointing out the model as suitable alternative for animal testing.

DOI: 10.1530/endoabs.73.NSA4

New Scientific Approaches 5: Whole genome sequencing in cancer care, lessons from the 100,000 Genomes Project and opportunities for NEN
NSA5

Abstract unavailable

Debate Sessions

Debate 1: Should the biochemical spectrum primary aldosteronism be expanded?

D1.1

Abstract unavailable

D1.2

Abstract unavailable

Debate 2: CGM for all people with diabetes?

D2.1

Abstract unavailable

D2.2

AGAINST: CGM for all people with diabetes?

Luigi Laviola
Department of Emergency and Organ Transplantation, Section on Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, University of Bari Aldo Moro, Bari, Italy

In people with diabetes, optimizing glucose control is critical to reduce the risk of both acute and chronic complications. Technologies measuring interstitial glucose concentrations provide professional teams and patients with glucose data and interpretation tools which can improve metabolic control and optimize therapy management. There is strong evidence supporting both rtCGM and FGM use in people with type 1 diabetes (T1DM), with benefits of reduced HbA1c and hypoglycaemia, and increased time in range. Similar benefits have been demonstrated in insulin-treated type 2 diabetic patients (T2DM). By contrast, evidence in non-insulin treated T2DM is less robust, with scarce RCTs and some observational studies showing limited or no impact on HbA1c and hypoglycemia. Notably, in most trials comparing CGM with SMBG in T2DM, the control arm was not on structured SMBG, which has been shown *per se* to significantly reduce HbA1c. Thus, the overall cost-benefit evaluation does not support continuous glucose monitoring in most T2DM. Thus, it seems reasonable to follow a personalized, patient-centered approach in taking advantage of the available CGM devices: T1DM and T2DM on MDI should be offered the opportunity to wear glucose sensors to improve metabolic control and glucose metrics. On the other hand, most DMT2 should be encouraged to exploit the benefits of adequately structured SMBG. Retrospective or intermittent CGM may be proposed in these patients, aiming at optimizing therapy and lifestyle management and increasing awareness of glucose patterns. As technology provides more and more accurate and reliable tools, more clinical research projects and a wider use of these devices will increase the expertise of diabetes teams and ultimately improve everyday life in people with diabetes.

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Debate 3: Selenium for autoimmune thyroid disorders: necessary or unnecessary?

D3.1

AGAINST: Selenium for autoimmune thyroid disorders: necessary or unnecessary?

Steen J. Bonnema
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Selenium is an essential element for humans. Important dietary sources of selenium include meat, seafood, and grains. Selenium is incorporated into a range of selenoenzymes with antioxidant properties. Being crucial for the activity of the deiodinase enzymes, selenium is especially important for the synthesis and metabolism of thyroid hormones. Selenium in relation to thyroid diseases has been widely explored. Epidemiological studies have shown that a low selenium status is associated with an increased risk of autoimmune thyroid diseases. This linkage may be causal as selenium supplementation seems to reduce the titer of thyroid autoantibodies in patients with autoimmune thyroiditis, probably by reducing proinflammatory cytokines. However, it is unsettled whether selenium supplementation affects the clinical course of autoimmune thyroiditis or improves quality of life in patients with this disease. In patients with mild Graves' orbitopathy, selenium supplementation reduces the orbital inflammation, while it remains to be shown that it also leads to faster remission of the hyperthyroidism. Two ongoing randomized clinical trials, one in Graves' disease and one in autoimmune thyroiditis, will help clarify the role of selenium supplementation in these disorders. Although current evidence does not support routine selenium supplementation as adjuvant treatment in patients with autoimmune thyroiditis or Graves' disease, such an approach is widely used by clinicians. While selenium deficiency should be corrected, a too high intake of selenium may result in adverse health effects. Therefore, the inclusion of selenium in the therapeutic armamentarium should be based on data from large and well-designed clinical trials.

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D3.2

Abstract unavailable

Debate 4: Endocrine disruptors harmonisation in EU: The new EU Chemicals Strategy will speed up efficient reduction of EDC exposure for EU citizens!

D4.1

Abstract unavailable

D4.2

Abstract unavailable

Debate 5: Treatment breaks should be mandatory in the majority of people taking oral bisphosphonates

D5.1

Abstract unavailable

D5.2

Abstract unavailable

Debate 6: What levels of prolactin to aim for... The lower the better?

D6.1

Abstract unavailable

D6.2

Abstract unavailable

Meet the Expert Basic Scientist Sessions

Meet The Expert Basic Scientist 1: Histopathology of human obese adipose organ: New insights
MTEBS1

Histopathology of human obese adipose organ: New insights
Saverio Cinti
Marche Polytechnic University, Piazza Roma, Italy

Since 2003 there is a large consensus on the fact that obese adipose tissues of mice and humans are inflammed. This low-grade chronic inflammation is linked to insulin resistance inducing to type2 diabetes (T2D). In 2005 we showed that inflammation is due to death of obese adipocytes whose debris require macrophages infiltration of the tissue and consequent formation of crown like structures (CLS) as the basic histopathology aspect of inflammation. In 2008 we showed that visceral adipocytes have a critical death size smaller that that of subcutaneous adipocytes and, accordingly, inflammation of visceral fat is more severe. This offer an explanation to the well known clinical data claiming visceral obesity as the condition more frequently linked to the usual obesity related disorders and mainly to the T2D. In 2013 we showed that obese adipocytes die for pyroptosis. Here we show data suggesting that in adipose tissues of obese humans (66 fat biopsies from 33 bariatric patients) a large proportion (about 13%) of hypertrophic adipocytes die for self-choking due to fibrosis. Histochemistry, immunohistochemistry, electron microscopy and gene expression data showed that single or groups of obese adipocytes are surrounded by thick bands of fibrous collagen with evidence of hypoxia and correlation with signs of death (loss of perilipin1 immunoreactivity). Inflammation was mainly sustained by macrophages, but only a minority of them formed CLS. While the increased fibrous collagen is widely accepted the amount of collagen VI in obese fat is debated. Our data showed a reduction in gene expression and the analysis of tissue from a patient with the rare mutation inducing a reduction of active collagen VI production showed fibrosis comparable with that in obese fat suggesting a causative role for this gene.

DOI: 10.1530/endoabs.73.MTEBS1

Meet The Expert Basic Scientist 2: When and how to employ molecular genetic testing in thyroid pathology?
MTEBS2

Meet The Expert Basic Scientist 2: When and how to employ molecular genetic testing in thyroid pathology?
Ralf Paschke
University of Calgary, Calgary, Canada

There are three main applications for molecular genetic testing in thyroid pathology:
1. As part of an integrated approach of careful clinical, ultrasound and FNBC assessment with local outcome data molecular analysis of fine needle biopsy cytology is able able to improve diagnostic outcomes for thyroid nodules by identifying patients with an indeterminate FNBC as most likely benign with < 5% false negatives and thus obviating diagnostic lobectomy or by identifying patients for upfront total thyroidectomy as definitive surgical treatment
2. 70% of high risk thyroid cancer patients develop a structural recurrence after total thyroidectomy and radioiodine treatment. Revision surgery and/or a second RAI treatment lead to remission in only 42 – 51% of these patients. Therefore, early prospective systematic detection of actionable driver mutations for thyroid cancer patients with local relapse or distant metastasis is needed to guide new targeted treatments such as NIS re-expression to re-enable RAI treatment or treatment with RET or NTRK inhibitors, ALK inhibitors, PAX8/PPARG agonists or emerging off label drugs. However, lack of systematic molecular analysis is the missing piece limiting access to emerging targeted and translational therapies for advanced thyroid cancer. All *BRAF* mutation-negative patients with progressive structural incomplete response to total thyroidectomy and RAI treatment, and ATA high/intermediate recurrence risk patients with progressive structural incomplete response, should be screened for *NTRK* and *RET* gene fusions to enable early intervention.
3. Several studies have reported large interobserver variability for the differential diagnosis between thyroid adenomas/adenomatous nodules and FTCs and other thyroid cancer histologies. Therefore, the current histology-based classification of thyroid tumors will ultimately most likely evolve into a blended histologic and molecular classification of thyroid tumours like for other endocrine tumors or other cancers.

DOI: 10.1530/endoabs.73.MTEBS2

Meet The Expert Basic Scientist 3: Interference of EDC with thyroid hormone binding and transport impacts on neural stem cell fate: from development to ageing
MTEBS3

Abstract unavailable

Meet The Expert Basic Scientist 4: GWAS and mendelian randomisation studies in osteoporosis diagnosis
MTEBS4

Abstract unavailable

Meet The Expert Sessions

Meet The Expert 1: New therapies in the treatment of thyroid ophthalmopathy
MTE1

New therapies in the treatment of thyroid ophthalmopathy
Mario Salvi
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Introduction
Medical immunosuppressive treatment of Graves' orbitopathy (GO) is advised for patents with moderate-severe disease. Steroids represent the mainstay of therapy, as they possess anti-inflammatory activity, but about 20 – 30% of patients are unresponsive and up to 20% of patients may relapse. Immunosuppressive therapeutics alternative to corticosteroids are those targeting the different antigens involved in the pathogenic reactions of GO. Some of these have already been challenged in clinical studies for potential use, although the lack of randomized and controlled trials may at the moment limit their use in clinical practice.
Evidence from studies
Potential targets for therapy in GO are B and T cells, the TSH receptor and the IGF-1 receptor on the fibroblasts, inflammatory cytokines involved in the cascade of immune reactions in the early phase of disease. Consistent open study reports on the efficacy of rituximab have been confirmed by randomized controlled trials. A recent study has shown non inferiority of belimumab, an anti-BAFF monoclonal antibody, with methylprednisolone. Significant improvement of proptosis has been shown with the anti-IGF-1R monoclonal antibody teprotumumab. A recent controlled study has also shown that tocilizumab, an anti-sIL-6R antibody, inactivates GO, and another is underway.
Conclusions
Clinical practice is seeking disease modifying agents in GO as an alternative to steroids, currently standard treatment for GO. Novel therapeutics are currently indicated, especially in patients resistant to steroid or with contraindications to steroids. However, larger randomized controlled trials are needed before these drugs are shown to be more effective and can be approved for routine clinical use in GO.

DOI: 10.1530/endoabs.73.MTE1

Meet The Expert 2: Non-contraceptive therapeutic use of combined oral contraceptives in PCOS
MTE2

Abstract unavailable

Meet The Expert 3: Long-term effects of testosterone replacement therapy
MTE3

Abstract unavailable

Meet The Expert 4: What one should know on PRRT-lessons from clinical practice
MTE4

What one should know on PRRT-lessons from clinical practice
David Taïeb
Aix-Marseille University

Personalized (precision) medicine has already made its mark and has the potential to enhance patient management. It consists in adapting healthcare strategies tailored to individual and disease characteristics. Nuclear medicine has a central role in personalized medicine via theranostics approaches. PRRT is now a well established treatment option for well-differentiated advanced neuroendocrine tumors (NETs). PRRT is based on the administration of somatostatin analogs (SSA) labeled with a therapeutic isotope (e.g. ^{177}Lu, ^{90}Yttrium (^{90}Y)). Before PRRT, assessment of *in vivo* SSTR expression is mandatory and is based on the use of a companion diagnostic agent corresponding to a SSA labeled with ^{68}Ga, which is now preferred for molecular imaging of NET. Beyond SSTR expression, several important factors need to be considered for determining whether an individual patient is likely to benefit from PRRT (e.g., age, general condition, tumor grade, SSTR expression profile...). In metastatic insulinomas, PRRT may be recommended as a second-line therapy after failure of diazoxide to control hypoglycemia. PRRT can also be considered in some grade 3 NETs. Overall, toxicity is limited, especially when using ^{177}Lu due to its lower tissue penetration range compared with ^{90}Y but needs to be monitor especially for hematological (bone marrow) toxicities.

DOI: 10.1530/endoabs.73.MTE4

Meet The Expert 5: Craniopharyngeoma management
MTE5

Abstract unavailable

Meet The Expert 6: Difficult phaeochromocytoma cases
MTE6

Difficult Phaeochromocytoma cases
Tomáš Zelinka
Charles University, Prague, Czech Republic

Phaeochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumours arising from chromaffine cells either from adrenal medulla (phaeochromocytoma) or extra-adrenal paraganglia (paraganglioma). Phaeochromocytomas and sympathetic paragangliomas (arising from thoracic, abdominal, or pelvic sympathetic ganglia) may secrete catecholamines which are associated with the most clinical symptoms and signs whereas parasympathetic paragangliomas (arising from parasympathetic ganglia of the head and neck region) are secretory inactive. PPGL may develop metastases, in particular in those patients harbouring mutation in the *SDHB* gene. Around two thirds of phaeochromocytomas are diagnosed incidentally during morphological examinations from other reasons and only one third after targeted biochemical screening in symptomatic subjects. Symptomatology of PPGL varies from mild symptoms on one side such as headache, palpitations, and sweating (reported in around 50 – 60% of patients) to life-threatening complications such as circulatory shock, takotsubo cardiomyopathy, arrhythmias on the other side. Unique combination of signs in PPGL is the association of hypertension with orthostatic hypotension, in some cases seriously limiting quality of life. Once is PPGL diagnosed (nowadays using metanephrines either in plasma or in urine), patients are scheduled for tumour removal and prepared with ńadrenergic receptor blockers. Experienced surgeons and anaesthesiologist are required for successful tumour removal due to hemodynamic instability during and after operation. Due to the risk of recurrence or metastases (may be present also at initial presentation), patients with PPGL should be followed-up for at least 10 after the surgery.
Conclusion
Awareness of PPGL among different medical specialties such as anaesthesiology, cardiology or internal medicine may contribute to early diagnosis of PPGL which is the best prevention of potentially lethal cardiovascular complications or development of metastases.

DOI: 10.1530/endoabs.73.MTE6

Do you know how to define sarcopenic obesity?
MTE7

Do you know how to define sarcopenic obesity?
Irene Bretón
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Sarcopenic obesity is a clinical condition characterized by the coexistence of excess fat mass and sarcopenia, i.e. a decrease in muscle mass or function. This coincidence leads to an increased risk of complications. Sarcopenia induces increased insulin resistance and worsens the metabolic status of obesity, while impairing functional capacity. Obesity itself can induce changes in muscle mass and function, as a consequence of changes in diet and physical activity and alterations in different hormonal axes (GH/IGF-1, hypogonadism, decreased adrenal androgens, etc.). Insulin resistance itself as well as the secretion of hormones and inflammatory mediators by adipose tissue may promote protein catabolism. There is no unanimous agreement on the diagnostic criteria for sarcopenic obesity or the most appropriate method of assessing body composition or muscle function. For this reason, the prevalence of this clinical condition is not well known, although it is more frequent in the elderly or in patients with a chronic disease that induce inflammation or increased catabolism (heart failure, pulmonary, renal or chronic liver disease). The clinical approach to the sarcopenic obese patient should be multifactorial, and treatment includes correction of predisposing factors, increased physical activity and adjustment of the dietary pattern. There is an urgent need to increase our knowledge of the factors influencing the genesis and progression of sarcopenic obesity and to define uniform diagnostic criteria accepted in the scientific community.

DOI: 10.1530/endoabs.73.MTE7

Meet The Expert 8: GH replacement in adults
MTE8

Growth hormone replacement therapy in adults

Maria Vorontsova
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Background
Growth hormone replacement therapy in adults is mostly used in case of adult growth hormone deficiency (AGHD). The condition is characterized by altered body composition, lower than average bone mineral density (BMD), elevated cardiovascular risks and, among other remaining factors, lower quality of life.
Main discussion topics
After over 30 years of recombinant growth hormone (rGH) usage substantial data has been accumulated to assess treatment efficacy and safety. Careful consideration should be given to the question who is eligible for rGH treatment. Transition patients warrant extra attention to determine the correct dose at a given period of time and to avoid losing the patient out of site. Body composition and increase of BMD seem to be the most prominent benefits with an increase in exercise capacity and quality of life following suit. The effects on cardiovascular risks are less certain. The ultimate end-point criteria – weather rGH therapy in adults decreases mortality – also remains unclear. With a growing interest toward endocrinology for anti-aging therapy and biohacking, physicians need to continue discussion as to what is safe and what is off-limits in situations outside of pathology. Therapy monitoring is very important during treatment to detect possible side effects and to make sure that treatment yields the expected benefits. These aspects find new importance with the development of long-lasting GH forms. Despite available data, optimal safety and efficacy biomarkers still pose a challenge. Combining rGH with other hormones warrants extra attention.
Conclusion
rGH therapy has proven positive effects on patients with GH deficiency. Some benefits, as in reduction of cardiovascular risks, remain to be determined. Finding optimal biomarkers to monitor treatment safety and efficacy remain somewhat elusive. Ever-growing interest of healthy individuals for GH treatment warrants and endocrinologist's attention.

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Meet The Expert 9: Sequential osteoporosis treatments
MTE9

Sequential osteoporosis treatments

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Postmenopausal osteoporosis is a chronic condition requiring long-term treatment. Based on personalized patient care the physician should decide the optimal treatment strategy, namely the use of the available osteoanabolic and antiresorptive agents, sequentially or even in combination, in the most effective and safe way. Transitioning from one antiresorptive to another is probably the most common treatment sequence in clinical practice. In this context transition to a potent oral or intravenous bisphosphonate is mandatory to maintain bone mineral density (BMD) gains and avoid the rebound phenomenon and the increase in fracture risk in patients discontinuing Denosumab. Initiation with an osteoanabolic agent followed by an antiresorptive seems to be the optimal treatment sequence, at least in patients with severe osteoporosis and prevalent fractures. Treatment with an osteoanabolic following an antiresorptive agent seems to lead in more modest responses in BMD and bone turnover markers. Although switching to teriparatide is a quite common strategy among patients that either did not adequately respond to antiresorptives or have completed the maximum duration of antiresorptive treatment, this could lead to a transient loss of hip BMD and probably strength, and therefore it should be carefully followed especially in high-risk patients. Combination of teriparatide with denosumab or zoledronate has achieved higher BMD gains compared to each agent alone. On the contrary, the combination of teriparatide with alendronate results in smaller BMD increases than teriparatide monotherapy. However, due to the high cost, combination therapy is rarely reimbursed. In conclusion, it is a real challenge for the physician to set the optimal long- term osteoporosis treatment plan for each individual patient based on different needs, preferences, and peculiarities.

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Meet The Expert 10: Outlook for male fertility preservation
MTE10

Outlook for male fertility preservation

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Cryopreservation of spermatozoa, has been utilized for decennia as an easily accessible tool in male fertility preservation, prior to treatment for cancer and autoimmune diseases. However, although this technique is well established, there is a number of questions regarding this procedure which still needs to be answered. Which patient groups should be offered semen cryopreservation? Are spermatozoa preserved prior to treatment safer to use for fertilization than fresh, ejaculated sperms produced after completion of cancer treatment including radiotherapy and/or medical treatment potentially hazardous to DNA? Should young cancer survivors with severe oligozoospermia be offered fertility preservation because they are at risk of azoospermia due to age related deterioration of spermatogenesis? Another emerging aspect is the question whether the indication for cryopreserving sperms should be widened: Increasing parental age is a global and well-known phenomenon. There is now an evidence showing that high paternal age is associated with increased risk of transmitting mutations and premature birth as well as higher infantile mortality. One could, therefore, consider offering freezing of spermatozoa to men wishing to postpone their fatherhood. Men with azoospermia as well as pre- and early pubertal boys represent a specific challenge due to lack of access to ejaculated sperms which can be used for cryobanking. Currently, several research groups are making attempts to develop techniques for *in vitro* and *in vivo* maturation and generation of germ cells suitable for assisted reproduction. Although we are still waiting for the final breakthrough in treatment of humans, the results of experimental studies give promises, that we in a near future will have access to one or more options for helping men for whom biological fatherhood, so far, is not possible. The development in the field of medical technology will provide new options for preserving male fertility. However, it will also lead to new ethical questions which need to be considered before the new methods become a clinical routine.

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Meet The Expert 11: Cardiovascular risk reduction in endocrine patients
MTE11

Abstract unavailable

Meet The Expert 12: Pituitary surgery bites
MTE12

Abstract unavailable

Meet The Expert 13: Marrow adiposity and bone
MTE13

Abstract unavailable

Meet The Expert 14: For the use of AMH as a diagnostic tool in female reproduction
MTE14

AMH as a diagnostic tool in female reproduction

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AMH is produced by the granulosa cells of growing follicles in the ovary, with peak expression at the small antral stage, followed by a sharp decline, and it is not produced by the corpus luteum. It therefore provides an indirect index of the ovarian reserve, and will also be affected by factors that influence folliculogenesis, such as hormonal contraception. This provides the basis for understanding and developing its potential use as a diagnostic tool in assessing the ovary. The most established role for AMH is prior to ovarian stimulation for assisted reproduction, where is has become very widely used in conjunction with ultrasound assessment of the antral follicle count. This allows identification of women who are likely to over-respond and are at high risk of ovarian hyperstimulation, and conversely those with an unexpectedly low AMH for their age, who will respond poorly: stimulation protocols can be tailored, and expectations managed. Allied to this is a potential diagnostic value in PCOS, and while it is clear that women with this condition often have markedly elevated AMH levels, it has not yet become part of diagnosis. The menopause results from exhaustion of the follicle pool, thus AMH may be of value in its diagnosis and indeed prediction. Initial ELISAs were inadequately sensitive, with AMH becoming undetectable some 5 years before the menopause, but more sensitive assays have been developed, and a role in menopause diagnosis is also now established. Prediction is more challenging, especially with a longer time to menopause and younger age. Thus its value in predicting premature ovarian insufficiency is unclear, although as a diagnostic it has value. Special circumstances include following chemotherapy, where diagnosis of permanent loss of ovarian function would be of value.

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Meet The Expert 15: Challenges in genetic counseling for hereditary endocrine neoplasia syndromes
MTE15

Challenges in genetic counseling for hereditary endocrine neoplasia syndromes

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Genetic counseling has long been an integral component of the care of individuals and families with hereditary endocrine neoplasia syndromes. Molecular biology has made a great progress during the past years, and genetic testing and genetic counseling have received more and more public attention. The recent progress, especially in the next-generation sequencing (NGS) technology allows multiple genes or even the whole-genome to be sequenced with high resolution and speed. Nowadays, the NGS has found a firm place in carrier identification and genetic counseling of individuals affected by endocrine neoplasia syndromes. However, generation of a large amount of genomic data in a short time has led to challenges in variant identification and interpretation of the test results. The NGS technology together with other high-throughput molecular methods have greatly increased the number of variants of uncertain significance (VUSs) in clinical practice and research. Also NGS-associated unintentional incidental findings as a by-product of genetic testing have become more frequent. Because the great deal of genetic variation is rare and even unique to individuals, the VUS "issue" is likely here to stay. However, the long-term solution to the VUS interpretation difficulties is to gain more data. Functional studies of genes and variants, and additional population-level data with accurate phenotyping will in the future improve variant classification. Reduced prices and even more sensitive screening methods coupled with advanced bioinformatics capabilities will increase the uptake of genetic testing and counseling in endocrine neoplasia. While there are many challenges in the area, there are even more significant opportunities to use genome-wide technologies in multiple medical situations, including the molecular characterization of rare endocrine neoplasia, the individualization of treatments, and population screening for disease risk.

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Oral Communications

Adrenal and Cardiovascular Endocrinology

OC1.1

Risk of developing autonomous cortisol secretion and/or significant tumor growth in non-functioning adrenal incidentalomas during follow-up

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Purpose
To assess the risk of developing hypercortisolism and/or tumor growth in non-functioning adrenal incidentalomas (NFAIs) during follow-up.
Methods
Seven Spanish institutions participated in this retrospective study for patients with AIs. 1097 patients with one or more AIs ≥ 1 cm evaluated by participating physicians between 2013 and 2020 were subject to inclusion. Patients with missing values in the overnight 1 mg-dexamethasone suppression test (DST) (n = 63); with pheochromocytoma (n = 7); primary aldosteronism (n = 26); autonomous cortisol secretion (ACS) (n = 337) overt Cushing syndrome (CS)(n = 10); or adrenal carcinoma (n = 3), were excluded. ACS was defined as a value >1.8 μg/dl after DST without specific data of CS. Tumor growth was defined as an increase in tumor maximum diameter >20% from baseline; and of at least 5 mm.
Results
654 patients with NFAIs were included. Mean age was 62.1 ± 10.8; and 56% (n = 368) were women. At presentation, median tumor size was 19.3 ± 9.8 mm; 130 patients (20.1%) had bilateral tumours and the median cortisol post-DST level was 1.1 μg/dl (0.4 – 1.8). Of the 654 subjects, tumor diameter and DST were re-evaluated during follow-up in 410 and 364 patients, respectively. After a median follow-up of 26.4 [IQR 10.6 – 50.6] months, 40 out of 364 patients with NFAIs (11%) developed ACS; and none developed overt CS. The risk for developing ACS during follow-up was higher for patients with higher cortisol post-DST values (HR 4.1 for each μg/dl, 95% CI 1.4 – 11.7), older age (HR 1.04 for each year, 95% CI 1.01 – 1.08); and smaller tumor size (HR 0.92 for each mm, 95% CI 0.86 – 0.99), at presentation. The best cortisol post-DST threshold to predict ACS development in NFAI patients was 1.4 μg/dl (AUC 0.67, 95% CI 0.62 – 0.72, sensitivity 58% and specificity 72%). Significant tumor growth was observed in 23 out of 401 patients (5.6%). Median tumor growth in these patients was 11.0 ± 4.9 mm. Unilateral laparoscopic adrenalectomy was performed in 2 patients, and histology was benign in both. Tumour growth was more common in women (HR 3.7, 95% CI 1.4 – 9.3), but other predictive variables were not identified. Final tumor size was linearly correlated with initial (r = 0.12, P = 0.012) and last-visit cortisol post-DST (r = 0.14, P = 0.018). ACS was developed during follow-up in 18.8% of tumours that demonstrated significant growth; and in 8.7% of tumors that remained stable in size (P = 0.181).
Conclusions
11% of patients with NFAIs developed ACS; and 5.6% of tumors grew during follow-up. Cortisol post-DST levels at presentation are associated with the risk of ACS development and are linearly associated with the follow-up adrenal tumor size.

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OC1.2

YAP/TAZ signaling is involved in the regulation of adrenocortical progenitors in stress

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A tightly regulated stress system is pivotal for health and the adrenal cortex is a master regulator of the endocrine stress response. The adrenal cortex is characterized by constant cell renewal in part mediated by differentiation and lineage conversion of undifferentiated cell types. To date, the contribution of stem cells to organ plasticity during stress has been implicated but is not fully understood. Recently, we were able to show that a prolonged stress exposure leads to differentiation of non-steroidogenic Nestin-GFP progenitors into specialized cell types in the adrenal cortex of mice. These cells reside in the stem cell niche during homeostasis. The niche in the outermost layer of the adrenal cortex, the capsule and zona glomerulosa, is tightly regulated by signaling pathways including SHH and WNT, which control maintenance and differentiation. However, recent research suggests that YAP/TAZ signaling may further regulate adrenocortical maintenance, since ablation of effector genes leads to degeneration of the organ. Our study explores a functional role for YAP/TAZ downstream signaling in the adrenal cortex during homeostasis and stress. We show that YAP/TAZ targets are normally expressed in different cell types throughout the adrenal cortex including in the stress-responsive Nestin-GFP(+) progenitor cells. We show that during stress, YAP/TAZ targets expressed in the stem cell niche are upregulated. This upregulation is accompanied by downregulation of WNT target genes in the zona Glomerulosa, suggesting differentiation of progenitor cells in this zone. In an in vitro cell differentiation model of adrenocortical progenitors, YAP/TAZ target upregulation accompanied by WNT target downregulation favors adrenocortical differentiation. We further show that YAP/TAZ signaling decreases in HPA-axis inhibiting conditions leading to quiescence of the cells. In summary, this study introduces the YAP/TAZ cascade as putative regulator of the adrenocortical stem cell niche which may be upregulated in stress conditions to mediate differentiation.

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OC1.3

PDE11A4 (Phosphodiesterase 11 A4) is a modulator of the primary bilateral macronodular adrenal hyperplasia (PBMAH) phenotype: genotype/phenotype analysis of a cohort of 354 patients analysed by next-generation sequencing (NGS)

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Introduction
Primary bilateral macronodular adrenal hyperplasia (PBMAH), the most common cause of adrenal Cushing's syndrome due to bilateral adrenal tumors, is an heterogenous disease with various clinical, hormonal and morphological characteristics. *ARMC5* inactivating mutations is the most frequent genetic cause of PBMAH and variants of *PDE11A4* have been associated with the disease. In order to better understand the heterogeneity of PBMAH, this study was undertaken to determine whether *PDE11A4* variants might be associated with a specific phenotype.
Methods
Leukocyte DNA of 354 index cases of PBMAH were sequenced for *ARMC5* and *PDE114A* by NGS (Ion Torrent). The frequency of variants was established in this cohort and the phenotypic characteristics were analysed in order to determine the genotype/phenotype correlations. Were considered pathogenic: *PDE11A4* variants with altered enzymatic function; *ARMC5* nonsense, frame shift and rare missense variants predicted deleterious *in silico*.
Results
ARMC5 mutations were present in 76 patients (21.5%) and pathogenic variants of *PDE11A4* in 65 patients (18.4%), with a similar frequency regardless of *ARMC5* status. Phenotype was more severe in *ARMC5* mutated patients compared to *ARMC5* wild type, with a higher 24-hour urinary

free cortisol, expressed as a multiple of the upper standard range (UFC) (2.04 vs 0.99, $P = 0.005$) and midnight plasma cortisol (MPC) (328.06 vs 187.24 nmol/l, $P = 0.003$), larger adrenals (122.7 vs 91.31 mm, $P = 4.87e – 05$) and higher number of nodules as determined on CT-scan (10.25 vs 3.44, $P = 8.62e – 07$). There were six *PDE11A4* pathogenic variants (p.R804H, p.R867G, p.M878V, p.D609N, p.Y727C, p.R307X). Patients with these variants had a less severe phenotype, with a lower MPC (162.17 vs 222.91 nmol/l, $P = 0.015$) and fewer adrenal nodules (3.45 vs 4.75, $P = 0.015$) in comparison with the *PDE11A4* wild type group. Regarding the initial management, 50% of patients with pathogenic variants of *PDE11A4* were abstaining from treatment, 37% were treated by adrenalectomy and 10.9% were treated medically. This phenotypic modulation of the *PDE11A4* was confirmed in *ARMC5* mutated patients: patients with pathogenic variants of *PDE11A4* ($n = 13$), had lower UFC (1.1 vs 2.25, $P = 0.014$), smaller adrenal glands (90 mm vs 127 mm, $P = 0.008$) and a lower number of nodules (6 vs 10.94, $P = 0.03$) compared to the *PDE11A4* wild type group.

Conclusion

This association of *PDE11A4* variants with a less severe PBMAH phenotype regardless of *ARMC5* status suggests that *PDE11A4* is a modulator of PBMAH development. The mechanisms of this modulation remain to be determined and will help to better describe the heterogeneity of PBMAH and to elucidate its pathophysiology.

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OC1.4

The impact of targeted treatment on echocardiographic indices in patients with overt and mild primary aldosteronism, compared to patients with essential hypertension.

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Introduction

Primary aldosteronism (PA) is associated with cardiovascular events and target organ damage, such as left ventricular (LV) hypertrophy and cardiac dysfunction. However the impact of subtle aldosterone secretion on cardiac function has not yet been evaluated.

Aim

To prospectively evaluate the cardiac function using echocardiographic indices in patients with biochemical overt, mild PA and essential hypertension (EH) and investigate the impact of targeted therapy.

Patients and methods

We included 72 (44 men) patients (mean age 55 ± 11 years) with hypertension. The diagnosis of PA was based on the combination of valsartan, captopril and dexamethasone suppression test (DCVT)[1]. The patients were divided in three groups: those with EH ($n = 30$) (negative DCVT), with biochemical overt ($n = 21$)(basal aldosterone/renin ratio (ARR) > 67 pmol/mU^2 and positive DCVT) and with mild PA ($n = 19$)(ARR < 67pmol/ mU and positive DCVT). Mean blood pressure, LV diastolic and systolic dimensions (LVEDD, LVEDDi, LVESD, LVESDi), left ventricular and atrial mass index (LVMI, LAVI), and total diastolic function were evaluated with cardiac ultrasound at presentation and after targeted treatment. The delta values of the abovementioned parameters were calculated to evaluate the magnitude of therapeutic impact among the three groups.

Results

At presentation, LVMI (88.19 17.44 vs 73.34 ± 11.85) ($P = 0.001$), LAVI (38.01 ± 14.5 vs 27.74 ± 5.12) ($P = 0.001$) and LVESDi (15.65 ± 2.36 vs 14.39 ± 2.01) ($P = 0.041$) were significant higher in overt PA vs EH patients. Mild PA have also higher LVMI(80.26 ± 19.99 vs 73.34 ± 11.85) ($P = 0.052$), LAVI(31.05 ± 5.6 vs 27.74 ± 5.12) ($P = 0.058$), and LVEDDi (22.82 ± 2.9 vs 22.41 ± 2.11) ($P = 0.015$) vs EH patients. When biochemical overt and mild PA patients were compared, ejection fraction (63.66 ± 6.25 vs 64.34 ± 11.83) was lower and LVMI (88.19 ± 17.44 vs 80.26 ± 19.99) was higher in biochemical overt PA patients, compared to mild PA.The mean follow up, during treatment (MRAs for PA and conventional therapy for EH) was 14 ± 2months. Delta values of LVEDD ($P < 0.001$) and LVEDDi ($P = 0.002$) were significant higher in overt and mild PA patients, showing a significant improvement of cardiac function from baseline in comparison with EH patients. Furthermore, biochemical overt PA patients exhibited a significant improvement of LVESD (-2.31 ± 3.5 vs -0.6 ± 2.32, $P = 0.015$), LVEDDi (-1.77 ± 1.8 vs -0.57 ± 1.15, $P = 0.013$) and LVESVi (-5.44 ± 3.93 vs 0.9 ± 7.76, $P = 0.002$) compared to mild PA patients.

Conclusion

The present study shows that milder forms of PA have a similar though more subtle effect on cardiac function, compared to biochemical overt forms. Furthermore, targeted treatment resulted in a significant greater improvement in patients with overt forms of PA.

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OC1.5

Primary results from MATCH: A randomised controlled trial in primary aldosteronism

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Primary aldosteronism (PA) is considered the sole, often curable, cause of hypertension in 5–10% of patients. Yet there has been only one RCT, and practice has changed little since the advent of CT scanning. Adrenal vein sampling (AVS) and adrenalectomy remain the standard, invasive interventions, leading to a 50% reduction in pill count as the average clinical improvement.

Study Design

In MATCH (Is Metomidate PET-CT superior to Adrenal vein sampling in predicting ouTCome from adrenalectomy in patients with primary Hyperaldosteronism), 142 patients, mean age 52, 32% female, 32% of African ancestry, 46% hypokalemic, had both AVS and 11C-metomidate PET CT (MTO) in random order, and were referred for surgery if aldosterone/cortisol ratio differed >4-fold between adequately cannulated adrenal veins, and/or SUVmax on MTO was >1.25x higher, in a definite tumour, than the opposite adrenal. The primary outcome is the proportion of patients in whom adrenalectomy achieved complete or partial biochemical or clinical cure, analysed hierarchically using PASO criteria.[1] Anticipating ~50% incidence of unilateral PA, MATCH is powered to detect 25% superiority of MTO vs AVS, or non-inferiority at a lower-bound CI of -17%. Secondary outcomes include non-randomised comparison of outcomes between unilateral and bilateral PA; prediction of clinical outcome from home BP readings before and after starting spironolactone 100mg daily for 4 weeks; quality-of-life assessments; and analyses, by RNAseq, of genotype and transcriptomes of tumors, correlated with ethnicity and outcomes.

Results

The analysis set is 75 patients who, on 31st Dec 2020, had undergone adrenalectomy with >6 months follow-up. 67 patients (89%) had complete biochemical cure following PASO criteria,[1] and 63 (84%) had complete or partial clinical cure. In 39/75 surgical patients, only one of MTO or AVS was scored as high-probability using criteria above. This score was confirmed at the multi-centre, MDT meeting which reviewed all MTO scans without knowledge of AVS. The primary analysis compared accuracy of MTO and AVS by McNemar test. The 39 discordant results were allocated as a win to the positive investigation if the patient was cured, or to the negative investigation, if not cured. 50/56 CYP11B2-positive tumors had a known mutation; the frequency was *CACNA1D>KCNJ5>ATP1A1>ATP2B3>CTNNB1>GNAQ>CLCN2*, differing between patients whose hypertension was completely or partially cured. Two other tumors had novel gene mutations. Several RNAseq transcripts varied with genotype and outcome, including some encoding measurable, secreted proteins.

Full primary and secondary outcomes will be presented.

Reference

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OC1.6

All-cause mortality in adrenal insufficiency patients using prednisolone or hydrocortisone replacement

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Background
Whilst hydrocortisone is standard glucocorticoid replacement therapy in patients with adrenal insufficiency, some have considered prednisolone an alternative. Some data have shown diabetes and osteoporosis risk. Mortality of patients using prednisolone in relation with those using hydrocortisone is not known. We compared all-cause mortality risk compared to matched controls in patients with primary or secondary adrenal insufficiency using prednisolone or hydrocortisone.
Subjects
In hydrocortisone cohort, 4228 patients with adrenal insufficiency of any type (1,405 primary adrenal insufficiency, 2,461 secondary) were compared with 41,934 matched controls (13,965 primary, 24,401 secondary). In prednisolone cohort, 1,250 adrenal insufficiency patients (137 primary, 897 secondary) were compared with 12,380 matched controls (1,347 primary, 8909 secondary).
Methods
Participants were extracted from a UK general practitioner database (Clinical Practice Research Datalink; CPRD) from 1987 to 2017. Each study patient was matched with up to 10 controls who had the same sex, GP practice, 5-year strata of the year of birth, and 5-year strata of the start of follow-up. Follow-up began on the latest of the date at which patients were diagnosed, registered to GP, or the GP provided standard information. Follow-up finished on the earliest date of death, or de-registering from the GP. All-cause mortality risk relative to controls was analysed separately in hydrocortisone and prednisolone cohorts then compared between cohorts.
Results
In adrenal insufficiency of any type, the hazard ratio for mortality of prednisolone users was 1.67 (95% CI, 1.47–1.90) with a follow-up period of 6725 and 66430 person-years for cases and controls, respectively. The HR was not different from that of hydrocortisone users (HR, 1.73 [95% CI, 1.61–1.87]; p for HR difference = 0.69) with a follow-up period of 24574 and 256815 person-years for cases and controls, respectively. In primary adrenal insufficiency, the hazard ratio of prednisolone users was 2.45 (95% CI, 1.86–3.23) which was higher than hydrocortisone users (HR, 1.82 [95% CI, 1.60–2.08]; p for HR difference =0.043). In secondary adrenal insufficiency the hazard ratio of prednisolone users was similar to hydrocortisone users (HR, 1.42 [95% CI, 1.18–1.72] vs. 1.59 [1.44–1.75]; p for HR difference = 0.34).
Conclusion
All-cause mortality risk in patients using prednisolone appeared is higher than those using hydrocortisone in patients with primary adrenal insufficiency. The mechanisms of this difference may be patient and care mechanism related.

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Diabetes, Obesity, Metabolism and Nutrition

OC2.1

Monogenic variants in the Finnish Pediatric Diabetes Register

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Background and aims
Monogenic forms of diabetes caused by a single gene defect include maturity onset diabetes of the young (MODY), neonatal diabetes mellitus and syndromic forms. They are estimated to account for 1–3% of all diabetes cases, but the prevalence is higher among pediatric patients without islet autoantibodies (AAB). Despite presenting with insulin deficiency, many patients can be treated with anti-hyperglycaemic agents to stimulate their insulin secretion. Our main objective was to assess the prevalence and clinical manifestations of monogenic diabetes in pediatric patients who were AAB-negative or positive only for low titer islet cell antibodies (ICAs) at diagnosis.
Materials and methods
At diagnosis, 6484 patients were tested for AAB through the Finnish Pediatric Diabetes Register, which covers approximately 90% of newly diagnosed diabetic patients aged < 16 years in Finland. Only 174 patients (3%) tested negative for all five AAB (ICAs, IAA, GADA, IA-2A and ZnT8A) and 58 patients (0,9%) had only low titer ICAs (< 10RU). DNA samples were available for 214 patients. A next generation sequencing (NGS) gene panel including 42 genes associated with monogenic diabetes (exons ± 50 nucleotides, and promoter regions harboring known pathogenic variants) was used for the detection of monogenic diabetes.
Results
We identified a monogenic cause for diabetes in 20 patients negative for all five AAB, accounting for 12% of the AAB-negative patients and 0,3% of all 6484 children in our cohort (n = 4 mutations in *GCK*, n = 6 mutations in transcription factors *HNF1A, HNF4A* or *HNF1B*, n = 4 mutations in *INS*, n = 6 rare monogenic forms caused by mutations in *KCNJ11, RFX6, LMNA* and *WFS1)*. At diagnosis, the median [IQR] age was 9.3 [6,6–13,8] years and the median ISO-BMI was 20.2 [17,7–25,2] kg/m^2. None of these 20 patients had presented with ketosis or ketoacidosis at diagnosis and none carried a high-risk HLA susceptibility genotype for type 1 diabetes. So far, two of these patients have been successfully transferred from insulin to oral treatment. The screening results of patients with low ICAs will be presented at e-ECE 2021.
Conclusion
A monogenic cause for diabetes was found in 12% of the AAB-negative patients screened by the NGS gene panel. As AAB-negative patients account for only approximately 3% of all diagnosed pediatric patients in Finland, screening of all AAB-negative pediatric patients for monogenic diabetes should be considered.

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OC2.2

Autoantibodies in prediction of diabetes after gestational diabetes – A 23-year prospective cohort study

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Objective
To study the predictive value of autoantibodies in progression to type 1 (T1DM) and type 2 (T2DM) diabetes after gestational diabetes (GDM) in a 23-year follow-up study.
Background
Women with GDM are at high risk for T2DM later in life, but also the risk of T1DM is increased. We have previously reported a prospective 6-year cohort study showing an association of islet cell and glutamic acid decarboxylase autoantibodies, GDM below the age of 30 years and the need for insulin treatment during pregnancy with a high risk of progression to T1DM. Recently, we reported the results of a 23-year follow-up showing that 5.7% of women with GDM developed T1DM and the disease progression was predictable with high OGTT 2-hour glucose levels during pregnancy. In addition, 50.4% of women developed T2DM after GDM with a linear incidence until the end of the study.

Study Design
This is a prospective cohort study including 391 women with GDM and 391 age-, parity−and delivery date-matched controls who delivered in 1984–1994. Four autoantibodies associated with T1DM were analysed from first trimester samples; islet cell (ICAs), glutamic acid decarboxylase (GADAs), insulin (IAAs) and insulinoma-associated antigen 2 autoantibodies (IA-2As). A follow-up questionnaire assessing later T1DM and T2DM morbidity was sent in 2012−2013. The mean follow-up time was 23.1 (18.7–28.8) years, which is to our knowledge, the longest follow-up to date.
Results
Single autoantibody positivity was detected in 12% (41/391) of the GDM cohort and in 2.3% (8/391) of the control cohort. In the GDM cohort, 2.6% (9/391) tested positive for two autoantibodies and 2.3% (8/391) for three autoantibodies, whereas only one subject in the control cohort had two autoantibodies detected. ICA positivity was found in 12.5% of the cases, followed by GADA (6.0%), IA2A (4.9%) and IAA (1.2%). In the control cohort, GADA positivity was found in 1.4%, IA2A in 0.8%, IAA in 0.6%, and ICA in 0.3% of the subjects. Detection of ICA, GADA and/or IA-2A autoantibodies decreased T1DM-free survival time and time to diagnosis. All subjects with three positive autoantibodies developed T1DM within seven years from the GDM pregnancy. Development of T2DM after GDM occurred independent of autoantibody positivity.
Conclusion
Development of T1DM can be reliably predicted with GADA and ICA autoantibodies during early pregnancy. We recommend that women with high glucose values in OGTT and insulin treatment be tested for autoantibodies to identify individuals with high risk of T1DM later in life.

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OC2.3

Long-term testosterone therapy improves glycaemic control and weight control in men with type 2 diabetes: 12-year observational data from a controlled registry study in a urological setting

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Background
Prevalence of hypogonadism has been reported as high as 50% in men with T2DM and/or obesity. ADA and AACE Guidelines recommend assessment of hypogonadism in men with T2DM and obesity.
Material and methods
In a registry of 865 men with hypogonadism, 361 men (41.7%) had T2DM. 183 received TU 1000 mg/12 weeks (T-group), 178 opted against treatment (CTRL). Changes over time between groups were compared and adjusted for age, weight, waist circumference, fasting glucose, blood pressure, lipids and quality of life to account for baseline differences between the two groups. 12-year data are reported.
Results
Mean follow-up: 8.7 ± 3.1, baseline age: 60.7 ± 5.5 (T-group) and 63.0 ± 4.9 (CTRL) years. Glycaemic control at 12 years (mean values ± SE): HbA1c (%) progressively decreased by 3.7 ± 0.2 in the T-group and increased by 3.2 ± 0.2 in CTRL, estimated adjusted difference between groups: -6.9 [95% CI: -7.4;-6.4] (P < 0.0001 for all). Fasting glucose (mmol/l) decreased by 1.9 ± 0.1 (T-group) and increased by 1.8 ± 0.1 (CTRL), difference between groups: -3.6 [95% CI: -4.0;-3.3] (P < 0.0001 for all). HOMA-IR decreased by 8.0 ± 0.3 (T-group) and increased by 6.5 ± 0.4 (CTRL), difference between groups: -14.4 [95% CI: -15.5;-13.4] (P < 0.0001 for all). In CTRL, 22 patients were started on insulin during the observation period. Weight control at 12 years (mean values ± SE): 293 men (81.2%) were obese, 61 (16.9%) overweight and 7 (1.9%) had normal weight. Weight (kg) decreased by 22.5 ± 0.5 (T-group) and increased by 8.5 ± 0.5 (CTRL), difference between groups: -31.0 [95% CI: -32.7;-29.2] (P < 0.0001 for all). Weight loss (%) was 19.7 ± 0.4 in the T-group, weight gain 9.1 ± 0.4 in CTRL, difference between groups: -28.8 [95% CI: -30.2;-27.4] (P < 0.0001 for all). Waist circumference (cm) decreased by 13.6 ± 0.4 (T-group) and increased by 8.5 ± 0.4 (CTRL), difference between groups: -22.1 [95% CI: -23.4;-20.8] (P < 0.0001 for all). BMI (kg/m^2) decreased by 7.4 ± 0.2 (T-group) and increased by 2.8 ± 0.2 (CTRL), difference between groups: -10.2 [95% CI: -10.8;-9.5] (P < 0.0001 for all). Since injections were administered in the office and documented, there was a 100% adherence to testosterone therapy.
Conclusion
Long-term testosterone therapy with TU in men with hypogonadism and T2DM progressively improved glycaemic as well as weight control which deteriorated in untreated men.

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OC2.4

Predicting optimal diabetes drug management using AI/ ML – Developing a prototype clinical decision support algorithm.

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Universal reach of diabetes care and assurance of minimum standard of care is a milestone yet to be achieved. Application of artificial intelligence/ machine learning (AI/ML) for diabetes care can help solve both these aspects of diabetes care.
Objective
Creating a clinical decision support system using AI/ML approach for predicting best anti-diabetes drug class to be introduced to help optimally manage glycaemic control in people living with diabetes mellitus type 2.
Methodology
Study was conducted at an Endocrinology clinic and data collected from electronic clinic management system. 15485 diabetes prescriptions of 4974 patients were accessed. A data subset of 1671 diabetes prescriptions with information on diabetes drugs, demographics (age, gender, body mass index), biochemical parameters (HbA1c, fasting blood glucose, creatinine) and patient clinical parameters (diabetes duration, compliance to diet/ exercise/medications, hypoglycemia, contraindication to any drug, summary of patient self monitoring of blood glucose data, diabetes complications) was used in analysis. The patients in this data set had mean HbA1c of 7.3% ±1.3% (median 7.05%, 25th percentile 6.5%, 75th percentile 7.89%). For analysis, 67% of the dataset was used as a training set and 33% as a testing set. An input of patient variables (current diabetes medications, demographics, biochemical parameters and patient clinical parameters) were used to predict all diabetes drug classes to be prescribed. Random forest algorithms were used to create decision trees for all diabetes drugs. Accuracy for predicting use of each individual drug class is depicted in Table 1 and varied from 85% to 99.4%. Multi-drug accuracy considering that all drug predictions in a prescription need to be correct stands at 72%. Multi drug class accuracy in clinical application may be higher than this result, as in a lot of clinical scenarios, two more diabetes drugs may be used interchangeably.

Table 1 Individual drug class prediction accuracy

Drug Class	Training Set Accuracy (%)	Testing Set Accuracy (%)
Metformin	100	97.8
Sulfonylureas	100	90
DPP-4 inhibitors	100	85
SGLT2-inhibitors	100	92.4
AGI	100	96.9
Pioglitazone	100	96.2
Meglitinides	100	99.3
Short acting insulin	100	99.4
Basal insulin	100	97.1
Premix Insulin	100	97.5

Clinical Impact
This report presents a first positive step in developing a robust clinical decision support system to transform access and quality of diabetes care. Multi-drug accuracy is likely to improve further with time as the depth of the dataset increases over time.

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OC2.5

Genetic characterization of MODY patients in greece

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Background
Maturity Onset Diabetes of the Young (MODY) constitutes a genetically and clinically heterogeneous type of Monogenic Diabetes (MD), characterized by early onset of hyperglycemia, autosomal dominant inheritance and defect in β-cell insulin secretion. To date, various MODY subtypes have been reported, each one of a distinct genetic etiology.
Materials and methods
A total of 114 patients of Greek origin fulfilling MODY criteria are reported. Twenty-four patients with GCK-MODY phenotype were tested by Sanger sequencing. Ninety patients were tested employing a Next Generation Sequencing Targeted Gene Panel of seven MODY genes (*GCK, HNF1A, HNF4A, HNF1B, INS, ABCC8* and *KCNJ11*), 40 of which had been previously tested by Sanger sequencing for *GCK, HNF1A* and *HNF4A*, according to patients' phenotypes. Patients, with no pathogenic variant detected, were tested by Multiplex Ligation-dependent Probe Amplification (MLPA) for CNVs.
Results
GCK-MODY was found to be the most frequent MODY subtype (18.4%), followed by *ABCC8*-MODY (9.6%) and *HNF1A*-MODY (6.1%), whereas *HNF4A*-MODY is rare (0.8%). Two patients were identified with *HNF1B* variants and another 3 with whole *HNF1B* gene deletion, making a total of 4.4% of *HNF1B*-MODY. The *ABCC8* MODY patients (9.6%) presented with a wide spectrum of clinical and biochemical characteristics: fasting blood glucose ranging from 103 to 365 mg/dl (5.7–20.3 mmol/l), HbA1c 5.4% to 11.9% (35.5–107 mmol/mol), age of onset of diabetes from 9 yrs to 42 yrs, BMI from 17.2 to 27.7 kg/m^2 and birth weight from 2700 g to 4100 g.
Conclusions
Overall in our cohort a diagnostic rate of 45% was achieved. The majority of the patients were GCK-MODY (18.4%), followed by ABCC8-MODY 9.6%, indicating that *ABCC8* gene variants are frequently related to MD. The phenotypic characteristics of the patients carrying *ABCC8* variants, exhibit genetic heterogeneity, ranging from a mild phenotype, similar to the mild *GCK* phenotype, to a more severe phenotype, similar to that of *HNF1A* and *HNF4A* defects. Molecular genetic diagnosis of the MODY subtype is of outmost importance for clinical diagnosis, disease progression prognosis and family counseling. Furthermore, it specifies pharmacologic treatment, since different MODY subtypes require different therapeutic approaches, constituting an example of personalized medicine.

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OC2.6

Insulin receptor isoforms in human adipogenesis: Possible role in the onset of adipose tissue expansion

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Insulin is a major endocrine hormone able to regulate whole-body energy disposal and lipid metabolism. Particularly, insulin stimulates the renewal of the adipose tissue (AT) via activation of insulin receptors (IR) consisting of two splicing variants: a short isoform (IRa) involved in cell proliferation, and a long isoform (IRb) mainly implicated in metabolic responses. The contribution of these isoforms to the AT expansion is still poorly understood. We investigated the expression of both isoforms in human adipose-derived stem cells (ASC), in vitro differentiated adipocytes (dASC), and whole AT obtained from subjects with different BMI. Gene expression analysis was performed in subcutaneous AT (S-AT), visceral AT (V-AT), and ASC before and after differentiation into adipocytes (dASC) by qPCR. Adipogenesis was evaluated according to protein levels of IR and Nile red (NR) staining by flow cytometry. mRNA levels of IRa were more expressed than IRb in both S-ASC and V-ASC. S-ASC showed higher mRNA levels of total IR, IRa and IRb than V-ASC, as well as greater activation of insulin signaling. IRa expression significantly correlated with BMI (r = 0.53) and waist circumference (r = 0.51) in S-ASC and with BMI (r = -0.36) in V-ASC. Increased mRNA levels of total IR, IRa and IRb was observed after adipocyte differentiation in both S-dASC and V-dASC, with higher expression levels in S-dASC than V-dASC. Accordingly, IRa was more expressed than IRb in both S-AT and V-AT. Flow cytometric analysis revealed a time-dependent and tissue-specific increase of differentiated adipocytes stained with NR (NR+: 60% S-dASC, 23% V-dASC) but only a fraction of NR+ cells expressed IR, particularly in S-dASC (day 16, NR+IR+: 64% of NR+; day 30, NR+IR+: 77% of NR+). Conversely, V-dASC showed a high proportion of IR+ cells in the early phases of adipogenesis (day 16, NR+IR+: 82% of NR+), while a consistent reduction of the percentage of triglyceride-filled cells expressing IR was observed in the late phases (day 30, NR+IR+: 61% of NR+). In conclusion, mRNA levels of IR, particularly IRa, increase with BMI and adipocyte maturation especially in S-ASC. S-ASC display greater activation of insulin signaling and adipogenic phenotype as compared to V-ASC. A greater percentage of V-dASC expressing IR was observed during early adipogenesis but not in the late phase. IRa expression levels are associated with AT expansion typically in S-AT. The role of IR in V-AT expansion, particularly in the early phase of adipocyte commitment, needs further elucidation.

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Pituitary and Neuroendocrinology

OC3.1

Osilodrostat is an effective and well-tolerated treatment for Cushing's Disease (CD): Results from a Phase III, multicentre, randomized, double-blind study with an initial placebo-controlled phase (LINC 4)

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Introduction
Osilodrostat, a potent, oral 11β-hydroxylase inhibitor, normalized mean urinary free cortisol (mUFC) in most patients with CD during a Phase III, randomized-withdrawal study. We now report findings from a Phase III study of osilodrostat in patients with CD that featured an initial double-blind, randomized, placebo-controlled period (LINC 4; NCT02697734).
Methods
Adults with CD (mUFC > 1.3 × ULN) were randomized 2:1 to osilodrostat 2 mg bid or matching placebo for a 12-week (W) double-blind period; dose adjustments (range 1–20 mg bid) were permitted based on efficacy at W2, W5, and W8 and tolerability. From W12 to W48, all patients received open-label osilodrostat, with dose adjustments permitted (range 1–30 mg bid). At W48, patients could enter an optional extension. Primary endpoint: proportion of randomized patients who received ≥1 treatment dose with mUFC ≤ ULN at W12.
Results
Seventy-three patients were randomized and received osilodrostat (n = 48) or placebo (n = 25; baseline median [range] mUFC 2.5 × ULN [0.7–12.5] vs 2.2 × ULN [0.2–18.9]). At W12, 77% of osilodrostat recipients achieved mUFC ≤ ULN vs 8% on placebo (OR 43.4; 95% CI 7.1–343.2; P < 0.0001). At W36, 81% (95% CI 69.9–89.1) of osilodrostat recipients achieved mUFC ≤ ULN (key secondary endpoint). Median time to first controlled mUFC response for osilodrostat patients was 35 days (95% CI 34–52). At data cut-off (25 February 2020), median osilodrostat exposure was 71.7 vs 62.3 weeks for patients initially randomized to osilodrostat vs placebo (median [IQR] osilodrostat dose: 4.7 [3.8–9.0] vs 6.0 mg/day [3.7–9.7]). Up to W12, three osilodrostat recipients discontinued, one because of an AE (arthralgia), vs 0 with placebo. Most commonly reported AEs by W12 were decreased appetite (38% osilodrostat vs 16% placebo), arthralgia (35%

vs 8%) and nausea (31% vs 12%). AEs related to hypocortisolism (15% osilodrostat vs 0% placebo) and adrenal hormone precursor accumulation (44% vs 36%) were mostly grade 1/2 and resolved with dose reduction/interruption and/or concomitant medication. Most common AEs occurring on osilodrostat treatment during the overall study period were arthralgia (45%), decreased appetite (45%), fatigue (38%), nausea (37%) and headache (33%). Improvements in clinical signs of hypercortisolism, including systolic/diastolic blood pressure and HbA_{1c}, were observed with osilodrostat at W12 and W48.

Conclusions

Osilodrostat was superior to placebo at normalizing mUFC at W12 (77% vs 8%). Improvements in mUFC were sustained at W36. Few patients discontinued treatment because of AEs; hypocortisolism-related AEs were infrequent and manageable. We conclude that osilodrostat is a highly effective and well-tolerated treatment for patients with CD.

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OC3.2

Antitumor effects of growth hormone-releasing hormone (GHRH) antagonists in ACTH–and GH-secreting pituitary neuroendocrine tumor (PitNETs) cell lines

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Pituitary neuroendocrine tumors (PitNETs) are mostly benign lesions originating from the anterior pituitary and represent 10–15% of all the intracranial neoplasms. PitNETs can be classified in non-secretory, clinically non-functioning pituitary adenomas (NFPAs), and secretory, comprising prolactin (PRL), growth hormone (GH) and adrenocoticotropic hormone (ACTH). Surgical resection is the first line treatment for PitNETs, whereas chemotherapy and radiotherapy are preferred for resistant or metastatic tumors. Growth hormone-releasing hormone (GHRH), besides promoting pituitary GH secretion, exerts many extrapituitary functions, including stimulation of cell proliferation and survival. GHRH, GHRH receptor (GHRH-R) and its splice variant 1 (SV1), are expressed in different cancer cell types, where they promote cell proliferation and tumor progression. Conversely, GHRH antagonists inhibit the growth of different tumors *in vitro* and *in vivo*; moreover, it has been demonstrated that first generation GHRH antagonists reduce GH secretion in tumoral rat GH-secreting (GH3) cells. However, to date the role of GHRH antagonists in PitNETs remains largely unknown. Thus, we aimed to clarify the potential antitumor effects of last generation GHRH antagonists, MIA-602 and MIA-690 in ACTH-secreting PitNET cells (AtT-20/D16v-F2), rat PRL–and GH-secreting PitNET cells, transfected with human GHRH-R (GH3-hGHRHR), and in primary cells isolated from patients with PitNETs. Our results show that MIA-602 and MIA-690 dose-dependently reduced cell survival and promoted apoptosis in AtT-20 and GH3-hGHRHR; in addition, we observed an increase in expression of the proapoptotic protein BAX and the tumor suppressor protein P53, paralleled by a reduction of the antiapoptotic protein Bcl-2. MIA-602 and MIA-690 also reduced colony formation and expression of c-Myc oncoprotein, indicating inhibitory activity on migration and proliferation. Furthermore, the combination of MIA-602 or MIA-690 with the main chemotherapy drug temozolomide showed a synergistic effect on inhibition of AtT-20/D16v-F2 cell survival. In addition, both GHRH antagonists reduced the secretion of GH, but not PRL, in GH3-hGHRHR, but showed no activity on ACTH secretion in AtT20/D16v-F2. Finally, preliminary results show a potential antitumor role for MIA-602 and MIA-690, alone or in combination with the somatostatin analog octreotide, in human primary cells isolated from NFPAs and ACTH–or GH-secreting PitNETs. Overall, these results indicate that GHRH antagonists display antitumor activities in ACTH and GH tumor cells and suggest their potential use for the treatment of PitNETs, alone or in combination with standard therapies.

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OC3.3

Metyrapone treatment in endogenous Cushing's syndrome. Long term efficacy and safety results of the extension of the phase III/IV study PROMPT

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Background

Retrospective studies led to European approval of the steroidogenesis inhibitor Metyrapone for the treatment of endogenous Cushing's syndrome (CS). We prospectively showed good efficacy and safety of Metyrapone after 12 weeks (Wk12) treatment in the phase III/IV PROMPT study and now report results of an extension study (EXT) sponsored by HRA Pharma Rare Diseases.

Design

This was a single arm, open-label, 24Wk extension of PROMPT that enrolled patients whose mean of 3 UFC (mUFC) was normal or less than 2-fold the upper limit of normal (ULN, 165 nmol/d) at Wk12. The EXT measured UFC at Wk24 (for dose titration) and Wk36 by liquid chromatography tandem–mass spectrometry.

Results

At the end of PROMPT (Wk 12), mUFC was normal in 23 of 49 patients and < 2-fold ULN in 19. The EXT baseline median mUFC was 0.96-fold ULN (159, range 5 – 333 nmol/d, n = 41). At Wk36, median mUFC in 35 completers was 1.04-fold ULN: mUFC was normal in 17 patients, < 2 × ULN in 11 and ≥ 2× ULN in 7. mUFC at Wk36 was normal in 5/14 evaluable patients with mUFC 1–2× normal at Wk12. mUFC at Wk24 was normal in all 20 patients with normal Wk12 mUFC; at Wk36 12 maintained normal values, 4 had mUFC < 2 × ULN, and 4 had mUFC ≥ 2× ULN. PROMPT and EXT response rates were similar (80%, 95% CI 66–89 vs 71%, 95% CI 55–84). Wk36 metyrapone dose was higher in mUFC 2-fold ULN group than others (2357 vs 1618–1750 mg/d). Median late night salivary cortisol was 4.8-fold ULN at Wk0 and 1.7-fold ULN at Wk36; 27% were normal. Clinical improvement of physical symptoms, cardiovascular and metabolic parameters continued. Adverse events (n = 3: hirsutism, acute glaucoma or hypotension) or patient's or physician's decision (n = 3) prompted discontinuations. Compared to

first 12-week period, good tolerability profile was maintained: no patient was treated for adrenal insufficiency and fewer patients reported nausea, vomiting, dizziness, or fatigue. There were 3 new cases of female hirsutism and one new case of hypertension.
Conclusions
mUFC was normal in 47–49% of completers at Wk12 and Wk36, and good tolerability continued. Normalization of mUFC during EXT validates continued titration after Wk12 in some patients. Variability of intra-patient steroidogenesis, baseline UFC and titration algorithms should be considered to improve overall UFC normalization. Late night salivary cortisol improvement was maintained during the extension and the distribution of metyrapone over the day should be considered to improve this rate.

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OC3.4

Truncated somatostatin receptor variant SST5TMD4 determines somatostatin analogs response in corticotropinomas

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Introduction
Cushing's disease is the result of prolonged exposure to excess cortisol caused by a pituitary tumor, known as corticotropinoma, which hypersecretes adrenocorticotropin (ACTH). Treatment with somatostatin analogs (SSA) has been shown to reduce hormone secretion and, to a lower extent, tumor growth in some subtypes of pituitary tumors, such as growth hormone secreting tumors. However, SSA are commonly ineffective in corticotropinomas. Previous studies indicated that the presence of the truncated receptor variant SST_5TMD4 is associated with a lack of response to SSA in growth hormone secreting tumors. However, its presence and functional role in corticotropinomas is still poorly defined.
Aims
The aim of this study was to explore the molecular and functional role of somatostatin receptors (SSTs) in corticotropinoma cells, and in particular to assess the contribution of SST_5TMD4 to SSA response.
Methods
The expression levels of SSTs were evaluated in 28 corticotropinomas and 8 normal pituitary samples. Functional assays (free cytosolic calcium kinetics, ACTH secretion and cell viability) were assessed in response to SSA in primary corticotropinoma cultures. Moreover, cell viability was evaluated after transiently SST_5TMD4 overexpression.
Results
In general, a lower expression of the receptors SST_1/SST_2/SST_3 was observed in corticotropinomas compared to normal pituitary samples. A more detailed analysis revealed the existence of two subpopulations of corticotropinomas that differed in the presence of high (n = 7) or low levels (n = 17) of expression of SST_5TMD4. The named 'high' population expresses all SSTs, presenting a higher expression of SST_2/SST_3/SST_5TMD4 compared to the 'low' subpopulation, which predominantly expresses SST_5. Furthermore, SST_5TMD4 was significantly over-expressed in the 'high' population compared to normal samples. Pilot functional studies in cell cultures derived from corticotropinomas revealed that both 'high' and 'low' corticotropinomas differentially respond to in vitro treatment with SSA, octreotide and pasireotide. Finally, SST_5TMD4 overexpression increased cell viability.
Conclusions
Our data indicate that there might be two discinct subpopulations of corticotropic tumors, one expressing most SSTs and another that predominantly expresses SST_5, which could confer differential responsiveness to SSA. Furthermore, the trasfection assay revealed that the presence of SST_5TMD4 seems to be associated with a higher proliferative rate in corticotropinomas. Consequently, a detailed expression profile of all the SSTs in corticotropinomas, especially SST_5 variants, could assist the prediction of response to SSA in patients with Cushing's disease.
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OC3.5

Pregnancies after childhood craniopharyngioma – Results of KRANIOPHARYNGEOM 2000/2007

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Background
Data on female fertility, pregnancy, and outcome of offspring after childhood-onset craniopharyngioma (CP) are rare.
Study design
Observational study on pregnancy rate and outcome of offspring after CP in postpubertal, female patients recruited in KRANIOPHARYNGEOM 2000/2007 since 2000.
Results
451 CP patients (223 female) have been recruited. 269 CP patients (133 female) were postpubertal at study. Six of 133 female CP patients (4.5%) with a median age of 14.9 years at CP diagnosis had 9 pregnancies, giving birth to 10 newborns. Three patients achieved complete surgical resections. No patient underwent postoperative irradiation. Five natural pregnancies occurred in 3 CP patients without pituitary deficiencies. Four pregnancies were achieved in 3 CP with hypopituitarism under assisted reproductive techniques (ART) (after median 4.5 cycles, range: 3–6 cycles). Median maternal age at pregnancy was 30 years (range: 22–41 years). Six babies (60%) were delivered by caesarean section. Median gestational age at delivery was 38 weeks (range: 34–43 weeks); median birth weight was 2,920 grams (range: 2,270–3,520 grams), the rate of preterm delivery was 33%. Enlargements of CP cysts occurred in 2 women during pregnancy. Other severe complications during pregnancy, delivery and postnatal period were not observed.
Conclusions
Pregnancies after CP are rare and achieved in 45% after ART. Close monitoring by an experienced reproductive physician is necessary. Due to a potentially increased risk for cystic enlargement, MRI of cystic CP is recommended during pregnancy. Severe perinatal complications, birth defects, and postnatal morbidity of mothers and offspring were not observed.

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OC3.6

Expression and possible role of integrins in corticotroph tumours

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Introduction
Integrins are heterodimeric transmembrane proteins composed of alpha and beta subunits that mediate cell-cell and cell-extracellular matrix (ECM) interactions. Several integrins are overexpressed in human cancers and their ECM recognition motif, arginine-glycine-aspartate (RGD), is being utilized for tumour imaging and targeting.
Aim
To explore the expression and function of RGD-binding integrins in corticotroph tumours.
Methods
We determined the expression of RGD-binding integrins by qPCR in 18 corticotroph tumours and compared transcript levels with gonadotroph

tumours ($n = 16$) and normal pituitaries ($n = 2$). To study the role of integrins, we established their expression profile in murine corticotroph tumour AtT-20 cells by RT-PCR and investigated the effect of their inhibition with RNA interference on human POMC promoter activity and cell viability (WST1 colorimetric assay). We used fluorescence microscopy to assess RGD peptide binding in these cells.
Results
Corticotroph tumours express αv (*ITGAV*), β1 (*ITGB1*), β5 (*ITGB5*), β8 (*ITGB8*), and α8 (ITGA8). Integrins αv, β1, β5 are overexpressed in corticotroph compared to gonadotroph tumours, where expression was almost undetectable ($P < 0.0001$) and human normal pituitary ($P < 0.001$). The expression of β8 was higher in corticotroph only compared to gonadotroph tumours ($P = 0.04$), but not to the normal pituitary. We found that AtT-20 cells express all these four integrins. Knocking down each αv, β1, and β5, decreased human *POMC* promoter activity compared to scramble control (% suppression 63 ± 22, 54 ± 23, and 69 ± 28 respectively; $P < 0.05$), while β8 had little effect. Knocking down αv and β1 had a small but significant effect on AtT-20 cell viability (% suppression 15.92 ± 1.6 and 27.4 ± 1.4 respectively; $P < 0.05$). Using immunofluorescence, we observed that an RGD peptide conjugated with the near-infrared fluorophore cyanine-5.5 could bind to and label AtT20 cells, with no deleterious effects on AtT-20 cell viability (WST1 assay) and function (determined by *POMC* promoter activity).
Conclusions
This study shows that corticotroph tumours express the genes encoding the alpha and beta subunits of the RGD-binding integrins αvβ1, αvβ5, and αvβ8. We have preliminary evidence that these integrins may regulate *POMC* promoter activity. RGD peptide conjugates potential as corticotroph tumour imaging agents.

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Reproductive and Developmental Endocrinology

OC4.1

Effect of IL-1 receptor antagonism on hyperandrogenemia in women with polycystic ovary syndrome

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Background
Polycystic Ovary Syndrome (PCOS) is the most prevalent endocrine disorder in women of reproductive age. The main components are hyperandrogenemia and oligo-/amenorrhea. The pathophysiology of PCOS is not fully understood which is why no causal treatment options are available. A multitude of observational studies demonstrated elevated C-reactive protein (CRP) levels in patients with PCOS compared with weight-matched controls. CRP is a sensitive marker for the proinflammatory cytokine Interleukin-(IL)-1. IL1 stimulated ovarian androgen production and impaired gonadotropin signaling and fertility in experimental studies. In clinical studies, therapeutic IL1 blockade had beneficial effects on cardiometabolic health. The aim of this study was to investigate whether IL1 blockade ameliorates hyperandrogenemia in patients with PCOS.
Methods
This is a prospective, interventional, single-arm, proof-of-concept trial. Seventeen patients with PCOS and C-reactive protein (CRP) levels ≥1 mg/l were treated with 100 mg of the IL1 receptor antagonist anakinra daily for 28 days. The primary endpoint was change in serum androstenedione levels on day 7 of treatment, assessed with liquid chromatography-tandem mass spectrometry. Secondary endpoints included changes in serum androgen concentrations, pituitary-gonadal axis hormones, and clinical parameters on treatment days 7, 14, 21, 28, and one week after end of treatment.
Results
Treatment with anakinra reduced CRP levels on days 7, 21, and 28 ($P < 0.001$). It increased serum androstenedione levels by a median (IQR) of 0.6 (0.2, 1.7) nmol/l to day 7 ($P = 0.008$). Serum testosterone as well as dihydrotestosterone levels increased from baseline to day 7 (both: $P = 0.03$). Estradiol levels were increased during the first three weeks of treatment ($P = 0.02$), which was followed by a menstrual bleeding in five patients of which three were previously oligo-/amenorrheic. There was no overall change in gonadotropins or other clinical parameters.
Discussion
We conclude that chronic low-grade inflammation is regulated by IL1 in PCOS as evidenced by a reduction of circulating CRP levels upon anakinra. Short-term IL1 blockade increased steroidogenesis likely by enabling gonadotropin action. Additionally, this increase might reflect the onset of a new anakinra-induced ovulatory cycle, since androgens as well as estradiol levels rise during the transition from the early to late follicular/ovulatory phase. Three patients experienced an unexpected menstrual bleeding by the end of the study. This data is reassuring to conduct a next randomized placebo-controlled long-term trial with menstrual cyclicity as primary endpoint.

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OC4.2

A molecular analysis of genes involved in disruption of hypothalamo-pituitary-gonadal axis causing delay in onset of male puberty

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Of 563 genes involved in multiple processes of development of hypothalamo-pituitary-gonadal (HPG) axis during embryogenesis, mutations in 62 genes cause delayed puberty. We selected 6 of 37 delayed puberty patients for whole exome sequencing (WES) based on advanced age (>18 years) and severity of disease symptoms. Genomic DNA extraction was done using Qiagen kit at Institute of Biomedical and Genetic Engineering, Islamabad, Pakistan. DNA samples were taken to ANZAC Research Institute (ARI), New South Wales (NSW), Australia for genetic analysis. Each sample was diluted to final concentration of 25 ng/µl DNA and was outsourced to Macrogen Inc., Seoul, South Korea for WES using Illumina HiSeq 2000 platform. Bioinformatics analysis was performed at ARI. Only missense, splice region, frameshift, exon lost, stop gained and stop lost variants expressed along HPG axis having minor allele frequency of < 1% were included. Manual evaluation of BAM files and In Silico analysis of missense variants were performed to assess functional consequences. Selected variants were confirmed by Sanger sequencing at Australian Cancer Research Foundation, Garvan Institute of Medical Research, NSW. We report mutations in 31 genes expressed along HPG axis, 7 already reported confirmed, 6 reported but unconfirmed and 18 novel mutations. Of 53 genes involved in hypothalamic regional territories development, mutation in one confirmed gene was identified. Of 60 genes for GnRH neuron differentiation, mutations in 2 confirmed, 1 reported unconfirmed and 2 new genes were identified. Among 101 genes for GnRH neuron migration, mutations in 4 confirmed, 1 reported unconfirmed and 6 new genes were identified. Of 60 genes for development of GnRH neural connections with supra-hypothalamic neurons, mutations in 3 confirmed, 1 reported unconfirmed and 6 novel genes were identified. Of 24 genes for neuron homeostasis, 2 novel mutations were observed. Among 46 genes coding for molecules regulating GnRH neuron activity, mutations were identified in 2 reported unconfirmed and 4 novel genes. Of 56 genes coding for receptors/proteins on GnRH neurons, mutations in 1 reported unconfirmed and 1 novel gene were observed. Among 21 genes coding for signaling molecules, mutations were identified in 1 reported unconfirmed and 3 novel genes. Of 95 genes for GnRH synthesis, mutations in 1 confirmed and 1 reported unconfirmed gene were observed. Of 31 genes for gonadotropins production/release, mutations in 1 confirmed, 1 reported unconfirmed and 1 novel gene were identified. Of 115 genes for steroid hormone action, mutations were identified in 1 confirmed and 1 new gene.

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OC4.3

Gender difference in genetic and diagnosis of congenital hypogonadotropic hypogonadism (CHH) in a large cohort from an Endo-ERN referral center

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Congenital hypogonadotropic hypogonadism (CHH) is a rare condition characterized by impairment of pubertal development, that can be associated with hypo/anosmia (Kallmann Syndrome, KS) or normosmia (nCHH). A genetic basis can be identified in nearly 50% of cases, with increasingly common detection of oligogenicity. CHH has a strong male predominance (MtoF ratio 5–3:1), although sex ratio for CHH in families with autosomal inheritance has been proven to be close to equal. The rationale for this epidemiologic difference is not clearly understood. Our study aims to evaluate gender differences in clinical and genetic diagnosis of CHH. 313 CHH patients with absent pubertal development, consecutively referred to our Center from 01/2016, were enrolled in this study. Data collection included clinical assessment at diagnosis and genetic analysis performed by next generation sequencing (NGS), employing a panel of 27 candidate genes (ANOS1, FGFR1, PROK2, PROK-R2, KISS1, KISS1R, GnRH, GnRHR, FGF8, TACR3, TAC3, HS6ST1, CHD7, DUSP6, FEZF1, FGF17, FLTR3, IL17RD, SEMA3A, SEMA3E, SEMA7A, SOX2, SOX10, SPRY4, WDR11, HESX1, NELF). Among 313 patients 87 were female (F) and 226 male (M) (FtoM ratio 1:2.6). 43.8% had a diagnosis of KS and 56.2% of nCHH (no significant gender difference). Rare genetic variants were found in 54.3% of patients (F 55.2% vs. M 54%). Monoallelic rare variants were found in 37.1% (F 33.3% vs. M 38.5%), biallelic monogenic rare variants in 4.2% (F 5.7 vs M 3.5%) and oligogenicity in 13.1% (16.1% vs. 11.9%), with no significant difference between sex, even after exclusion of X-linked ANOS1. Prevalence of rare variants in each candidate gene resulted in line with literature, showing no significant gender differences, except for IL17RD (F 5,7% vs. M 1,3%, *P* 0.040). Age at diagnosis was 17.2 ± 2.9 for F and 16.8 ± 3.5 for M (*P* 0.065). Presence of clinical "red flags" (family history, hypo/anosmia, micropenis, cryptorchidism, midline defects, bimanual synkinesis, renal abnormality, deafness) was significant higher in male (F 64.4% vs. M 79.2%, *P* 0.008), but not related to age at diagnosis or presence of rare variants. Nevertheless, these rates become similar after excluding micropenis and cryptorchidism, as only male manifestations. Our data confirm the male predominance in CHH but they do not allow to identify substantial differences in genetic or clinical presentation between gender, suggesting that gender gap in CHH prevalence do not depend upon variability of the underlying pathogenic mechanisms, but rather to gender specific characteristics of GnRH function or differences in diagnostic capability.

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OC4.4

Fertility outcomes in women with hypopituitarism compared to women with hypogonadotrophic hypogonadism in a single UK centre

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Objective
Previous studies have documented poor fertility results in women with hypopituitarism (HP) both in terms of pregnancy rates and outcomes. We aimed to assess ovulation induction (OI) and pregnancy outcomes in women with HP compared to women with hypogonadotrophic hypogonadism (HH) treated at University College London Hospitals.
Design
A retrospective study.
Patients
39 women with HP and 57 women with HH underwent 143 and 266 cycles of OI respectively (median age at cycle 33.5 years [interquartile range (IQR) 31.4–37.0] vs 34.3 years [IQR 32.3–36.6] respectively, $P = 0.35$).
Methods
OI was carried out by using human menopausal gonadotropin (hMG) according to a standard protocol and a 10,000 IU human chorionic gonadotropin trigger. Baseline serum oestradiol, follicle stimulating hormone, luteinizing hormone, prolactin, thyroid functions tests and insulin-like growth factor-1 were measured together with a uterine scan. Ovulation was confirmed by a mid-luteal phase progesterone of >30 nmol/l or ultrasound evidence of corpus luteum. Clinical pregnancy was defined by the presence of at least one heartbeat on an ultrasound scan.
Results
Ovulation rates were similar between women with HP and HH. Although pregnancy and live birth rates per cycle were greater in women with HP compared to women with HH (28.7% vs 16.2%, $P = 0.003$ and 17.0% vs 9.4%, $P = 0.025$ respectively), pregnancy and live birth rates per patient were similar (66.7% vs 50.9%, $P = 0.125$ and 48.6% vs 37.5%, $P = 0.286$ respectively). Foetal loss per pregnancy was not different between women HP and HH (29.3% vs 39.5%, $P = 0.323$ respectively), with a similar proportion of multiple pregnancies per live births between the 2 groups of women (HP 8.3% vs HH 20.0%, $P = 0.243$). There were no major complications in most of the deliveries. Median number of cycles to pregnancy in women with HH was 9 (Standard Error [SE] 0.0) vs 6 cycles (SE 0.8) in women with HP (Log Rank: $P = 0.001$).
Conclusions
Encouraging ovulation and pregnancy rates can be obtained in women with HP using hMG. A smaller uterine size and lack of size normalisation following standard oestrogen replacement therapy may in part explain the greater miscarriage rate compared to the general population in these women. Management in a multidisciplinary team is advised.

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OC4.5

Lower level of sexual maturation rating and reduced concentrations of reproductive hormones, luteinizing hormone, follicle stimulating hormone, testosterone and estradiol in short stature children with mutations in growth hormone secretagogue receptor 1a

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Puberty onset is sensitive to the energy reserves of the organism, especially in females where there is an association between obesity and early puberty. Studies have shown that in the presence of growth hormone secretagogue receptor 1a (GHSR1a) mutations, there is a decrease in ghrelin-mediated appetite, resulting in relatively low BMI, which contributes to the delayed onset of puberty. Furthermore, delayed puberty is observed in clinical conditions associated with low IGF1, suggesting that IGF1 also exerts stimulatory, synergistic, or permissive effects on the onset of puberty. Thus, low IGF1 levels due to a decrease in GH secretion caused by GHSR1a insufficiency may also negatively modulate the timing of puberty onset. The present study was designed to determine the level of sexual maturation rating (SMR) and the concentrations of reproductive hormones, luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone (T) and estradiol (E2) in normal and short stature children having GHSR1a mutations. SMR including penile length, testicular volume, pubic hair and facial hair stage for boys ($n = 21$) and breast development and pubic hair stage for girls ($n = 14$) having short stature between the ages of 2 and 14 years was measured and compared with age matched control subjects ($n = 50$). The stage of pubertal development was assessed by using the criteria described by Tanner and Whitehouse. ELISA was used for analysis of plasma LH and E2 and specific RIA systems were used for analysis of plasma FSH and T. Data were analyzed using Student's t test, ANOVA and Pearson correlation r. The results revealed a significant difference between mean penile length and testicular volume of normal boys and short stature boys at early and mid-pubertal stages. Similarly, breast development was significantly delayed in short stature girls than normal girls at early and mid-puberty. Pubic hair development in short stature girls and pubic and facial hair development in short stature boys were also significantly delayed as compared to normal girls and boys at early and mid-puberty. The levels of LH, FSH, T and E2 were higher in normal than short stature boys and girls and a significant difference was witnessed at early and mid-pubertal stages. In conclusion, SMR was higher in normal children as compared to short

stature children. Furthermore, the concentrations of gonadotropins LH and FSH and sex steroids, T and E2 were significantly higher in normal children as compared to short stature children.

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OC4.6

The potential role of androgens as early determinants of body composition and metabolic health.

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Introduction
Even in healthy men, androgen levels start decreasing from early adulthood and these decreases are more pronounced in men with an increasing body mass index (BMI). It is, however, unclear to what extent changes in other indices of body composition and metabolic health are associated with changes in sex steroid exposure in healthy men over time.
Objective
Investigating longitudinal changes in body composition and metabolic health in relation to sex steroid levels in young adult men.
Methods
Longitudinal, population-based, observational study: 999 healthy men aged 24–46 years of whom 691 were re-evaluated after 12 ± 2 years. Serum sex hormone binding globulin (SHBG) and insulin levels were measured using immuno-assay, glucose by hexokinase method, testosterone (T) using LC-MS/MS, free T (cFT) and homeostasis model for insulin resistance (HOMA-IR) calculated. Body composition was determined using DXA (Hologic) at the whole body minus head. Fat (FM%) and lean mass (LM%) percentages were calculated. Mixed models were used for statistical analyses. All models were adjusted for baseline age.
Results
Baseline age was 34 ± 6 years. Mean BMI increased by 4.7% (25.1 kg/m^2 vs 26.3 kg/m^2). Mean T levels decreased by 14.2% (20.8 nmol/l vs 17.8 nmol/l), cFT by 19.1% (392 pmol/l vs 317 pmol/l) and SHBG increased by 3.0% (39.8 nmol/l vs 41.0 nmol/l) (all $P < 0.001$). FM% increased by 10.2% (19.6% vs 21.6%; $P < 0.001$), especially at the trunk (8.1 kg vs 9.6 kg; $P < 0.001$). LM% decreased by 1.8% (77.3% vs 75.4%; $P < 0.001$). HOMA-IR increased from 1.7 to 2.2 ($P < 0.001$). At baseline, total T, cFT and SHBG were inversely associated with truncal fat, FM% and HOMA-IR and positively associated with LM% (all $P < 0.001$). Longitudinally, changes in sex steroids were not associated with changes in either FM% and LM%. However, changes in total T, cFT and SHBG were inversely associated with changes in truncal fat and HOMA-IR (all $P < 0.018$).
Conclusion
In healthy young men, adiposity and insulin resistance increased while LM% decreased over a period of 12 years. We found that a stronger decline in both total and free T levels was associated with stronger increases in truncal adiposity and insulin resistance. Our findings suggest a direct role of sex steroids as determinants of metabolic state. Whether these findings result from residual confounding or are mediated by the intriguing relationship between SHBG levels and metabolic health remains to be established. Moreover, the possibility of a reverse causality between changes in androgen levels and metabolic state should be taken into account.

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Thyroid

OC5.1

Identification of iodothyronine deiodinase 2 inhibitors among FDA-approved drug library using high throughput screening

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Background
Development and application of novel drugs frequently fail due to adverse changes of TH-levels or thyroid histology in animal experiments. Such effects potentially arise from interference with thyroid gland function or key regulators of local thyroid hormone (TH) transport, metabolism and action. Deiodinases are key enzymes in TH in-/activation, with impact on development, cell differentiation and energy metabolism among other physiological processes, and have therefore been identified as molecular initiating events (MIE) in the assessment of chemicals for endocrine disruption.
Method
A robust semi-automatic 384-well High Throughput Screening (HTS) platform was developed and now employed for screening substances interfering with DIO2 activity, utilizing the non-radioactive Sandell-Kolthoff (SK) reaction to determine DIO-depending iodide release. In an initial HTS using recombinantly expressed human DIO2, 1759 components from a FDA-approved drug library were tested at a single concentration of 20 μM.
Results
At the given concentration, 1.1% of the tested drugs showed DIO2 inhibition by >25% and 0.2 % an inhibition by >€50%. 11.5% of the screened drugs had characteristics of either potential DIO2 activators or SK interference. Among the inactive compounds were some well-known DIO1-selective inhibitors such as PTU or Genistein, a finding which supports the specific and predictive quality of this HTS approach.
Conclusion & outlook
In this pilot study, we were able to demonstrate that even a library of FDA-approved drugs does contain compounds that may exert adverse effects on TH metabolism by DIO2 inhibition. In perspective, such compound should be revised regarding potential side effects that might appear from such interference, e.g. abnormal patterning of TH metabolites in serum or defects that might appear from local suppression of DIO2 activity. While this screening setup is appropriate to detect endocrine disruptors (ED) affecting DIO2 activity, it does, on the other hand, also opens the perspective to identify highly potent drug candidates and reference compounds for ED research. In summary, this study represents a major success in the development of an in vitro strategy to identify endocrine disruptors, characterized by inhibition of deiodinases. The established 384-well assay protocol also provides the basis for further testing of large chemical libraries against DIO2, and can be adapted to other deiodinating enzymes modulating TH availability, e.g. DIO1 or dehalogenase (IYD). Furthermore, generated data pools provide the basis to select Quantitative Structure Activity Relationship training sets to develop predictive in silico tools for preselection and toxicological assessment.
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OC5.2

Use of thyroid hormones in hypothyroid and euthyroid patients: A 2020 THESIS* questionnaire survey of members of the Danish Endocrine Society (*Treatment of hypothyroidism in europe by specialists: An international survey)

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Purpose
The standard treatment of hypothyroidism is levothyroxine (LT4), which is available as tablets or soft-gel capsules in Denmark. This study aimed to investigate Danish endocrinologists' use of thyroid hormones in hypothyroid and euthyroid patients.
Method
An e-mail with an invitation to participate in an online survey investigating practices about substitution with thyroid hormones was sent to all members of the Danish Endocrine Society (DES) on 27th February 2020. The initial e-mail was followed by three reminders between February and May 2020, and where after it was closed. Survey responses were collected and electronically stored by the Lime-Survey service.

Results
Out of 488 eligible DES members, a total of 152 (31.2%) respondents were included in the analysis. The majority (94.1%) of responding DES members use LT4 as the treatment of choice. Other treatment options for hypothyroidism are also used, as 58.6% prescribe combination therapy with liothyronine (LT3)+LT4 in their clinical practice. LT4+LT3 combination is preferred in patients with persistent symptoms of hypothyroidism despite biochemical euthyroidism on LT4 treatment. Over half of the respondents answered that thyroid hormone therapy is never indicated for euthyroid patients, but 42.1% will consider it for euthyroid infertile women with high antibody levels. In various conditions that could interfere with the absorption of LT4, most responding Danish endocrinologists prefer tablets to soft-gel capsules or liquid LT4 and do not expect a significant difference when switching from one type of tablet formulation to another. The Danish endocrinologists are nearly equally divided into two categories regarding supplementation; 57 (37.5%) answered that supplementation with selenium or iodine can be used if requested by the patient, while 62 (40.8%) stated that such supplementation should never be used.
Conclusion
The treatment of choice for hypothyroidism is LT4. Combination therapy with LT4+LT3 is considered for patients with persistent symptoms. Even in the presence of conditions affecting bioavailability, responding Danish endocrinologists prefer LT4 tablets rather than newer LT4 formulations, such as soft-gel capsules.

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OC5.3

Derivation of thyroid progenitors from human induced pluripotent stem cells

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Despite the availability of synthetic thyroid hormone for therapeutic use, a significant number of patients with hypothyroidism do not feel well on replacement doses of thyroid hormones suggesting that better individualized therapy is needed. For this reason, hypothyroidism resulting from congenital lack of functional thyrocytes, surgical tissue removal, or gland ablation, represents a particularly attractive endocrine disease target that may be conceivably cured by transplantation of long-lived functional thyroid progenitors or mature follicular epithelial cells, provided a source of autologous cells can be generated and a variety of technical or biological challenges can be surmounted. To generate thyroid follicular progenitors from human induced pluripotent stem cells (hiPSCs), we sought to develop a directed differentiation approach by activating or inhibiting endogenous developmental signaling pathways previously identified in the mouse. To facilitate tracking and purification of candidate human thyroid progenitors, we engineered a hiPSC-line carrying a tdTomato reporter targeted to the PAX8 locus and a GFP reporter targeted to the NKX2–1 locus. We adapted our published in vitro differentiation protocol previously used to differentiate mouse PSCs into endoderm, foregut endoderm and then thyroid progenitors and observed tdTomato/GFP co-expressing cells first emerging from our hiPSC line by day 12 of culture and persisting for at least 2 months of further culture in thyroid maturation media, supplemented with TSH. We profiled all cells (regardless of fluorochrome expression) deriving from hiPSCs using this protocol by single cell RNA sequencing >6.000 cells captured on days 12 and 29 of *in vitro* differentiation. At day 12 of differentiation, tdTomato/GFP co-expression was observed in 17% of all cells and these cells appeared to be early thyroid follicular progenitors as they uniquely co-expressed the tetrad of thyroid lineage selective transcription factors, NKX2–1, PAX8, FOXE1, and HHEX, and already expressed thyroid maturation markers, TG or TPO. By day 29 tdTomato+/GFP+ cells represented 72.1% of all cells and had upregulated TG, TSHR, NIS and TPO expression in addition to the previously described four thyroid lineage markers, suggesting time dependent differentiation and maturation of thyroid follicular epithelial cells. Thus, we have employed a novel hiPSC line to optimize a protocol able to generate human thyroid progenitors and mature follicular epithelial cells, representing a purifiable source of human thyroid lineage cells whose functional and thyroid reconstituting potential can be tested in vivo in animal models of hypothyroidism.

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OC5.4

The ablation of thyroid nodule's afferent arteries before radiofrequency ablation: preliminary data.

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Induced radiofrequency thermal ablation is cytoreductive treatment of symptomatic benign thyroid nodules, metastatic and recurrent thyroid tumors and papillary thyroid microcarcinomas. It is a safe and effective alternative to surgery and it allows to obtain satisfactory results in terms of volumetric reduction of the nodule with significant improvement in the quality of life. The trans-isthmic approach and the moving shot technique are the two basic techniques; however, an advanced technique, as artery-first feeding radiofrequency ablation has been developed and validated. We have prospectively included 29 consecutive patients who have undergone radiofrequency ablation (Group A) or artery–first vRFA (Group B). All included patients had a diagnosis of benign nodular goiter and they were undergoing to a single session of radiofrequency ablation. All patients followed a follow-up program at 1 month, 3 months and 6 months. Continuous variables (age, TSH value, basal volume of nodule, used Joule, time in second of the procedure, nodules' volume at 1-, 3–and 6–months of follow-up and percentage of volume reduction at 1-, 3–and 6–months of follow-up) were described as mean, standard deviation and range, while categorical variables (gender, nodule structure and nodule vascularization) were described as number of cases and percentage. Independent samples t-test were performed to compare the continuous variables. A Test of Proportions was applied to the categorical variables. The Fisher's exact test was used to analyze the gender. Statistical significance was considered in case of P-value < 0.05. Solid structure and spongiform structure showed statistic differences with p-values of 0.022 and 0.023 respectively between two groups. The percentage of reduction at 1 month did not show a significant difference between two groups; instead, the percentage of volume reduction was decreased mostly in the Group B at 3 months and 6 months of follow-up with a p-value of 0.003 and 0.013, respectively. The Joules/energy used showed a statistically significant difference (P –value = 0.05), more energy must be used in vascular radiofrequency ablation. These data allow us to hypothesize that vRFA may improve the effectiveness of the procedure, allowing for a reduction in volume more quickly. They were preliminary but promising results, clearly a larger series of cases and prolonged follow-up are needed to clarify and confirm our observations.

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OC5.5

Role of miR-139–5p in radioiodine-refractory thyroid cancers

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Radioiodide 131I (RAI) is the therapy of choice for radioiodine-avid differentiated thyroid cancer (DTC). However, 5–15% of DTC patients become RAI refractory (RAIR), and the 10-year survival rate for metastatic disease decreases to 10%. The failure of RAI response is mainly due to the loss of thyroid differentiation, that leads to the loss of expression/function of components of iodide metabolism, first of all the Na/I symporter (NIS). The

finding that the MAPK pathway is involved in this process suggested that the protein kinase inhibitors therapy may be effective for redifferentiation in the treatment of RAIR patients. However, nowadays, fully efficient treatments for advanced thyroid cancer patients are still missed. Different approaches aimed to re-activate radioiodine uptake in RAIR tumors have been trying, including the use of a miRNA-based strategy. Although MiRNAs have been shown to be useful predictive biomarkers and targets of therapeutic options in thyroid cancers, only few studies investigated their role in response to RAI therapy. We investigated the miRNA signature associated with RAI refractory DTC in order to identify novel biomarkers that will be potential target for a redifferentiation therapy. Using the real-time PCR we analysed the expression of 734 miRNA in 26 DTC tissues, 13 responsive (R) and 13 not-responsive (NR) to RAI therapy. By comparing both groups we found a statistically significant dysregulation of 15 miRNAs analysed: 14 miRNAs were upregulated and only one (miR-139–5p), was down-regulated in RAI refractory tumors. Then, we performed in-vitro experiments to investigate the role of miR-139–5p in the iodine uptake metabolism. Using two primary cell lines and five immortalized cell lines, we overexpressed miR-139–5p, and we analysed the transcript and protein levels of NIS. Moreover, we investigate the NIS activation status through the iodine uptake assay and the subcellular protein localization. The findings of a higher intracellular iodine level and of an increase in cells' membrane protein localization in miR-139–5p overexpressing cells, supported the effect of such miRNA in increasing NIS function. Although the downregulation of miR-139–5p expression has already been found to correlate with the thyroid cancer's aggressiveness, this is the first study aimed to investigate its role in the iodine uptake metabolism. However further studies are necessary to confirm the possible role of miR-139–5p as therapeutic target for RAI refractory DTCs.

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OC5.6

Comparison of Simultaneous calcitonin washout and cytology procedure success in recurrent medullary thyroid cancer

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Background

Medullary thyroid carcinoma (MTC) accounts for 3–5% of thyroid cancers, but recurrent MTC, manifested by elevated calcitonin levels, is a common problem. We aimed to perform a calcitonin washout procedure simultaneously with cytological evaluation and compare their effectiveness to diagnose metastatic lymph nodes.

Methods

94 patients diagnosed with MTC were recruited from our institutional database from 2010–2021. The analysis of calcitonin washout procedure (CTW) and fine-needle aspiration (FNA) cytology for metastatic lymph nodes were recorded for recurrent MTC. Only one cytologist performed the cytological examination. The cut-off level above ≥100 pg/ml was determined as a pathologic lymph node. The demographic features, mean age at diagnosis, laboratory analysis of preoperative and postoperative calcitonin and Carcinoembryonic antigen (CEA), cytopathological data were all collected.

Results

The median age at diagnosis was 40.7 ± 17 years; the mean CTW level was 1800 (142–9000) pg/ml, the mean preoperative CT level was 620 (54–9000) pg/ml, and the mean CEA level was 9.4 (0.5–1958). Out of 94 patients, 32 were recurrent cases. CTW and FNA procedures were applied for 44 suspicious lymph nodes. 43 cytological examination were done for these lymph nodes. The FNA results' distribution was 4.6% reactive lymph node(n:2), 11.6% non-diagnostic(n:5), 81.3% (n:35) MTC and 2.32% (n:1) suspicious for malignancy. The two reactive lymph node cytology had CTW levels of 800 pg/ml and 2942 pg/ml, so they were operated on and diagnosed as MTC. 44 positive CTW procedures were applied, and 42 of them were compatible with MTC. The false positive lymph nodes were; a reactive lymph node with a CTW result of 221 pg/ml and a cytologically non-diagnostic lymph node with a CTW result of 800 pg/ml.

Conclusion

Recurrent MTC is a progressive disease in half of the cases, but it can be handled with correct diagnostic methods and surgery. CTW procedure is an easy and quick laboratory test as compared with cytological evaluation. According to our results, CTW measurements were also more accurate than cytological examination when defining pathological lymph nodes. CTW evaluation was mainly evaluated for either thyroid nodules alone or combined with neck lymph nodes. This is the first and largest study evaluating the metastatic lymph nodes of MTC with CTW and cytology together.

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Calcium and Bone

OC6.1

Osteocalcin actives GPRC6A and calcium-sensing receptor modulating intracellular signaling pathways, cell cycle genes, and apoptosis in human parathyroid tumor cells

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Parathyroid glands regulate bone metabolism through PTH, while bone modulates parathyroid function through calcium and FGF23. We tested the hypothesis that the matrix protein osteocalcin (OC), secreted by osteoblasts, may modulate parathyroid function. In human parathyroid cells derived from adenomas (PAds), incubation with g-carboxylated OC (GlaOC) or undercarboxylated OC (GluOC) modulated the intracellular signaling pathways: both GlaOC and GluOC inhibited the basal phosphorylated ERK/total ERK ratio (pERK/ERK) and increased the basal phosphorylated AKT/total AKT ratio (pAKT/AKT) and active b-catenin levels. Moreover, GlaOC and GluOC modulated the expression of parathyroid genes: GlaOC increased the expression levels of the *PTH* gene, modulated the expression of genes involved in cell cycle, increasing *CCND1* and reducing *CDKN1B*/*p27* and *TP73*, and increased the expression of *CASR*. GluOC also stimulated the transcription of *PTH*, while it did not exert any effect on the other genes, except by inhibiting *MEN1* expression. Of note, GlaOC and GluOC treatments reduced the proportion of apoptotic cells induced by incubation with staurosporin. OC acts through the putative membrane receptor GPRC6A, whose transcripts and proteins were variably detected in human PAds and did not correlate with the expression of CASR. Immunohistochemistry showed specific GPRC6A cytoplasmic staining in some cells and membrane staining in other cells scattered throughout the parenchyma, both in normal and tumor parathyroids. As GPRC6A and CASR share high homology, OC may activate both the receptors. Reducing the CASR expression by treating PAds-derived cells with *CASR* siRNA, we observed that GlaOC and GluOC modulated the ERK pathway mainly through GPRC6A activation, while CASR activation was involved in the modulation of the AKT and b-catenin pathways. Using HEK293A cells transfected with GPRC6A and with CASR, we further dissected the effects of GlaOC and GluOC on the signalling pathways in presence of different extracellular calcium concentrations ($[Ca^{2+}]_o$), finding that GlaOC and GluOC can activate CASR, that $[Ca^{2+}]_o$ is needed to activate CASR by GlaOC and GluOC, and that GlaOC activates GPRC6A also in calcium-free medium as well as in presence of 5.0 mM $[Ca^{2+}]_o$ but exerting opposite effects with respect that observed in presence of 1.5 mM $[Ca^{2+}]_o$.

Conclusion

OC can be added to the bone-parathyroid cross-talk; it may modulate the CASR sensitivity to $[Ca^{2+}]_o$ of the parathyroid cells, representing a target for potential medical treatment of parathyroid disorders.

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OC6.2

AAV liver gene therapy-mediated inhibition of FGF23 signaling as a therapeutic strategy for X-linked hypophosphatemia

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Adeno-associated virus (AAV) gene therapy reached the maturity and a liver-targeting approach is currently used as a replacement treatment for rare hepatic and muscular diseases. X-linked hypophosphatemia (XLH) is a rare disease associated with hyperfunction of fibroblast growth factor 23 (FGF23) in bone and characterized by severe skeletal deformities and short stature. The current medical therapies for XLH requires life-long repeated treatment presenting major limitations as an inadequate treatment compliance due to i) multiple doses per day and severe long-term side effects for the conventional treatment (based on phosphate supplementation and active vitamin D analogs) or ii) an extremely expensive cost for the health care system for the monoclonal anti-FGF23 antibody therapeutic. Here we studied the hypothesis whether the liver-targeting approach could be used as a therapeutic modality for rare diseases associated with hyperfunction of growth factors as XLH, treating this bone pathology with a single injection. We elaborated a novel therapeutic approach for XLH based on a single injection of AAV gene therapy aiming to stimulate the production of a FGF23 neutralizing factor (cFGF23) in the liver in a murine model of XLH, the Hyp-Duk mouse. We demonstrated that one single injection of AAV-cFGF23 treatment led to restoration of impaired skeletal phenotype, and to significant reduction of osteomalacia, bone and joint alterations in Hyp-Duk mice. This provides a proof-of-concept that the liver-targeting approach represents an adequate modality to rescue the growth factor's hyperfunction, thus opening the new perspectives on the treatment of skeletal diseases by gene therapy.

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OC6.3

Bone material strength index is altered in patients with Cushing's syndrome even after long-term remission

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Background
Endogenous Cushing's syndrome (CS) is detrimental to bone. The skeletal complications are characterized by decreased bone formation and increased bone resorption, resulting in decreased bone mineral density (BMD) and an increased risk of fractures at time of diagnosis. After remission of the disease, BMD improves towards normal values but fracture rate remains elevated. Therefore, components of bone quality other than BMD, such as bone material properties, must be affected in CS, even after remission. Bone material properties can be assessed by Impact Microindentation (IMI) in a minimally-invasive way.
Aim
To evaluate bone material properties using IMI in patients with CS in remission.
Methods
In this cross-sectional study, 57 consecutive patients (45 women), 16 with prevalent fragility fractures, and 57 controls matched for age, sex, and BMD (45 women), 25 with fragility fractures, were included. Bone material strength index (BMSi) was measured by IMI using the OsteoProbe device at the midshaft of the tibia after applying local anesthetic. In addition, laboratory investigation, BMD, and vertebral fracture assessment were performed. Remission was defined according to the Endocrine Society Clinical Practice guidelines.
Results
Mean age of the patients was 54.5 ± 12.5 years and 55.2 ± 12.4 years in controls, (P = 0.70). The main origin of hypercortisolism was pituitary in 47 patients, followed by adrenal (n = 8) and ectopic origin (n = 2). Median time of remission was 6 years (IQR 3 to 15 years). BMD was comparable in patients and controls at the lumbar spine (0.98 ± 0.16 g/cm^2 vs 0.95 ± 0.11 g/cm^2, P = 0.49) and the femoral neck (0.75 ± 0.12 g/cm^2 vs 0.74 ± 0.12 g/cm^2, P = 0.73). However, BMSi was significantly lower in patients compared to controls (76.5 ± 6.9 vs 81.4 ± 5.1, P < 0.001). In patients, BMSi was negatively correlated with BMI (r = -0.51, P < 0.001), but not related to the presence of fragility fractures, dependence, duration and dosage of hydrocortisone suppletion, or other pituitary failure. In controls, BMSi was not related to BMI, but significantly lower in those with fragility fractures compared to those without fragility fractures (78.1 ± 4.5 vs 84.0 ± 4.1, P < 0.001).
Conclusion
BMSi was significantly lower in CS patients in remission than in matched controls, independently of BMD. Our findings indicate that bone material properties are permanently altered in patients with endogenous Cushing's syndrome even after long-term remission, which may contribute for their persisting increased fracture risk. The IMI technique might be a valuable additional tool in the evaluation of bone fragility in these patients.

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OC6.4

Bisphosphonates after Denosumab withdrawal reduce the vertebral fractures incidence

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Objective
Several studies showed that patients discontinuing denosumab (Dmab) may experience bone loss and incident vertebral fractures (VFx) due to a rebound bone turnover increase, suggesting the need of anti-resorptive (i.e. bisphosphonate BPs) therapy to mitigate this occurrence. However, the morphometric VFx (morphoVFx) incidence after Dmab discontinuation is unknown and scarce data are available about the BPs effect on BMD changes and Fx risk in this setting.
Methods
In this monocentric retrospective study, 120 patients (111 females) discontinuing Dmab (mean injections n. 6.2 ± 2.7) were included. After Dmab discontinuation, 19 patients have not been treated with BPs (Not-treated Group, 16 females, age 63.5 ± 15.0 years) and 101 patients have been treated (Treated Group, 95 females, age 70.0 ± 10.6 years) with BPs (28 alendronate, 73 zoledronate single infusion). We evaluated the BMD variation (Δ) and the incidence of both clinical VFx and morphoVFx in Treated Group and Non-treated Group.
Results
After Dmab discontinuation the mean ΔBMD at lumbar spine (LS), femoral neck (FN) and total hip (TH) were not different between the Treated Group (-2.7 ± 6.5%, -3.0 ± 7.3% and 2.3 ± 0.8%, respectively) and Not-Treated Group (-0.8 ± 5.8%, -5.1 ± 6.7% and -0.2 ± 7.7%, respectively, P = ns for all comparisons). The number of patients with BMD at TH lower than prior to Dmab administration was lower in Treated Group (8.9%) than in Not Treated Group (35.7%, P = 0.046), while no differences were found between the two groups at LS (12.9% and 26.3%, respectively) and FN (17.8% and 21.1%, respectively, P = ns for all comparisons). Patients in Treated Group had a lower VFx incidence (n = 6, 5.9%, 3 clinical, 3 morphoVFx) than patients in Not-treated Group (n = 4, 21.1%, 4 clinical, 3 multiple), respectively, in spite of a comparable fracture risk profile at the time of Dmab initiation. The VFx incidence was independently associated with the lack of BPs treatment (odds ratio 16.7, 95% confidence interval 1.8–142.8, P = 0.013) but not with number of Dmab injections, age, discontinuation of BPs administration at least 12 months before Dmab initiation, BMD at Dmab withdrawal and multiple VFx prevalence at Dmab initiation.
Conclusions
The Dmab withdrawal is associated with an increased risk of clinical VFx. The treatment with oral BPs or with a single zoledronate infusion reduces but not abolishes the increased VFx risk after Dmab withdrawal.

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OC6.5

Safety, tolerability and pharmacodynamics of AZP-3601, a novel long-acting PTH analog, in healthy adults: Data from a randomized, double-blind, placebo-controlled phase 1 study

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Hypoparathyroidism is a rare disease characterized by a deficiency in parathyroid hormone (PTH) that results in hypocalcemia and hyperphosphatemia. Current treatment approaches, including high dose oral calcium and active vitamin D, as well as recombinant human PTH (1–84), do not provide adequate or consistent control of either serum calcium or clinical symptoms over a full 24-hour period. AZP-3601 is a novel 36 amino-acid PTH analog that has been designed to potently bind to the R^0 conformation of the PTH1 receptor, which results in prolonged signaling responses in vitro and prolonged calcemic responses in animals despite having a short circulating half-life. A Phase 1 double-blind, placebo-controlled, single and multiple ascending dose study is being conducted to evaluate the safety, tolerability and pharmacodynamics of AZP-3601 in healthy adults. Here we report data from the first cohorts of the single ascending dose portion of the study. Sequential cohorts of 4 (cohort 1) to 8 (cohort 2 to 4) healthy male subjects aged 18–60 years, with a body mass index of 19–28 kg/m^2, were assigned to receive 5, 10, 20 or 40 μg of AZP-3601 or placebo at a ratio of 3:1. The study drug was administered in the morning by subcutaneous injection in the abdominal wall and was well tolerated with no remarkable adverse events. As compared with placebo controls, AZP-3601 treatment produced a clear, dose-dependent increase in mean albumin-adjusted serum calcium values from baseline. The normal physiological diurnal variation of albumin-adjusted serum calcium was gradually attenuated with 5 and 10 μg AZP-3601, and was completely eliminated with 20 μg. With the dose of 40 μg AZP-3601, mean albumin-adjusted serum calcium values were significantly increased but stayed within normal laboratory range and remained elevated through at least 24 hours post-administration. We observed a dose-dependent decrease in mean endogenous serum PTH that was significantly correlated with the concomitant increase in mean serum calcium. Data from these 4 cohorts of subjects provide initial evidence of the pharmacodynamic effect of AZP-3601 in healthy humans characterized by a sustained calcemic response for at least 24 hours following a single administration. The study is ongoing and updates will be reported.

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OC6.6

TransCon PTH as a potential hormone replacement therapy for patients with hypoparathyroidism: PaTH forward open-label extension trial week 26 results

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Background
Hypoparathyroidism is characterized by insufficient levels of parathyroid hormone (PTH), resulting in hypocalcemia, hyperphosphatemia, hypercalciuria, and a reduced quality of life (QoL). PTH replacement therapy should restore physiologic levels of PTH and restore downstream physiologic levels of calcitriol, promoting independence from Ca and active vitamin D supplements and normalization of QoL. TransCon PTH is an investigational long-acting prodrug of PTH(1–34) for the treatment of hypoparathyroidism. Week 26 results from the PaTH Forward open-label extension (OLE) Trial in adult patients with hypoparathyroidism are reported.
Methods
Subjects received fixed doses of TransCon PTH 15, 18, or 21 μg PTH(1–34)/day or placebo for 4 weeks, followed by an OLE period during which TransCon PTH dose was titrated (6–30 μg PTH[1–34]/day) with the goal to maintain normocalcemia. Safety and efficacy endpoints were evaluated at predefined timepoints over the OLE. Efficacy end points evaluated at Week 26 included intake of active vitamin D and calcium supplements, 24-hour uCa, sCa, sP, and CaxP. QoL was assessed by the SF-36 and the Hypoparathyroidism Patient Experience Scales (HPES).
Results
All 59 subjects completed the initial 4-week period and continued in the OLE; 58 subjects continue in the OLE beyond 6 months (1 withdrew unrelated to safety or efficacy). By Week 26, TransCon PTH enabled 91% of subjects to achieve independence from SoC (active vitamin D = 0 mg/day and calcium ≤ 500 mg/day) and 76% of subjects to achieve complete independence from SoC (active vitamin D = 0 mg/day and calcium = 0 mg/day). Mean 24-hour uCa decreased from a baseline mean of 415 mg/24 h to 178 mg/24 h by Week 26 (n = 44) while maintaining sCa and reducing sP and CaxP to fall within the normal range. By Week 26, the mean scores for all SF-36 summary and domains increased from below normal at baseline to within the normal range. The HPES Symptom and Impact scores decreased through 26 weeks for TransCon PTH and placebo subjects switching to TransCon PTH (lower scores are associated with less symptoms/impact). TransCon PTH continued to be well-tolerated with no treatment-related serious or severe adverse events.
Conclusions
Through Week 26 of the PaTH Forward OLE Trial, TransCon PTH enabled independence from active vitamin D and calcium supplements for most subjects while maintaining normal sCa, sP, uCa, CaxP, and demonstrating enhanced QoL. These results support TransCon PTH as a potential hormone replacement therapy for adults with hypoparathyroidism.

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Diabetes, Obesity, Metabolism and Nutrition

OC7.1

Circulating concentrations of TMAO is associated with all-cause mortality in subjects with Non-alcoholic fatty liver disease. Results from a dutch prospective cohort

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Objective
Due to the increasing prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD), it has become a global health challenge by being the most common cause of chronic liver disease. Recently, the microbiota has been linked to NAFLD, via altered bile acid and lipid metabolism. Whether serum Trimethylamine-N-oxide (TMAO), a gut microbiota-dependent metabolite, is associated with NAFLD and NAFLD health outcomes remains unclear. The aim was to investigate the association of TMAO with NAFLD and to assess the extent to which the association of TMAO with all-cause mortality is dependent on the presence of NAFLD in the general population.
Methods
We included 6415 participants enrolled in the PREVEND (Prevention of Renal and Vascular End-stage Disease) general population-based cohort study. TMAO was measured by Nuclear Magnetic Resonance Spectroscopy. Cox proportional-hazards regression analyses, adjusted for traditional risk factors, were performed to study the association of TMAO with all-cause mortality in subjects with and without NAFLD, determined by Fatty Liver Index (FLI) ≥ 60.
Results
A total of 3694 had a FLI score < 60, and 1598 ≥ 60. During a median follow-up of 8.2 years, 307 participants died, of whom 133 were classified with NAFLD. TMAO concentrations were positively associated with FLI at baseline (Std β 0.08, 95% CI 0.05; 0.11, P < 0.001). Cox regression analyses revealed that TMAO was associated with increased risk of all-cause mortality in crude analysis (Hazard Ratio (HR), 2.55, 95% CI 1.60, 4.05, P < 0.001) and after full adjustment for age, sex, blood pressure, smoking status, alcohol consumption, cancer history, type 2 diabetes, use of lipid lowering medication, total cholesterol, HDL-cholesterol, glucose, albuminuria and eGFR ($_{adj}$HR 1.90, 95% CI 1.18, 3.04, P = 0.008), in subjects with NAFLD.

Such an association was not present in subjects without NAFLD, neither in the crude model (HR 1.14, 95% CI 0.81,1.71, $P = 0.39$), nor in the fully adjusted model ($_{adj}$HR 0.95, 95% CI 0.65, 1.39, $P = 0.78$).
Conclusion
This prospective study revealed that plasma concentrations of TMAO were associated with all-cause mortality in subjects with NAFLD independently of traditional risk factors.

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OC7.2

Hepatocyte GH signaling regulates carbohydrate processing in a STAT5b-independent manner

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In the healthy liver, GH signals through multiple pathways to modulate hepatic function, with JAK2/STAT5b required to maintain circulating IGF1 levels. It has been previously reported that mice with developmental knockout of hepatocyte GHR, JAK2 or STAT5 develop steatosis associated with glucose intolerance, systemic insulin resistance and white adipose tissue (WAT) lipolysis. These changes are thought to be secondary to increased circulating GH, due to loss of IGF1 negative feedback. However, we have previously reported that mice with adult-onset hepatocyte-specific GHR knockdown (aHepGHRkd), that present with reduced IGF1 and elevated GH in the circulation, develop steatosis associated with enhanced *de novo* lipogenesis (DNL), without major alterations in systemic metabolic function. Importantly, steatosis and enhanced DNL are still evident in aHepGHRkd mice after normalization of GH by IGF1 treatment, indicating GH acts directly on the hepatocyte to control fat accumulation. We have extended our investigations to determine if loss of GHR-mediated STAT5b is the primary cause of sustained steatosis/DNL in the aHepGHRkd model. Specifically, male aHepGHRkd mice were treated with a hepatocyte-specific vector expressing constitutively active mouse STAT5b (AAV8-TBGp-STAT5b^{CA}) and compared to GHR-intact mice [treated with control vector (Null)] 0010 h after 0700 h food withdrawal (post-absorptive state). STAT5b normalized IGF1 and GH levels in aHepGHRkd mice to that observed in GHR-intact controls and reduced, but did not completely normalize hepatic lipid content and DNL. Hepatic protein levels of glucokinase (GCK), fructokinase (KHK) and carbohydrate response element binding protein (ChREBP) were increased in aHepGHRkd mice with or without STAT5b reconstitution, suggesting the GHR signals independent of STAT5b, to control early events in hepatocyte carbohydrate processing. RNAseq analysis revealed 1278 hepatic genes were altered by aHepGHRkd. Of those genes, 942 were STAT5b-independent and included *Gck* and *Khk*, as well as liver pyruvate kinase (*Pklr*) and the glycogen branching enzyme (*Gbe1*). Taken together, these suggest GH acts directly on the hepatocyte, in a STAT5b-independent manner, to suppress carbohydrate processing. These actions may limit substrates for DNL and prevent steatosis. Additional studies in fed conditions are underway to test this hypothesis.

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OC7.3

Long-term glucocorticoids are associated with increased odds of metabolic syndrome after an intensive combined lifestyle intervention

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Background
Long-term glucocorticoids, as measured in scalp hair (HairGC), are associated with obesity and the metabolic syndrome (MetS). It is not known whether this represents a state of obesity or whether chronic hypercortisolism may influence the course or reversibility of obesity. In this study we longitudinally examine the relation between HairGC concentrations and metabolic syndrome parameters in patients with obesity who participate in a 1.5 year intensive combined lifestyle intervention (CLI).
Methods
A total of 99 adults with a body-mass index (BMI) ≥30 kg/m^2 (mean age 42, 75% females) were enrolled in the CLI at our academic obesity center. They received guidance on a healthy eating pattern, exercise and psychoeducation. Anthropometric measures, metabolic parameters (blood) and HairGC were assessed at baseline and at the end of the program (75 weeks). A hair sample of 3 cm closest to the scalp was cut and analyzed for cortisol (HairF) and cortisone (HairE) concentrations using liquid chromatography-mass spectrometry (LC/MS). Covariates for regression analyses were age, sex, ethnicity, smoking, alcohol intake, use of antidepressant and glucocorticoid drugs.
Results
Mean weight, BMI and waist circumference decreased from 117 kg, 39.9 kg/m^2, and 114 cm at baseline to 111 kg, 37.8 kg/m^2, and 107 cm after 75 weeks (all $P < 0.001$). Median HairF and HairE decreased from 3.60 pg/mg and 11.46 pg/mg at baseline to 2.37 and 9.36 pg/mg($P = 0.004$ and $P = 0.604$ respectively). Median insulin levels and HOMA-IR significantly decreased from 140 pmol/l and 5.03 at baseline to 118 pmol/l and 4.31 after 75 weeks ($P = 0.004$, and $P = 0.002$ respectively). Baseline HairGC were not related to anthropometrics or the presence of MetS at baseline. However, baseline HairF was a significant predictor for the presence of MetS at 75 weeks (OR per quartile increase in baseline HairF was 1.78 (95% CI: 0.97–3.27), OR for the highest HairF quartile vs HairF in quartile 1–3 was 8.05 (95% CI: 1.64–39.55)). Baseline HairE was not associated with higher odds of MetS at 75 weeks.
Discussion/Conclusion
High baseline hair cortisol concentrations are associated with higher odds for no remission of the metabolic syndrome after an intensive combined lifestyle intervention. This may indicate that high baseline hair cortisol concentration may impair cardiometabolic improvement by a lifestyle intervention, although causality is yet to be proven. Further studies should assess whether such cases require an accelerated intensification of obesity treatment, e.g. by adding anti-obesity medicine to the lifestyle intervention.

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OC7.4

Liver GPR55 regulates NAFLD progression from steatosis to fibrosis

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Background and aims
G protein-coupled receptor 55 (GPR55) is a putative cannabinoid receptor, and l-α-lysophosphatidylinositol (LPI) is its only known endogenous ligand. Although GPR55 has been linked to energy homeostasis in different organs, its specific role in lipid metabolism in the liver and its contribution to the pathophysiology of non-alcoholic fatty liver disease (NAFLD) remains unknown.
Method
We measured (1) GPR55 expression in the liver of patients with NAFLD compared with individuals without obesity and without liver disease, as well as animal models with steatosis and non-alcoholic steatohepatitis (NASH), and (2) the effects of LPI and genetic disruption of GPR55 in mice, human hepatocytes, and human hepatic stellate cells.
Results
Notably, we found that circulating LPI and liver expression of GPR55 were up-regulated in patients with NASH. LPI induced adenosine monophosphate-activated protein kinase activation of acetyl-coenzyme A carboxylase (ACC) and increased lipid content in human hepatocytes and in the liver of treated mice by inducing *de novo* lipogenesis and decreasing β-oxidation. The inhibition of GPR55 and ACCα blocked the effects of LPI,

and the *in vivo* knockdown of GPR55 was enough to improve liver damage in mice fed a high-fat diet and in mice fed a methionine-choline-deficient diet. Finally, LPI promoted the initiation of hepatic stellate cell activation by stimulating GPR55 and activation of ACC.
Conclusion
The LPI/GPR55 system plays a role in the development of NAFLD and NASH by activating ACC.

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OC7.5

Hepatic O-GlcNAcylated-p53 as a hub integrating the glucose counterregulatory response and insulin-suppressed gluconeogenesis

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Background and aims
Glucose homeostasis is essential for life. The liver is among the key tissues for maintaining an adequate metabolic homeostasis and its alterations are at the root of the pathogenesis of many disease states. A perfect balance between glucose production, mainly at the liver, and glucose consumption in different tissues, is provided by the action of insulin and counterregulatory hormones as glucagon, cortisol or catecholamines. There is nowadays growing evidence demonstrating that cell cycle regulators have important actions in the metabolic control. In cancer cells, p53 regulates glucose metabolism, opposing the Warburg effect. Nevertheless, the relevance of endogenous hepatic p53 in the physiological fluctuation of gluconeogenesis, as well as the molecular pathways mediating these effects, remains totally unknown.
Method
Either *wild type* (WT) mice or hepatic p53-deficient littermates were subjected to different nutritional conditions to evaluate p53 expression and function. These experiments were also performed *in vitro*, in both THLE-2 cells and HEP3B cells (a hepatic KOp53 cell line). PTT, Gly, GTT and ITT were performed to study glucose homeostasis in WT mice and p53-deficient mice, as well as a clamp to further test their gluconeogenic capacity. Gain-of-function experiments were also performed, over-expressing p53 in the liver. *In vitro* and *in vivo* models were treated with gluconeogenic hormones and insulin, to study the role and function of p53 mediating their hepatic actions. Mutagenesis experiments were also performed to evaluate the relevance of *O*-GlcNAcylation on p53 gluconeogenic actions.
Results
We show that upon starvation hepatic p53 is stabilized by O-GlcNAcylation, and plays an essential role in the physiological regulation of glucose homeostasis. p53 binds to PCK1 promoter and regulates its transcriptional activation, thereby controlling hepatic glucose production. Mutant p53 that cannot be O-GlcNAcylated is unable to promote PCK1 activity gluconeogenesis. Mice lacking p53 in the liver show a reduced gluconeogenic response during calorie restriction. Glucagon, adrenaline and glucocorticoids augmented protein levels of p53, and administration of these hormones to human hepatocytes and to liver-specific p53 deficient mice fails to increase glucose levels. Moreover, insulin decreases p53 levels, and over-expression of p53 impairs insulin sensitivity. Finally, protein levels of p53, as well as genes responsible of O-GlcNAcylation are elevated in the liver of T2D patients, and positively correlate with glucose and HOMA-IR.
Conclusion
Our results indicate that O-GlcNAcylation of p53 plays an unsuspected key role regulating *in vivo* glucose homeostasis, with a potential therapeutic target interest.

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OC7.6

NTCP is a new promising target for treatment of metabolic diseases: A proof of mechanism from double-blind phase I clinical trials of Hepalatide

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Bile acids (BAs) are potent signaling molecules that regulate glucose, lipid and energy homeostasis predominantly via farnesoid X receptor (FXR) and transmembrane G protein-coupled receptor 5 (TGR5). Modulation of bile acid profiles might affect the treatment of metabolic diseases, indicating new possible therapeutic avenues. The sodium taurocholate co-transporting polypeptide (NTCP) plays a pivotal role in the enterohepatic circulation of bile salts as the main uptake transporter of conjugated BAs from the (portal) blood into the liver. The inhibition on NTCP will lead to a temporary increase in systemic bile acid levels in humans. However, either the direct quantitative relation between NTCP and BAs in systemic circulation or the metabolic effect by inhibiting NTCP has not been studied previously in human. Hepalatide is a NTCP inhibitor with 47aa synthetic peptide. In our current randomized placebo-controlled double-blind phase I clinical trials, 80 healthy subjects were administrated with s.c. single dose or multiple dose (once/day for 7 days). The BA profiles were analyzed. The conjugated BAs (GCDCA, GCA, TCDCA, GDCA, TCA, TDCA, GUDCA, TUDCA, TLCA, and GLCA) and unconjugated BAs (CA, UDCA, CDCA, DCA, and LCA) in peripheral plasma sampled before injection (bi) and at 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, and 24 h post injection (pi) were measured by HPLC-mass method. Among 17 healthy subjects with placebo, just as physiological state, circulating conjugated BAs peak at day, while unconjugated BAs peak late at night. Hepalatide dramatically amplified conjugated BAs diurnal rhythm in a dose dependent manner but not affected unconjugated BAs. The mean AUC0–24 h of total conjugated BAs in cohort with single hepalatide adminstration at 10.5 mg was 20.64 times of that in placebo-controlled subjects. BAs are synthesized in hepatocytes from cholesterol and feedback represses BAs synthesis. Hepalatide is expected to uncouple BA synthesis from negative feedback leading more cholesterol to break down. At the end of the 7-day treatment, serum total cholesterol (TC) was reduced in a dose-dependent manner, and it was significantly lower in 8.4 mg cohort than in placebo cohort (P = 0.0029). The LDL-c also decreased with an average of 20% in the 6.3 mg and 8.4 mg cohorts vs the placebo cohort, with a maximum decrease of 39% in one healthy subject. In conclusion, NTCP is a surprising molecule to redistribute BAs between liver and peripheral tissues, which make it a promising target to modulate BAs signal with therapeutic effects on metabolic diseases.

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Pituitary and Neuroendocrinology

OC8.1

Expression and putative role of 14–3-3 proteins in corticotroph tumours

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Introduction
Somatic USP8 mutations are found in around 50% of Cushing's disease tumours and are located in a single mutational hotspot that contains the recognition site for 14–3-3. These proteins bind to phosphoserine recognition motifs to alter the function and location of their target proteins, and are deregulated in several cancers.
Aim
To explore the expression and function of 14–3-3 proteins in corticotroph tumours.

Methods
We analysed the expression of 14–3-3 epsilon (*YWHAE*), gamma (*YWHAG*), sigma (*SFN*) and zeta (*YWHAZ*) on 16 fresh frozen human corticotroph (8 USP8 wild type, 6 USP8 mutant, 2 unknown) and 3 normal pituitaries by qPCR. We determined 14–3-3 epsilon immunoreactivity on 54 FFPE human corticotroph tumours (23 USP8wt, 31 USP8mut) by immunohistochemistry (H-score). To investigate the possible role of 14–3-3 epsilon on corticotroph physiology, we overexpressed human 14–3-3 epsilon in AtT-20 corticotroph tumour cells and examined its action on human *POMC* promoter activity. A ligand-binding defective 14–3-3 epsilon mutant (14–3-3 epsilon K49E) that cannot interact with client proteins was used as control.
Results
Transcripts for 14–3-3 epsilon and zeta were 3× and 7× higher in corticotroph tumours compared to normal pituitary ($P = 0.04$ and $P = 0.009$ respectively). In contrast we did not detect differences in the expression levels of 14–3-3 gamma and sigma ($P = 0.875$ and $P = 0.21$ respectively). 14–3-3 epsilon is the most abundant transcript in corticotroph tumours and its levels are 2.2× higher in *USP8mut* corticotroph tumours compared to *USP8wt* ($P = 0.006$). Cytoplasmic 14–3-3 epsilon immunoreactivity was detected in all but two FFPE corticotroph tumours. Overexpressing human 14–3-3 epsilon in AtT-20 cells significantly increased *POMC* promoter activity (% increase 234 ± 68, $P < 0.05$), while the binding defective K49E mutant had no effect.
Conclusions
Corticotroph tumours overexpress 14–3-3 epsilon compared to the normal pituitary, and this expression is higher in *USP8mut* tumours. 14–3-3 epsilon triggers *POMC* promoter activity in a yet to be delineated mechanism with potential role to corticotroph pathophysiology.

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OC8.2

Osilodrostat is an effective and well-tolerated treatment option for patients with Cushing's disease (CD): Final results from the LINC3 study

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Introduction
Osilodrostat, a potent oral 11β-hydroxylase inhibitor, normalized mean urinary free cortisol (mUFC) in most patients with CD during the 48-week (W) core phase of a Phase III study (LINC3: NCT02180217). We present efficacy and safety results following an extension to LINC3.
Methods
CD patients with mUFC > 1.5× upper limit of normal (ULN) received osilodrostat during the core. Patients benefiting from osilodrostat at W48 could enter an extension. Dose adjustments were permitted (maximum dose 30mg bid). LINC3 ended when all ongoing patients had received ≥72 weeks' treatment and could enter a separate safety study (results of which are not presented here). Efficacy/safety are reported for all enrolled patients unless otherwise stated. Mean change is calculated for patients with evaluable assessments at core baseline and W72.
Results
106 of 137 enrolled patients entered the extension. Median osilodrostat exposure from core baseline to study end for all enrolled patients was 130 weeks (range, 7–245), with a median dose of 7.4mg/day. 98 patients completed W72 and 52 received ≥3 years of treatment. At W72, 81% (86/106) of patients who entered the extension had mUFC ≤ ULN. Mean mUFC and serum and late-night salivary cortisol levels remained ≤ULN during the extension. Improvements in cardiovascular-related parameters were maintained during the extension; mean (SD) change from core baseline to W72: systolic BP, –10.1 (18.1) mmHg; diastolic BP, –5.8 (11.3) mmHg; HbA_{1c}, –0.4% (0.6); BMI, –1.8 (2.5) kg/m^2. AEs related to hypocortisolism and adrenal hormone precursor accumulation, respectively, occurred in 54% (74/137) and 58% (80/137) of patients during the study. Most hypocortisolism-related AEs emerged during the first 26 weeks of treatment. AEs related to adrenal hormone precursor accumulation were less frequent in the extension than the core (occurring in 46%, 19%, 15% and 15% of patients with a safety assessment during the following intervals: baseline–W26, W26–48, W48–72 and W72–study end). Overall, 32% (34/106) of patients who entered the extension discontinued, most commonly because of AEs or patient/guardian decision ($n = 12$ each). Median change in tumour volume from core baseline to W72 was 1.0 mm^3 (range: –74.7 to 1268.5). Mean (SD) 11-deoxycortisol level was stable during the extension (7.4 [6.7] ×ULN at W72). Mean (SD) testosterone level tended to decrease in females during the extension (0.8 [0.7] ×ULN at W72).
Conclusions
Osilodrostat provided long-term control of mUFC in CD patients and improved clinical signs of hypercortisolism and QoL. Osilodrostat was well tolerated, with no new safety signals reported during long-term treatment.

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OC8.3

GFRα2 as a GPS marker: Role of GFRα2 in pituitary gland

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The pituitary gland is the master gland of the endocrine system, controlling important physiological steps like growth, puberty or reproduction. There are different endocrine cell types within the adenopituitary, each one producing a specific hormone. Adaptation to different life stages and moments requires a plastic capacity based in proliferation and differentiation of pituitary stem cells. We ans others discovered the existence of a stem cell niche in the pituitary. Parenchymal stem cells from this niche are called GPS, as they co-express especific markers such as GFRa2, Prop1, Sox2 and Sox9 together with Cytokeratins and b-catenin, which are not co-expressed in any other pituitary cell. The objective of this study is to investigate about the role of GFRa2 in pituitary stem cells. To do so, we have used the GFRa2 knockout (KO) mouse strain compared to wild-type (WT) littermates. Characterization and validation for pituitary stem cell study was performed by postnatal growth assessment, serum hormone assays, qRT-PCR for gene expression and also Western Blot and image techniques for protein expression. Pituitary Gfra2 knockout was validated as we found absence of gene expression at mRNA and protein levels in comparison with littermate WT mice. Adult KO mice present a significant and marked difference in weight and size; those differences appear postnatally and increases during childhood to puberty. Gfra2 KO have decreased pituitary volume with significant less cells per section in the adenopituitary. Molecular analysis consisted on PCR and Western Blot to study gene and protein expression of RET pathway members and also different markers related to stem cells. Further research involving image techniques was also performed, demonstrating different distribution of stem cells in adenopituitary from KO mice in comparison to WT. Our data suggest an increased in proportion of Sox2 positive cells within the adenopituitary in KO mice. Moreover, Sox2+ cells in adenopituitary from KO mice are grouped. However, there is no difference in Sox+2 positive cells in the stem cell niche. Finally, we studied cell proliferation using the EdU click chemistry technique, suggesting that proliferation rates in KO mice are increased when compared to WT. In conclusion, absence of Gfra2 produces pituitary phenotype in mice, however, further investigation about the biology and cellular mechanisms is needed.

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OC8.4

Novel insight into ACTH-secreting pituitary tumors biological behavior: hormone secretion and cell proliferation modulation by Ubiquitin Specific Peptidase 8 inhibitor RA-9

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Cushing's Disease (CD) is a rare condition mostly caused by an ACTH-secreting pituitary tumor resulting in excess of cortisol release by the adrenal glands. Although pasireotide is the only pituitary-targeted drug approved to treat adult patients, many side effects are encountered during the clinical practice and a curative therapy for CD is still challenging. Recently, the discover of somatic mutations in the deubiquitinase *USP8* gene in a subset of patients has shed new light on the crucial role played by the ubiquitin system in the modulation of corticotroph cells growth and hormone secretion. However, the anticancer potential of USP8 inhibition in the corticotrophs has been poor explored so far. Aim of this study was to characterize the *in vitro* responses induced by the USP8 inhibitor RA-9, in murine corticotroph AtT-20 cells and primary cultures from ACTHomas, and to compare them with those triggered by pasireotide. First, AtT-20 cells and ACTHomas were screened for USP8 mutations, all samples resulting wild type. Then, 48 h of incubation with RA-9 caused cell proliferation decrease (-24.3 ± 5.2%, $P < 0.01$ vs basal) and cell apoptosis increase (207.4 ± 75.3%, $P < 0.05$ vs basal) in AtT-20 cells, as observed with pasireotide. Interestingly, RA-9 significantly reduced ACTH secretion in AtT-20 cells (-34.1 ± 19.5%, $P < 0.01$ vs basal), as well as in 1 out of 2 primary cultures *in vitro* responsive to pasireotide (-40.3 ± 6% reduction at RA-9). Western blot experiments revealed that, similarly to pasireotide, RA-9 lowered phospho-ERK1/2 levels in AtT-20 cells (-52.3 ± 13.4%, $P < 0.001$ vs basal) and in all primary cultures regardless of their *in vitro* responsiveness to pasireotide (-32.9 ± 19.8% vs basal in the sensitive group, $P < 0.001$; -33.1 ± 11.8% vs basal in the resistant group, $P < 0.05$). On the contrary, upregulation of $p27^{kip1}$ was observed at 48 h of treatment with RA-9 only, both in AtT-20 cells (167.1 ± 36.7%, $P < 0.05$ vs basal) and one primary culture tested (168.4% vs basal), whilst phospho-CREB expression level was similarly halved in AtT-20 cells by both RA-9 and pasireotide. No synergic effect was observed in any experiments when RA-9 and pasireotide were co-administrated. Altogether, our data demonstrate that RA-9 is able to exert cytotoxic effects and inhibitory actions on cell proliferation and hormone secretion in tumor corticotrophs by modulating the expression of phospho-ERK1/2, phospho-CREB and $p27^{kip1}$. Moreover, although acting on different targets, RA-9 and pasireotide elicit a comparable spectrum of biological responses *in vitro,* therefore inhibition of USP8 might represent a novel mean to pharmacologically target ACTHomas in patients with CD.

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OC8.5

The clinical effects of miR-26a, miR-16, let-7,miR-128a and miR-223 in acromegaly patients

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Background and aim
MicroRNAs (miRNA) are small nucleotide sequences that affect gene expression in cells at the posttranscriptional level. Some miRNAs behave like oncogenes, while others behave like tumor suppressors. In this study, it was aimed to investigate the role of miRNAs in tumor development and its effects on clinical and metabolic parameters of the patients with acromegaly.
Methods
39 patients diagnosed with acromegaly (20 F / 19 M, mean age 51.6 ± 10.1 years) and 39 age–and gender-matched healthy controls (27 F/ 12 M, mean age 52.1 ± 12 years) were included in the study. The levels of miR-16, miR-26a, let-7, miR-128a and miR-223 were measured in peripheral blood by real-time PCR methods. Demographic features of the patients, radiological features of the adenoma, treatment modalities and comorbidities of the patients were evaluated. The relationship between these parameters and miRNAs was evaluated.
Results
While there was no significant difference in miR-16, miR-26a and miR-128a levels between acromegalic patients and the control group, let-7 levels were found to be lower in acromegalics compared to the control group [0.945 (0.29–5.77) vs1.261 (0.25–3.1); $P = 0.053$]. Moreover, acromegalic patients had significantly higher miR-223 levels compared to controls [2.101 (0.004–7.56) vs1.52 (0.36–10.22); $P = 0.021$]. There was no effect of miRNAs on adenoma size, optic chiasm compression and cavernous sinus invasion of the adenoma. Regarding the effects of miRNAs on need of medical treatment, miR-26a expression is demonstrated to be increased in patients who use medical treatment (N: 26, 66.6%) [1.22 (0.63–5.98) vs 0.74 (0.51–2.62); $P = 0.004$] whereas miR-16, let-7, miR-128a and miR-223 levels were found to be similar in both groups. When the patients were evaluated according to the presence of of coronary artery disease, hypertension, hyperlipidemia, Type 2 diabetes mellitus, malignancy and colonic polyps, no statistically significant difference was found between the groups in all miRNA levels.
Conclusion
Decreased expression of tumor suppressor gene let-7 miRNA levels and increased expression of oncogene miR-223 levels suggest that these two microRNAs may have a role in tumor development in acromegaly. While these was no effect of these miRNAs on the development of clinical features and comorbidities of acromegalic patients, increased miR-26a expression in patients receiving medical therapy supports the potential role of miR-26a in determining the long-term prognosis of acromegalic patients.

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OC8.6

Increased PCSK1N in silent corticotroph pituitary adenomas may explain their "silence"

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Background
Corticotroph pituitary adenomas present different degrees of functionality, from silent to whispering and finally to functioning adenomas leading to Cushing's disease. Compared to their functioning (FCA) counterpart, the silent corticotroph adenomas (SCA) express lower levels of the corticotroph cell lineage marker–TBX19 (TPIT), proopiomelanocortin (POMC), and prohormone converting enzyme 1/3 (PC1/3, PCSK1)–the main enzyme involved in the cleavage of POMC towards a functional ACTH molecule. Our recent data (Eieland, Normann et al. 2020) suggests that SCA may express higher levels of PCSK1N, a specific inhibitor of PC1/3. In vitro studies with AtT-20 cells demonstrated that overproduction of PCSK1N, coding for the protein called Pro-SAAS, reduced the processing of POMC leading to diminished ACTH production.
Aim
To study key molecules involved in the processing of POMC including the regulator proteins PCSK1N/Pro-SAAS and PC1/3 and characterize possible differences between FCA and SCA.
Material and methods
Clinical and imaging characteristics were recorded in a cohort of 30 FCA (18 women, 15 microadenomas) and 18 SCA (7 women, all macroadenomas). Measurement of gene expression by RT-qPCR of POMC, TBX19, PCSK1 and PCSK1N was performed in adenoma tissue from the patients. Data was analyzed with IBM SPPS version 27.0.0.0.

Results
Morning plasma ACTH and cortisol levels, measured preoperatively, were significantly lower ($P = 0.032$ and $P = 0.01$) in SCA compared with FCA patients: ACTH median (IQR): SCA 5.6 (1.8–13.2) pmol/l, vs FCA 14.1 (11.6–30.1) pmol/l, $P = 0.032$; cortisol: mean (SD) SCA 314 (154.6) nmol/l vs FCA 577.6 (230.9) nmol/l, $P = 0.01$. Tumor size (mm) was significantly larger in SCA ($P < 0.001$). In SCA as compared to FCA, gene expression of TBX19 ($P < 0.001$), POMC ($P < 0.001$) and PCSK1 ($P = 0.008$) was significantly lower and PCSK1N was higher ($P < 0.001$). For FCA and SCA combined, POMC gene expression was associated with PCSK1 ($r = 0.339$, $P = 0.018$) and PCSK1N ($r = -0.678$ $P < 0.001$). TBX19 gene expression likewise correlated strongly with PCSK1 ($r = 0.421$, $P = 0.003$) and PCSK1N ($r = -0.531$, $P < 0.001$). Plasma cortisol correlated with gene expression of POMC ($r = 0.401$, $P = 0.017$) and PCSK1 ($r = 0.448$, $P = 0.007$). Tumor size correlated with gene expression of POMC (r=-0.618, $P < 0.001$), TBX19 ($r = -0.385$, $P = 0.014$), PCSK1 ($r = -0.340$, $P = 0.032$), PCSK1N ($r = 0.739$, $P = 0.000$) and plasma cortisol ($r = -0.496$, $P = 0.003$).
Conclusion
We present a strong negative correlation between gene expression of POMC and PCSK1N in human corticotroph pituitary adenomas. In addition to being a new potential differentiation marker distinguishing between SCA and FCA and possibly a marker of tumor growth of corticotroph adenomas, the higher PCSK1N expression in the SCA might explain their diminished ACTH production.

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Endocrine-Related Cancer

OC9.1

Thymic neuroendocrine tumor and mortality in MEN 1 patients: the spanish registry

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Background
Thymic neuroendocrine tumor (THY-NET) accounts for almost 20% of multiple endocrine neoplasia type 1 (MEN1)-associated mortality. Diagnosis at early tumor stage is associated with improved survival.
Objective
To study the prevalence, clinical features and prognosis of THY-NET in MEN 1. To describe the overall causes of death among the registered MEN1 patients. To compare and discuss our results with the literature, identifying risk factors for the development and prognostic factors of survival of THY-NET.
Design and patients
Retrospective analysis of the 201-patient MEN1 cohort from the Spanish registry (REGMEN).
Results
THY-NET was detected in seven (3.5%) of 201 MEN1 patients, six (85.7%) were men and the mean age at diagnosis was 40.7 ± 10.5 years [range: 29–53]. Three were index cases and none had a prophylactic thymectomy performed. No particular genetic pathological variation was found to be associated with THY-NET. At presentation six were asymptomatic, and only one had chest pain; two developed Cushing's syndrome later on (10 and 12 y). All the patients were operated on with a mean tumor size of 6.1 ± 2.9 cm, corresponding to five intermediate (atypical) and two high grade NET. Six patients received SSA and further approaches on the progression were reoperation (a second time in 2, three times in 2 patients), radiotherapy (1), everolimus (4), INFalpha (1), temozolomide (2), cisplatin-etoposide (1). After a mean follow up of 9 ± 3.2 years only one patient is free of disease (3 cm, stage I) at 64 months. Two are alive with metastatic disease after 55 and 146 months of follow-up, and four have died after 10.3 ± 2 years (mortality 57.1%), at a mean age of 46.5 ± 8.9 y. The causes of death were cardiac failure secondary to local metastatic disease, pneumonia in a patient with Cushing's syndrome, Cushing's syndrome, and postsurgical complication of a lung metastasis. Among the whole MEN1 cohort, 17 deaths have been reported (8.5%). THY-NET accounted for 23.5% of the mortality. Other causes of death were: duodenopancreatic tumors (4), adrenocortical cancer (1), pituitary macroadenoma (1), and others (mesothelioma, hepatocellular-carcinoma, adenocarcinoma (2), endocarditis, pancreatitis, covid-19). Age of death was 12 years younger in THY-NET patients (58 ± 14.1 vs 46.5 ± 9 y).
Conclusion
We found a similar prevalence, male predominance and prognosis of THY-NET in Spanish MEN 1 to other European/American series. Advanced stage and ectopic Cushing's syndrome conferred worse prognosis. THY-NET is a rare but fatal component of MEN1. Screening and earlier detection of THY-NET is mandatory.

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OC9.2

Utility of In1-ghrelin as a novel non-invasive diagnostic and prognostic biomarker of prostate cancer in patients with PSA in the grey-zone

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Prostate cancer (PCa) is one of the leading causes of cancer deaths among men population worldwide. This tumour pathology is commonly diagnosed through the determination of serum PSA levels. However, the diagnostic capability of PSA dramatically drops when considering patients with PSA levels lower than 10 ng/ml, the so-called "grey-zone"[1]. Therefore, additional non-invasive diagnostic biomarkers are urgently needed to substitute/complement PSA. In this sense, the ghrelin system has been found to be altered in PCa, whether the splicing variant In1-ghrelin plays a relevant role[2]. Additionally, it has been reported that serum In1-ghrelin levels are elevated in PCa patients[2]. However, the potential utility of urine In1-ghrelin levels in PCa diagnosis has not been explored. Therefore, this study aimed to analyse the diagnostic utility of urine In1-ghrelin levels in PCa. Herein, In1-ghrelin levels were determined by RIA in urine from an ample cohort of patients with PSA in the grey-zone ($n = 600$). Our results showed that urine In1-ghrelin levels were higher in PCa patients vs. patients with a suspect of PCa but negative biopsy result, whereas serum PSA levels did not differ between these two groups. Moreover, In1-ghrelin added significant diagnostic value to a clinical model consisting of age, suspicious digital rectal examination (DRE), previous biopsy, and PSA levels. Consistently, high In1-ghrelin levels [OR = 2.93, $P < 0.0001$], but not PSA levels [OR = 1.09, $P > 0.05$], were associated to an increased PCa risk. Moreover, urine In1-ghrelin levels were linked to PCa-aggressiveness parameters (e.g. tumour stage, lymphovascular invasion). Furthermore, several metabolic-factors [e.g. body-mass index (BMI), diabetes mellitus (DM), glucose, and insulin levels] were strongly correlated to urine In1-ghrelin levels as well as associated with PCa risk. Finally, a multivariate model consisting of metabolic [i.e. BMI, waist-circumference, DM, glucose, insulin, cholesterol, and Ghrelyn-O-acyl transferase (GOAT) levels] and clinical (i.e. age, DRE, previous biopsy, and PSA levels) variables, and In1-ghrelin levels showed high specificity and sensitivity to diagnose PCa in our patients cohort (AUC = 0.741, $P < 0.0001$). Taken together, our results pose the potential for urine In1-ghrelin levels as a useful clinical diagnostic and prognostic biomarker of PCa in patients with PSA in the grey-zone.
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OC9.3

Dysregulation of alternative splicing unveils new avenues for targeting pulmonary carcinoids

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Introduction
Dysregulation of alternative splicing is emerging as a new hallmark of cancer. This dysregulation may originate from mutations and/or altered expression of specific components of the splicing machinery. Indeed, our group has shown that the expression profile of the splicing machinery is altered in several types of cancer, including endocrine-related cancers. However, to date, the status of alternative splicing and its putative dysregulation has not been reported in pulmonary neuroendocrine neoplasms (LungNENs), specifically typical and atypical pulmonary carcinoids.
Aims
The aim of this work was to explore the potential dysregulation of the splicing machinery in LungNENs and whether it contributes to splicing alterations and pathophysiology in these tumors.
Methods
A custom-made qPCR array was used to measure the expression of 45 components of the splicing machinery in tumor and non-tumor adjacent tissue samples of a cohort of 33 typical and atypical pulmonary carcinoids patients. Results were validated using a publicly available external cohort of 51 patients (GSE108055). Further analyses were made with immunohistochemistry in paraffin-embedded samples. Statistical analyses were made to explore the potential associations between expression levels of the components of the splicing machinery measured and relevant clinical parameters of patients. In addition, alternative splicing analyses were performed in an RNAseq of an independent cohort of 20 patients, to test whether intratumoral expression of key dysregulated components of the splicing machinery could be associated to an alteration of alternative splicing of specific molecular pathways.
Results
One third of the components of the splicing machinery were dysregulated in pulmonary carcinoids. Remarkably, a discrete subset of specific components of the major and minor spliceosome, as well as key splicing factors displayed significant associations to key clinical parameters, including tumor stage, node invasion and/or tumor dissemination. These results were validated in the external cohort of patients, and key components were selected based on their relevance and the association to clinical parameters. Alternative splicing analyses in the available RNAseq showed that the expression of these key components was correlated to altered patterns of alternative splicing.
Conclusions
Our results show that the splicing machinery is profoundly dysregulated in pulmonary carcinoids, where some of its components are associated to key clinical parameters of tumor malignancy. These results pave the way to employ novel avenues to study pulmonary carcinoids and discover new diagnostic, prognostic and therapeutic tools.
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OC9.4

Splicing machinery landscape is dysregulated in chronic liver disease: central role of EIF4A3 in hepatocarcinogenesis.

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Endocrine-metabolic alterations such as obesity and metabolic syndrome are closely linked to the development of chronic liver diseases, from metabolic-associated fatty liver (MAFLD) to non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC). An emerging hallmark of endocrine-metabolic and hepatic diseases is the appearance or altered expression of pathological splicing variants (SVs). In fact, the components of the cellular machinery involved in the splicing process (spliceosome) represent pivotal players in the generation of SVs in different pathologies, suggesting their putative contribution to liver disease development/progression. Here, we aimed to explore the putative dysregulation and pathophysiological role of key spliceosome components (SCs) in liver disease. Specifically, expression (mRNA/protein) of key (n = 72) SCs and clinical implications were assessed in HCC patients with different aetiologies (alcohol consumption, viral infection, MAFLD/NASH) from two retrospective (n = 154 and n = 172) and six *in silico* [TCGA (n = 369), Wurmbach (n = 45), Roessler (n = 43), Roessler-2 (n = 445), Chen (n = 179) and Mas (n = 57)] cohorts. Functional and molecular consequences of siRNA-mediated *EIF4A3*-silencing were evaluated in liver-derived cell-lines (HepG2/Hep3B/SNU-387). Gene Set Enrichment Analysis (GSEA) and mutational landscape were analysed in TCGA patients with high EIF4A3 expression. Moreover, RNAseq from EIF4A3-silenced HepG2 cells were analysed. The results showed a profound dysregulation in the expression of 41,42% SCs analyzed (at mRNA/protein levels) in HCC vs control-tissues in all cohorts studied. Among them, *EIF4A3, SLM2, ESRP2, SRPK1* and *HNRNPA2B1* were the SCs more profoundly dysregulated in tumor samples, being EIF4A3 the element most consistently altered in the different cohorts. Expression levels of these SCs were associated with clinical (survival, recurrence) and molecular (oncogenic SVs expression) parameters of aggressiveness. Particularly, *EIF4A3* expression was higher in NASH-related HCC compared to other aetiologies, and high *EIF4A3* expression was associated with alterations in key cancer-related pathways (Cell Cycle Mitotic, DNA-Repair, etc.) and with relevant mutations (CTNNB1, TP53). Furthermore, *EIF4A3*-silencing *in vitro* resulted in reduced proliferation, migration, tumorsphere-/colony-formation and higher sensitivity to standard clinical treatments in HCC (e.g. lenvatinib). Finally, RNAseq showed that *EIF4A3*-silencing altered the expression and splicing pattern of multiple genes involved in 3 functional clusters (RNA splicing, translational initiation and metabolic-processes), including key genes associated to chronic liver disease progression (e.g., FGFR4). Altogether, these results demonstrate that the splicing machinery is profoundly dysregulated in liver cancer, wherein it may represent a promising source of novel diagnostic, prognostic or therapeutic targets worth to be explored.
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OC9.5

Reassessment of the diagnostic criteria of insulinoma: A retrospective monocentric cohort study of 72-h fasting trial in 124 patients

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Introduction
Fasting trial remains the gold standard to confirm the diagnosis of insulinoma, based on low blood glucose level concomitant with inadequate high insulin level. However, diagnostic criteria are not consensual. Glycemia and insulin thresholds differ between the different consensus statements : endogenous hyperinsulism diagnosis relies on a glycemia < 3 mmol/l associated with an insulin level > 3 mUI/l in Endocrine Society guidelines (2009) whereas in NANETS 2010 and ENETS 2012 consensus guidelines, diagnosis is based on a glycemia < 2,2 mmol/l concomitant with an insulin level > 6 mUI/l or

> 3 mUI/l, depending on the assays. It has been admitted that the previously used diagnostic insulin level cut-off is challenged by the more specific and sensitive currently routinely used assays.
Methods
We retrospectively analyzed fasting trials results from the 124 patients explored in the Endocrinology department of Cochin Hospital from February 2012 to July 2020 to reevaluate insulinoma diagnosis criteria in terms of glycemia, insulin and C-peptide levels. Insulin and C-peptide levels were determined by automated chemiluminescent sandwich immunoassays.
Results
On the 124 patients included, 51 presented an hypoglycemia < 2.5 mmol/l during fasting trial and 19 were diagnosed with insulinoma, histologically proven. In all insulinoma cases, glycemia nadir was < 2.5 mmol/l (min =1.3 mmol/l; max =2.3 mmol/l; median = 1.7 mmol/l) concomitant with an insulin level ranging from 2.6 to 51.7 mUI/l (median = 10.3 mUI/l) and a C-peptide level ranging from 0.22 to 1.58 nmol/l (median = 0.6 nmol/l). The only insulinoma case presenting an insulinemia < 3 mUI/l at the time of hypoglycemia, harbored a concomitant C-peptide level at 1.21 nmol/l. Such a discordance between insulin and C-peptide levels could only be explained by an hemolyzed blood sample, insulin being very sensible to hemolysis. Insulinoma diagnosis criteria based on a glycemia nadir < 2,5 mmol/l concomitant with an insulin level > 3 mUI/l and a C-peptide level > 0.2 nmol/l, applied to our retrospective cohort, had a sensibility of 95%, a specificity of 97%, a positive predictive value of 86% and a negative predictive value of 99%.
Conclusion
Using current insulin immunoassays, it seems reasonable to make the diagnosis of insulinoma on the occurrence of a glycemia < 2,5 mmol/l concomitant with a C-peptide level > 0,2 nmol/l associated with an insulin level > 3 mUI/l on non-hemolyzed blood samples.

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OC9.6

Presence and pathophysiological role of sst5TMD4, an aberrant spliced variant of the somatostatin receptor subtype 5, in human high-grade astrocytomas

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Gliomas are derived from glial-cells and are the most common primary brain tumor, characterized by rapid growth and invasion. Astrocytomas are a subset of malignant gliomas which are classified, based on their agresiveness features, in low grades (I and II) to high grades (HGAs; III and IV), being grade-IV (glioblastoma multiforme; GBM) the most malignant and aggressive type. Current standard treatment for GBMs consists on surgery followed by radiotherapy/chemotherapy; however, this is only a palliative approach with an average post-operative survival of ~12–16 months. Therefore, there is a clear need for identification of novel therapeutic targets to treat this devastating pathology. In this context, the truncated splicing variant of the somatostatn receptor subtype-5, named sst5TMD4, which is produced by aberrant alternative splicing process, has been demonstrated to be overexpressed and associated with increased aggressiveness features in several endocrine-related tumours (e.g. pituitary, breast, prostate, thyroid and neuroendocrine tumors). However, the presence, functional role, and associated molecular mechanisms of sst5TMD4 in astrocytomas has not been explored. Therefore, the main objetive of this study was to carried out a comprehensive analysis to characterized the expression of sst5TMD4 in HGA human samples, and to determine its pathophysiological role by using human primary GBM cell cultures and GBM cell-lines (U-87 MG/U-118 MG). Our results revealed that sst5TMD4 splicing variant was significantly overexpressed in human HGA tissues [n = 34, grade III (n = 10) and grade IV (n = 24)] compared to healthy-control brain tissues (n = 4). Remarkably, overexpression of sst5TMD4 variant (with a specific plasmid) increased the proliferation and migration capacity, whereas sst5TMD4 silencing (by specific siRNAs) decreased proliferation and migration rate of GBM cells. Our data also indicate that the modulation of the level of expression of sst5TMD4 significantly altered key signaling pathways associated with tumor aggressiveness in GBM cells, including the decrease in pAKT/AKT ratio, a key pathway robustly associated with tumor progression and aggressiveness. Taken together, our results demonstrate that sst5TMD4 is overexpressed in human HGAs and its presence is associated to enhanced malignancy. Therefore, our data provide an original approach to use sst5TMD4 as novel diagnostic and/or prognostic biomarker and as a new target with therapeutic potential in this poor prognosis type of CNS tumors.
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Thyroid

OC10.1

The role of VEGF expression in the development of papillary thyroid carcinoma in patients with lymphocytic thyroiditis

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Background
Vascular endothelial growth factor (VEGF) has been implicated in angiogenesis of papillary thyroid carcinoma (PTC). As VEGF expression is increased in PTC and even in lymphocytic thyroiditis (LT), we hypothesized that VEGF may play a role in the development of PTC in patients with LT. In order to find an association between VEGF and these disorders, we examined both the tumoral and adjacent tissues of PTC patients with and without LT.
Methods
Fifty patients with PTC and 17 patients with nodular goiter were, 52.50 7.41 years old (range between 41 and 68), and 50.47 10.38 years old (range between 31 and 67), respectively. According to existing LT within the adjacent tumor tissue, patients with PTC further divided into two groups. The immunohistochemical analyses of VEGF were carried out in both tumor tissue and their adjacent tissue in patients with PTC. For this purpose, each sample was scored: a) for the intensity of the immunostaining and b) for the percentage of the labeled thyrocytes.
Results
The intensity of staining scores and percentage of labeled thyrocytes scores were found to be significantly higher in PTC group than in nodular goiter group (P < 0.001 and P < 0.001, respectively). There was no correlation between VEGF staining scores and age, body mass index, tumor size, tumor subtype, vascular invasion, extrathyroidal extension, and lymph node metastasis in PTC group. In the subgroup analyses of PTC, 17 (34%) patients had LT. The VEGF staining scores in adjacent tumor tissue were statistically significant higher in PTC with LT than in patients without LT (Figure 1). Tumor size, tumor subtype, multifocality, vascular invasion, extrathyroidal extension, and lymph node metastasis were similar in PTC with or without LT.
Conclusion
Our results imply that co-existing LT rises the expression of VEGF in the adjacent tumor tissues of patients with PTC. Future prospective cohort studies are needed to demonstrate whether increased expressions of VEGF is also associated with increased risk of developing PTC in patients with LT.

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OC10.2

NTRK fusion genes in thyroid cancer

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Objectives
Rearrangement involving one of the neurotrophic-tropomyosin receptor kinase (*NTRK*) genes belonging to the *NTRK* family represents a significant oncogenic event in thyroid cancer (TC). Recently, there has been a growing interest in testing and characterizing *NTRK* fusion genes because they are therapeutically targetable. This study aimed to determine a frequency, clinical and histopathological features of a large cohort of *NTRK* fusion-positive TC and mainly to determine the prognostic significance of *NTRK* fusion genes based on long-term follow-up of patients with TC harboring this mutation.
Methods
The cohort consisted of 989 different TC tissue samples. Based on the detected mutation, samples were triaged. Samples positive for the *BRAF*, *HRAS*, *KRAS*, *NRAS, RET*, *RET*/*PTC* or *PAX8*/*PPARG*γ mutation were excluded from the further *NTRK* fusion gene analyses. RNA from 259 samples was analysed using the *NTRK* Gene Fusions Detection Kit (AmoyDx) by Real-Time PCR (LC480, Roche) or using the FusionPlex Comprehensive Thyroid and Lung panel (ArcherDx) by next generation sequencing using MiSeq (Illumina).
Results
NTRK fusion genes were detected in 57 of 846 (6.7%) papillary thyroid cancer (PTC) and in 2 of 10 (20.0%) poorly differentiated thyroid cancer (PDTC). A total of eight types of *NTRK* fusions were found, including *ETV6*/*NTRK3*, *EML4*/*NTRK3*, *RBPMS*/*NTRK3*, *SQSTM1*/*NTRK3*, *TPM3*/*NTRK1*, *IRF2BP2*/*NTRK1*, *SQSTM1*/*NTRK1*, *TPR*/*NTRK1*. In PTC, a follicular growth pattern was identified in 78.0% of *NTRK* fusion-positive cases, and both cases of PDTC dedifferentiated from PTC with a mixed papillary and follicular growth pattern. Lymph node and distant metastases were found in 54.2% and 6.8% of cases, respectively. Initially within 2 years of postoperative treatment, 58.9% of *NTRK* fusion-positive patients had an excellent response (ER), 16.1% had an indeterminate response (IR) and 25.0% of patients had a structural incomplete response (SIR) to treatment. During the follow-up, response to treatment had an improving tendency. After 10 years of follow-up, 82.3% of patients had ER, 11.8% had IR, 5.9% had a biochemical incomplete response, no patient had SIR, and three patients died.
Conclusion
In summary, *NTRK* fusions are rare markers occurring mostly in PTC but also in PDTC. Patients without metastases had a favourable prognosis and patients with metastases often suffered from persistent disease. The genetic molecular testing of *NTRK* fusions is important not only for patient's diagnosis and prognosis, but also for possible targeted therapy with Trk inhibitors.
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OC10.3

Predictive factors for recurrent non-diagnostic fine-needle aspiration biopsy in thyroid nodules

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Introduction
The most cost-effective, minimally invasive and accurate tool to discriminate benign from malignant thyroid nodules is a fine-needle aspiration biopsy (FNAB). However, 2%–24% of FNABs provide non-diagnostic results, which are a clinical challenge, particularly when this result is recurrent.
Aim
To determine the predictive factors for recurrent non-diagnostic FNAB in thyroid nodules.
Methods
We present a retrospective study including all non-diagnostic FNABs of thyroid nodules, performed in our appoiment between january 2016 and december 2019. Demographic and clinical data, the number and location of nodules, their ultrasound characteristics and the respective EU-TIRADS classification, their cytological results according to Bethesda's classification, and the moment when each FNAB was performed were recorded.
Results
Of a total of 1497 FNABs executed in the evaluated period, 494 (33.1%) were non-diagnostic. The FNAB was repeated in 225 (45.5%) nodules (76.4% in female's patient with a median age of 59 years [P25-P75:48.5–68.5]), of which 108 (48.0%) presented again a non-diagnostic result; 43.6%, 7.5% and 0.9% had a benign, indeterminate and malignant cytological diagnosis. The presence of a single nodule shows to be an independent predictive factor to recurrent non-diagnostic FNAB (41.7% vs 23.9%; OR 2.270; 95% CI 1.282–4.021; P = 0.005). Nodules with benign ultrasound characteristics classified as EU-TIRADS 2 have a reduced risk of a repeated non-diagnostic cytology (1.9% vs 9.4%; OR 0.182; 95% CI 0.039–0.840; P = 0.029). Gender (P = 0.421), patient's age (P = 0.632), cervical radiotherapy (P = 0.658), nodule's location (P = 0.755), levothyroxine (P = 0.336) or anti-thyroid drugs treatment (P = 0.400) and time to repeat FNAB (P = 0.952) did not significantly influence the cytological result of the second biopsy. Despite without statistical significance, the recurrently non-diagnostic nodules appear to be larger (median larger diameter 24 mm [P25-P75:18–31] vs 21 mm [P25-P75:17–30]; P = 0.288).
Conclusion
In this study we concluded that the risk of a *second non-diagnostic* result was significantly *higher* in patients with single thyroid nodules. In contrast, the presence of a nodule corresponding to EU-TIRADS 2 classification reduce the probability of this outcome.

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OC10.4

Targeting TSHR and ICAM-1 for treatment of Graves' disease in BALB/c mice

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Objective
In BALB/c mice with GD model, the TSHR and ICAM-1 were targeted for treatment, and new approaches to GD targeted therapy were explored.
Methods
The siRNA targeting TSHR and the ICAM-1 mAb specifically binding ICAM-1 were designed and synthesized. Thirty GD model mice were randomly divided into siRNA treatment group, ICAM-1 mAb treatment group, and untreated GD group, with 10 mice in each group, and 10 normal mice in a control group. Serum T_4, TSH, TSAb and TSBAb were measured before and after treatment. At the end of the treatment, weight and heart rate of each group were measured, thyroid uptake of $^{99m}TcO_4^-$, thyroid size and pathological changes were evaluated.
Results
After three treatments, the weights of mice in the siRNA group and the ICAM-1 mAb group were still lower than that of normal mice. The heart rate of the mice in the siRNA group and the ICAM-1 mAb group were significantly lower than that of the GD mice. Heart rate of mice treated with siRNA decreased significantly, close to that of normal mice. After treatment, T_4, TSAb and TSBAb levels in both the siRNA group and the ICAM-1 mAb group were significantly decreased, while serum TSH levels were significantly increased, and the above changes were statistically different from those in GD mice. There was no significant difference in the decreased levels of T_4 and TSBAb between the siRNA group and the ICAM-1 mAb group. The elevated TSH level and decreased TSAb level of mice treated with ICAM-1 mAb were significantly different from those treated with siRNA. After treatment, both the siRNA group and the ICAM-1 mAb group showed reduced uptake ability of $^{99m}TcO_4^-$–in part of the thyroid lobes, and reduced enlargement degree of the same lobes. The thyroid pathology of the treated groups showed that the absorption vacuoles of thyroid follicles were reduced, and the phenomenon of thinner colloids was improved. No obvious damage was observed in the heart, liver and kidneys of the mice.

Conclusions
Both the siRNA targeting TSHR and the ICAM-1 mAb specifically binding to ICAM-1 have therapeutic effects on GD model mice. The siRNA was better at controlling heart rate, and the ICAM-1 mAb was better at increasing TSH and decreasing TSAb. Each of the above treatment methods had its own advantages and had good application prospects, which can provide new ideas for GD targeted therapy.

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OC10.5

External validation of AIBx, an artificial intelligence model for risk stratification, in surgically resected thyroid nodules

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Background
Artificial intelligence algorithms can be used in classification of thyroid nodules to reduce subjectivity. External validation on images collected from different ultrasound machines and other institutions are vital before wider use of these algorithms. We retrospectively analyzed the performance of AIBx on thyroid nodules with surgically proven pathology.
Materials and methods
Patients harboring thyroid nodules 1–4 cm in size, who underwent thyroid surgery from 2014 to 2016 in a single institution, were included in this study. Medullary thyroid cancer, metastasis from other cancers, thyroid lymphomas, and purely cystic nodules were excluded. Results were compared with TI-RADS calculated by experienced physicians. A subgroup analysis was done on cytologically indeterminate nodules.
Results
Out of 329 patients, 257 nodules from 209 individuals met the eligibility criteria. 51 nodules (19.8%) were malignant. AIBx had a negative predictive value (NPV) of 89.2%. Sensitivity, specificity, and positive predictive values (PPV) were 78.4%, 44.2% and 25.8% respectively. Considering both TI-RADS 4 and TI-RADS 5 nodules as malignant lesions resulted in an NPV of 93%, while PPV and specificity were only 22.4% and 19.4%, respectively. NPV was 89.6% if only TI-RADS 5 nodules were considered malignant. TI-RADS predicted all Bethesda category III nodules as malignant, despite the fact that none of them were malignant on histology. In contrast, only 25% of nodules in the Bethesda category III were predicted to be malignant by AIBx. On subgroup analysis, AIBx had a NPV of 95.8% in classical papillary thyroid cancer, while TI-RADS had an NPV of 93.0%.
Conclusion
When applied to an external dataset consisting of ultrasound images obtained in a different setting than used for training, AIBx had comparable negative predictive values to TI-RADS. AIBx performed even better than TI-RADS in Bethesda category III and classical papillary thyroid cancer. These data prove the concept of AIBx for thyroid nodules, and this tool may help less experienced operators by reducing the subjectivity inherent to thyroid ultrasound interpretation.

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OC10.6

Impact of allogeneic stem cell transplantation on thyroid function

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Introduction
Primary hypothyroidism, which is one of the main endocrine complications of allogenic stem cells transplantation (allo-SCT), has been largely studied in children. Conversely, data on adults are still limited with a reported incidence widely ranging between 9 and 47%. Older age, multiple allo-SCT, chronic Graft vs Host Disease (cGVHD), prolonged immunosuppressive therapy and high-dose total body irradiation (TBI) have been indicated as potential risk factors. The aims of this observational, cross-sectional study were to assess the prevalence of post-allo-SCT hypothyroidism in adult recipients, to analyse its variation over time and to detect predictive factors.
Methods
Among 462 patients who underwent allo-SCT at our hospital between January 2010 and December 2017, 218 where alive and in active follow-up at the time of the study. Of them, 195 (M 107; F 88; median age 53.3 years) were recruited and divided into 3 groups according to time elapsed after allo-SCT (1–3 years: n 78; 3–5 years: n 50; >5 years: n 67). Data on pre-transplant TSH and fT_4 levels were available for all patients. After the transplant, TSH, fT4 and anti-thyroperoxidase antibodies (AbTPO) were evaluated.
Results
TSH levels were significantly lower before (median 1.7, IQR 1.2–2.4 µU/ml) than after allo-SCT (median 2.3, IQR 1.5–3.5 µU/ml; $P < 0.0001$). Forty-six (23.6%) patients developed post-transplant hypothyroidism, with a higher prevalence in females (F 35.2%, M 14.0%; $P < 0.001$) and at earlier time points (1–3 yrs: 28.2%; 3–5 yrs: 24%; >5 yrs: 17.9%). At the pre-transplant evaluation, patients who developed hypothyroidism showed higher TSH and lower fT_4 levels (TSH median 2.4, IQR 1.7–3.3 µU/ml; fT4 median 10.2, IQR 8.9–11.7 pg/ml) compared to those with preserved thyroid function (TSH median 1.5, IQR 1.1–2.1 µU/ml; fT4 median 11.2, IQR 10.0–12.1 pg/ml; $P < 0.0001$ and < 0.05, respectively). Patients with post-transplant hypothyroidism had higher prevalence of AbTPO positivity and of acute GvHD ($P < 0.05$ for both). Multiple regression analysis, corrected for time after allo-SCT, radiotherapy and acute GVHD, identified male gender as a negative predictor of hypothyroidism (OR 0.283, 95%IC 0.121–0.660; $P < 0.05$) and higher pre-transplant TSH levels as a positive one (OR 1.797, 95%IC 1.275–2.534; $P < 0.001$).
Conclusions
About one out of four patients developed hypothyroidism after allo-SCT, with a greater risk for females and in the presence of acute GHVD. Pre-transplant TSH levels seem to predict the onset of post-SCT hypothyroidism.

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Adrenal and Cardiovascular Endocrinology

OC11.1

Circulating cell-free DNA for prognostication and disease surveillance in adrenocortical carcinoma

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Background
Adrenocortical Carcinoma (ACC) is a rare aggressive cancer with a heterogeneous behaviour. Disease surveillance relies on frequent imaging, which has limited sensitivity and results in significant radiation exposure. Aim of the study was to investigate the role of circulating cell-free DNA (ccfDNA) as a biomarker for prognostication and disease monitoring in ACC.
Methods
ccfDNA was extracted from 1–4 ml EDTA-plasma using the Nonacus Cell3 Xtract or the Qiagen QIAamp MinElute ccfDNA kit and quantified by fluorimetry. The experimental cohort included 60 patients with ACC (22M/36F, 52 ± 15 yrs): 22 primary tumours (ACC-P) and 38 disease recurrences (ACC-R). Twenty-three patients with adrenocortical adenomas (ACA, 8M/15F, 55 ± 17 yrs) and 19 healthy subjects (9M/10F, 37 ± 9 yrs) served as controls. Targeted next generation sequencing was performed on 23 ccfDNA samples (8 ACC-P, 11 ACC-R, 4 ACA) using a customised panel

of 30 ACC-specific genes (Cell3 Target Nonacus) and Illumina NextSeq500 Sequencer. Leucocyte DNA was sequenced to discriminate germline from somatic variants. Sequencing data from corresponding tumour DNA (tDNA) were available for comparison in 13/19 ACC.

Results

ACC-P had the highest ccfDNA concentrations (1.23 ± 1.56 ng/µl) compared to ACC-R (0.31 ± 0.27 ng/µl, $P < 0.05$), ACA (0.16 ± 0.10 ng/µl, $P < 0.005$) and healthy subjects (0.12 ± 0.09 ng/µl, $P < 0.005$). In the entire ACC cohort, ccfDNA concentrations correlated with the tumour burden, i.e. size of primary tumours or local recurrence plus size and number of metastasis ($P < 0.001$, R = 0.57 by linear regression). In ACC-P, the ccfDNA levels correlated with the ENSAT tumour stage ($P = 0.059$), but not with Ki67 index ($P = 0.22$). Moreover, high pre-surgery ccfDNA levels tended to be associated with shorter recurrence-free survival, but the number of cases is still limited ($n = 11$, $P = 0.10$, HR 6.23, 95% CI 0.7–55.4). Among sequenced ccfDNA samples, 3 ACC-P (37%) and 3 ACC-R (27%), but no ACA, showed somatic mutations in at least one known driver gene (2 *CTNNB1*, 2 *TP53,* 2 *MEN1,* 2 *ZNRF3*). The variant allele frequency ranged between 1.9 and 30.9%. The ccfDNA sequencing matched with the t-DNA in 9 of 13 cases (i.e. 6 without somatic variants and 3 with superimposable mutations).

Conclusion

ccfDNA concentrations correlated with tumour burden in patients with ACC and may have utility in predicting disease recurrence. Targeted ccfDNA sequencing detected ACC-specific mutations in ~30% of ACC. Serial ccfDNA quantitative and genomic analysis may represent an efficient, non-invasive tool complementary to imaging to improve the disease surveillance in ACC. This will be investigated in a large cohort of operated patients.

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OC11.2

Extensive preclinical screening of chemotherapeutic agents and molecular targeted Inhibitors reveals potent combinatory treatment for adrenocortical carcinoma (ACC)

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Current systemic treatment options for patients with ACCs are far from being satisfactory. DNA damage/repair mechanisms, which involve e.g. ATM/ATR-signalling or RRM1/RRM2 encoded ribonucleotide reductase (RNR) activation commonly contribute to drug resistance. Moreover, also the regulation of RRM2b, the p53-induced alternative to RRM2, is of unclear importance for ACC. Upon extensive drug screening, including a large panel of classical chemotherapies (doxorubicin, etoposide, cisplatin, mitotane, gemcitabine, paclitaxel), phytochemicals (9-cis-retinoic-acid, Isoquercitrin) and molecular targeted inhibitors (Erlotinib, Linsitinib, Sorafenib, Sunitinib, XAV-939), we recently provided strong evidence for anti-tumoral efficacy of combined Gemcitabine (G) and Cisplatin (P) treatment against adrenocortical cells (NCI-H295R and MUC-1). However, accompanying induction of RRM1 and RRM2 expression also indicated developing G-resistance, an effect that was partially reversed upon addition of P. Our findings were confirmed for RRM2 protein (NCI-H295R: G: 2.51 ± 0.14, $P < 0.001$; P: 1.14 ± 0.85, ns; G+P 0.85 ± 0.10, ns vs controls; MUC-1: G: 3.84 ± 0.72, $P = 0.002$; P: 2.55 ± 0.44, ns; G+P 1.57 ± 0.22, ns vs. controls), RNR-dependent dATP-levels (NCI-H295R: G: 1.64%; P: 83.61%; G+P 124% vs controls; MUC-1: G: 13.33%; P: 101.11%; G+P 102.22% vs. controls) and modulations of related ATM/ATR-signalling (Chk1, Chk2, H2AX). The applied models carry different TP53-mutations from which both enabled significant induction of RRM2b-expression upon specific treatments. However, the P-induced reversal to baseline or below differed in both models. Finally, we screened for complementing inhibitors of the DNA damage/repair system targeting RNR, Wee1, CHK1/2, ATR and ATM applying MTT and BrdU assays. Many tested inhibitors demonstrated already as single agents significant anti-tumour potential (MTT NCI-H295R: untreated 100.0 ± 1.9%; COH29 (dual RRM1/RRM2-complex-inhibitor): 60.2 ± 6.2%, $P < 0.001$; Adavosertib (Wee1-inhibitor): 84.9 ± 3.0%, $P = 0.107$;Prexasertib (CHK1/2-inhibitor): 65.61 ± 1.5%, $P < 0.001$;VE822 (ATR-inhibitor): 101.2 ± 0.7%, $P = 0.999$; AZD0156 (ATM-inhibitor): 104.3 ± 8.2%,$P = 0.995$; MUC-1: untreated 100.0 ± 1.0;COH29 50.2 ± 1.5%, $P < 0.001$;Adavosertib 50.5 ± 2.6%, $P < 0.001$;Prexasertib 86.5 ± 0.9%, $P = 0.002$;VE822 89.7 ± 3.1%, $P = 0.024$;AZD0156 91.9 ± 1.3%,$P = 0.119$). Of note, the combination G, P and COH29 resulted in previously unreached total cell killing of both, NCI-H295R (untreated 100.0 ± 4.3%; G: 110.7 ± 20.1%, $P = 0.196$; P: 14.3 ± 0.4%, $P < 0.001$; G+P: 11.7 ± 1.2%, $P < 0.001$; G+P+COH29: 0.0 ± 0.1%, $P < 0.001$) and the commonly highly drug resistant MUC-1 cells (untreated 100.0 ± 1.3; G: 96.4 ± 9.6%, $P = 0.996$; P: 57.9 ± 6.3%, $P < 0.001$; G+P: 47.2 ± 4.2%, $P < 0.001$; G+P+COH29 0.0 ± 0.1%, $P < 0.001$;). Clinically, our analysis of TCGA and own patient samples revealed for both data sets significantly elevated expression levels of RRM2 ($P < 0.001$) but not RRM1 in ACC ($n = 33/30$) compared to normal adrenals ($n = 10/21$) and adenomas ($n = 22/20$). Higher RRM2 expression was correlated with larger tumour size ($P = 0.02$) and strong tendency towards poorer overall survival ($P = 0.05$). In summary, we provide evidence that RNR-modulating therapies might represent a new therapeutic option for ACC.

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OC11.3

Efficacy and safety of radiation therapy in advanced adrenocortical carcinoma (ACC)

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Background

The ESE-ENSAT guidelines emphasize the role of local therapies and suggest radiotherapy (RT) as an individualized treatment in patients with advanced ACC. However, the evidence for this recommendation is very low. The aim of this study was to retrospectively investigate the efficacy and tolerance of radiation therapy in advanced ACC.

Methods

We screened all patients in five European reference centers for ACC since 2000 for RT of advanced ACC. Primary endpoint was progression-free survival of the treated lesion (tPFS). Secondary endpoints were best objective response, overall progression-free survival, toxicity of the treatment, explorative analysis of predictive factors (e.g. size of lesions, Ki67 of the primary tumor, disease-free interval prior RT or time interval between primary diagnosis and RT).

Results

116 tumoral lesions with a median tumor size of 26 –(7–140) mm (local recurrences ($n = 23$), metastases in liver ($n = 6$), lung ($n = 33$), bone ($n = 39$), and other regions ($n = 15$)) in 76 patients (28 male, median age 47.5 (18–78) years) were identified. They were treated with various RT modalities (stereotactic body radiation therapy (SBRT) 35–50Gy ($n = 32$), 'non-SBRT' with 50–60 Gy ($n = 24$) or with 20–49 Gy ($n = 55$), single dose RT (SDRT) 12–25Gy ($n = 5$)). Median time between primary diagnosis and start of RT was 34.9 months, median number of therapies (including surgery) before RT was 3(1–17). Complete response was detected in 7 lesions (6%). 47 metastases showed partial response (40.5%), 48 were stable and in only 16 lesions (10%) progression was diagnosed at the first imaging after radiotherapy. Median tPFS was 7.3 (1–148.5) months, whereas overall

PFS was 4.4 (1–101) months. At last follow-up, 39 patients were still alive and the median overall survival was 18.5 (2.5–152) months. In comparison to non-SBRT with 50–60 Gy, risk for local recurrence was significantly higher in non-SBRT with 20–49Gy (multivariate adjusted HR 5.1; 95% CI 0.039–0.972; P = 0.046), but quite similar as to SBRT (HR 1.1; 95% 0.18–4.93; P = 0.95) and SDRT (HR 2.2 95% CI 0.11–1.96; P = 0.29). Higher age (P = 0.042) and ki67 index >15 % (P = 0.002) appeared to be important prognostic factors. Toxicities with grade 3 or higher did not occur.
Conclusions
Our study provides for the first time evidence from a larger cohort that radiotherapy is effective in a significant proportion of patients with advanced ACC. The retrospective nature and the size of the study are major limitations.

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OC11.4

The management of post-operative recurrences in patients with adrenocortical carcinoma (ACC): The experience of San Luigi Hospital

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Background
The management of post-operative recurrences of ACC remains controversial, although the current guidelines recommend a surgical approach whenever feasible with radical intent.
Aim
The aim of our study was to evaluate retrospectively the management of recurrences in patients with ACC. We collected data of 106 patients with ACC followed at the San Luigi Hospital for the management of recurrence. Median follow up was 34 months.
Outcome
Baseline characteristics of our patients were: 59.4% women, median age 46 yrs, 31.4% ACC were incidentally discovered, 52.4% patients reported symptoms related to hormone excess (72.7% cortisol) and 7.6% to tumor mass, 71.7% ACC were stage I-II ENSAT, 73.8% underwent open surgery, and all were macroscopically resected (R0 or Rx surgery). Median Weiss Score was 7, median ki67 20%, and 59.4% of patients underwent adjuvant mitotane treatment following surgery. Median RFS was 12 months (IQR: 6–23), and median OS was 64 months (IQR 34–162). ACC recurrences occurred as a unique lesion (group A) in 35.8%, multiple lesions in a single organ (group B) in 20.8%, and affecting multiple organs (group C) in 43.4%. Baseline characteristics of patients stratified by the type of recurrence did not differ between them. Local treatment (surgery, radiotherapy or RFA) was used in 100% of patients of the group A, 66.7% in group B, and 26% in group C. After treatment of recurrence, 60% of patients were free of disease. Stratifying patients by type of recurrences, we found a significantly better OS for group A (P < 0.001). Stratifying patients by treatment of recurrence, we found a significant better OS for patients who underwent local treatment (P < 0.001). This finding may be linked to the better outcome of local recurrences. None of the variables considered (sex, age, symptomatology, ACC stage, type of surgery, Weiss Score, ki67) was a factor predicting the type of recurrence in multivariate analysis.
Conclusion
We managed ACC recurrences mainly with a local approach, not only when recurrences occurred as a unique lesion, and we were able to attain a disease-free status in 60% of patients. The chance of future survival was better when ACC recurred as a unique lesion allowing a local treatment.

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OC11.5

Results of the ADIUVO trial, the first randomized study on post-operative adjuvant mitotane in patients with adrenocortical carcinoma

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Background
The ESE-ENSAT guidelines suggest adjuvant mitotane for patients with adrenocortical carcinoma (ACC) at high risk of recurrence following radical surgery. This indication has a limited evidence base, lacking results from randomized controlled trials. No suggestion is available in low-risk patients, since studies did not stratify patients for prognosis. The randomized controlled study ADIUVO compared the efficacy of adjuvant mitotane (MIT) treatment vs. observation (OBS) in prolonging recurrence-free survival (RFS) in patients at low-intermediate risk of recurrence.
Methods
The main inclusion criteria were: stage I-III ACC, R0 surgery, and Ki-67 ≤10%. Patients were randomly assigned 1:1 to MIT or OBS. The primary endpoint of the study was RFS. Patients who refused randomization were eligible for the ADIUVO OBSERVATIONAL study. In this prospective, observational study, patients were managed as in ADIUVO except for randomization. A total of 91 patients were enrolled in ADIUVO, 45 in the MIT and 46 in the OBS arm. Baseline characteristics of patients were perfectly matched between the 2 arms: median age, 51 vs. 50.5 years; female, 73% vs 67%; stage I, 20% vs 26%; stage II, 67% vs 63%, stage III, 13% vs 11%; ACC secretion 44% vs 36%; Weiss 5 vs 5; respectively. In ADIUVO OBSERVATIONAL, 42 patients were treated with mitotane and 53 were untreated. Baseline characteristics of patients were matched between the 2 groups and with MIT and OBS groups in ADIUVO. Thus, the ADIUVO OBSERVATIONAL cohort was analyzed in parallel to deal with the difficult recruitment in ADIUVO.
Results
In the ADIUVO study, recurrences were 8 in the MIT and 11 in the OBS arm, while deaths were 2 and 5, respectively. RFS and overall survival (OS) did not significantly differ between the 2 arms. Tumor size was a predictor of RFS in multivariable analysis. In the OBS arm, the HR for recurrence was 1.321 (95% CI, 0.55–3.32, P = 0.54) and HR for death 2.171 (95% CI, 0.52–12.12, P = 0.29). The survival analysis in the ADIUVO OBSERVATIONAL study confirmed that of ADIUVO. Given the outcome of both studies, the NNT is 55.
Conclusions
ACC patients at low-intermediate risk of recurrence show a rather good prognosis (5-yr RFS of 75%) and do not benefit significantly from adjuvant mitotane. The results of the ADIUVO study do not support routine use of adjuvant mitotane in this subset of patients, who may thus avoid a potentially toxic treatment. This is an important step toward personalization of ACC care.

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OC11.6

Investigating the role of cholesterol and lipid trafficking in mitotane resistance in adrenocortical carcinoma

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Introduction
Adrenocortical Carcinoma (ACC) is a rare aggressive cancer which carries a poor prognosis. Adjuvant mitotane improves survival but is limited by poor response rates and resistance following tumour recurrence. Mitotane's efficacy has been attributed to intracellular accumulation of toxic free cholesterol (FC) predominantly through inhibition of cholesterol storage through SOAT1. Yet SOAT1 specific inhibitors demonstrate inferior efficacy to mitotane in inducing ACC cell death. We hypothesize that mitotane's efficacy to induce toxic FC accumulation in ACC cells is also mediated through enhanced breakdown of lipid droplets (LDs).
Methodology
ATCC-H295R (mitotane sensitive) and MUC-1 (mitotane resistant) ACC cells were evaluated for neutral lipid content using BODIPY493/503 under baseline and cholesterol loaded conditions using Amnis ImageStream, additionally cells were treated with mitotane (H295R 20/40/50 μM; MUC1 – 50/100/200 μM) for 6 hrs. Analysis of LDs using CE-BODIPY and FA-BODIPY identified cholesteryl ester (CE) and triacylglycerol (TAG)-containing LDs, respectively. Lipid droplet-associated proteins (LDAPs) Perilipin (PLIN) 1–4 and hormone sensitive lipase (HSL) were evaluated using western blotting and PCR.
Results
Mitotane treatment, within its therapeutic range, decreased staining for neutral lipid droplets significantly in H295R. This was also reflected by decreased expression of LDAPs PLIN1 and PLIN3. Decreased LDs was associated with increased activation of HSL (pHSL and LIPE). However, this effect was only evident in MUC-1 at supratherapeutic 200 μM mitotane. H295R and MUC-1 demonstrated similar overall neutral LD numbers at baseline and under cholesterol supplementation. Expression of PLIN3 was high in both cell lines, while PLIN1, PLIN2 and PLIN4 demonstrated distinct LD profiles in each. Investigation of LD content showed H295R preferentially store CEs, while MUC-1 store only TAG, irrespective of cholesterol-loading. Mitotane treatment significantly reduces CE and TAG LD stores in H295R and MUC-1. Pharmacological inhibition of HSL decreases mitotane-induced toxicity and CE-LD reduction, however, does not affect TAG-LDs. Additionally, toxic mitotane increases glycerol production in H295R and MUC-1.
Conclusion
We highlight that LD breakdown and activation of HSL represents a putative additional mechanism for mitotane induced FC cytotoxicity in ACC. We also demonstrate significant overall differences in cholesterol handling and LDAPs between mitotane-sensitive and mitotane-resistant models, in particular, the absence of CE-LDs in MUC-1. However, inhibition of HSL and CE-LD breakdown does not fully attenuate mitotane toxicity. Increased glycerol production and decreased TAG-LDs following mitotane treatment highlights an additional toxic mechanism through TAG lipolysis. Further understanding of cholesterol and lipid handling in ACC offers potential for novel therapeutic exploitation, especially in mitotane-resistant disease.

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Diabetes, Obesity, Metabolism and Nutrition

OC12.1

Prevention of glucocorticoid-induced adipose dysfunction through selective activation of β3-adrenergic signaling in mice

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Despite their therapeutic effectiveness, glucocorticoids' (GC) clinical usage is frequently limited due to the deleterious metabolic effects. GC-induced obesity arises from excessive fat accumulation in white adipose tissue (WAT) as well as suppressed thermogenic capacity in brown adipose tissue (BAT). Since the sympathetic nervous system (SNS) plays a fundamental role in adipose tissue biology, we examined the interaction between GCs and SNS signaling in the adipose organ. To that end, we modulated the SNS activity by altering the housing temperature of corticosterone-treated mice and respective controls to either 29°C, 22°C, or 13°C. Following four weeks of corticosterone treatment, mice housed at 29°C and 22°C gained more weight and accumulated more fat than their temperature-matched controls. Interestingly, mice maintained in the 13°C environment were protected from GC-driven weight gain and obesity. Additionally, the cold adaptation of mice effectively protected against GC-induced hyperglycemia, hyperinsulinemia and hyperleptinemia, all of which were readily observed at 29°C and 22°C. Furthermore, the sympathetic innervation as well as the thermogenic capacity of BAT were preserved in mice maintained at 13°C in spite of corticosterone treatment, whereas mice housed at 29°C and 22°C showed a marked reduction in both sympathetic nerve endings and thermogenic capacity following GC exposure. To test whether preservation of sympathetic activity is sufficient to prevent GC-induced dysmetabolism, we co-treated mice with corticosterone and CL-316.243 – a β3-adrenergic agonist. Selective activation of β3-adrenergic receptors not only averted the development of GC-induced fat accumulation and hyperinsulinemia, but also preserved the thermogenic capacity in BAT. Taken together, our data demonstrate that both cold-exposure, as well as β3-adrenergic activation, prevent the onset of GC-induced adipose dysfunction and related metabolic comorbidities. Thus, β3-adrenergic receptors can be considered a potential therapeutic target in the prevention of GC-induced obesity.

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OC12.2

Improved glucose metabolism and decreased weight gain in leptin-resistant, IGFBP2-deficient, db/db mice induced by AZP-3404, a 9-amino acid analog of IGFBP2

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Insulin-like growth factor binding protein-2 (IGFBP2) has been demonstrated to be a key mediator of the peripheral actions of leptin, and its deficiency is associated with impaired metabolic function. The metabolic activity of IGFBP2 can be localized to a unique heparin-binding domain (HBD-1) within its structure. AZP-3404 is a 9-amino acid analog of the IGFBP2 HBD-1 that has been demonstrated to increase glucose uptake by differentiated mouse myotubes in vitro, and to increase glucose disposal in leptin-deficient, and consequently IGFBP2-deficient, ob/ob mice. In the present study, we examined whether AZP-3404 could improve metabolic regulation in the db/db mouse which, as a result of a mutation in the leptin receptor, is leptin-resistant and consequently has elevated leptin levels but is IGFBP2-deficient. Nine-week old male db/db mice were treated with either vehicle or AZP-3404 at doses of 1, 3 or 6 mg/kg, sc, bid (n = 10/group). After 8 weeks of treatment, the impact on glucose disposal was assessed by administering an intraperitoneal glucose tolerance test (IPGTT; 1g glucose/kg, ip), following an overnight fast. All three doses of AZP-3404 produced similar increases in glucose disposal (AUC glucose decreased by 18.8, 21.4 and 23.1% with 1, 3 and 6 mg/kg AZP-3404, respectively) vs vehicle controls. Correspondingly, 4-hour fasted plasma insulin was decreased by 54, 48 and 52%, and the HOMA measure of insulin resistance was decreased by 55, 52 and 67%, following treatment with 1, 3 and 6 mg/kg AZP-3404, respectively, as compared with vehicle-treated mice. Over the 8 weeks of treatment, mice receiving vehicle gained an average 8.2 + 1.6 grams of body weight. Mice treated with AZP-3404 displayed a progressive decrease in body weight gain that began after 2 weeks and that continued through the 8 weeks of treatment, ultimately resulting in less than 50% of the weight gain observed in the vehicle-treated mice, and without an apparent change in food intake. Postmortem examination by micro-computerized tomography (μCT) imaging revealed decreases in both total and visceral fat mass that mirrored the AZP-3404-induced decrease in body weight gain, without effect on lean mass. These results, demonstrating both improved glucose metabolism and decreased body weight gain in the leptin-resistant, IGFBP2-deficient, db/db mouse, further confirms the ability of AZP-3404 to reproduce the metabolic

activity of IGFBP2, as well as its potential benefit as a novel therapy for disease states characterized by insulin resistance and/or obesity.

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OC12.3

Comparative evaluation of empagliflozin, canagliflozin and sitagliptin cardioprotective effect in diabetic rats with experimental myocardial infarction

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Background:
Myocardial infarction (MI) is one of the leading causes of mortality in patients with type 2 diabetes mellitus (DM), therefore it is essential to give preference to a glucose-lowering drug having most prominent cardioprotective properties. Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) have demonstrated an ability to decrease heart failure manifestations, cardiovascular death frequency not having a certain influence on MI occurrence. On the other hand, the influence of SGLT-2i therapy on MI manifestations was not fully investigated, neither in clinical nor in experimental studies. Moreover, comparative study of the various SGLT-2i representatives' protective effects in experimental MI was not carried out within the framework of one study.
Aim
To evaluate the influence of empagliflozin (EMPA) and canagliflozin (CANA), in comparison with sitagliptin (SITA), on hemodynamic parameters and myocardial damage area in type 2 diabetic rats in experimental MI.
Materials and methods
Type 2 DM was modelled in Wistar rats by means of 4-week high-fat diet followed by nicotinamide 230 mg/kg and streptozotocin 60 mg/kg administration. 4 weeks after DM induction the following groups were made: «DM+SITA»–treatment with SITA 50 mg/kg, «DM+EMPA»–treatment with EMPA 2 mg/kg, «DM+CANA»–treatment with CANA 25 mg/kg per os once daily for 8 weeks. Animals in «DM» group remained untreated for the following 8 weeks. Rats in control group were fed with standard chow. 16 weeks after the experiment beginning transient global myocardial ischemia was modelled in all rats. Hemodynamic parameters (ischemic contracture, left ventricle diastolic pressure, left ventricle developed pressure, coronary blood flow) and myocardium necrosis area were evaluated.
Results
The necrosis area was larger in «DM» group, than in control one (P = 0.018). Infarction size in «DM+SITA» did not differ from that in «DM» group (62.92 (41.29; 75.84) and 57.26 (45.51;70.08) %, respectively, P = 0.554). Necrosis area in «DM+EMPA» and «DM+CANA» groups was smaller than in «DM» group (37.90 (20.76; 54.66) %, 46.15 (29.77; 50.55) vs 57.26 (45.51; 70.08) %, P = 0.008 and P=0.009, respectively). Necrosis size did not differ between «DM+EMPA» and «DM+CANA» groups (P = 0.630). Ischemic contracture in «DM+CANA» group was less prominent than under the use of all other glucose-lowering drugs. We observed increase of coronary blood flow in «DM+EMPA» group, in comparison with «DM», «DM+CANA» and «DM+SITA» groups.
Conclusions
SITA does not have cardioprotective effect in ischemia-reperfusion injury in diabetic rats. EMPA and CANA have similarly prominent infarct-limiting properties. EMPA is able to increase coronary blood flow, whereas cardioprotective action of CANA is associated with ischemic contracture diminishing.

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OC12.4

Improvements in long-term appetite-regulating hormones in response to a combined lifestyle intervention for obesity

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Introduction
Altered levels of hormonal appetite regulators have been observed in obesity (BMI ≥ 30.0 kg/m^2), most prominently increases of insulin and leptin (indicating resistance) as well as decreases of adiponectin–all of which are long-term energy regulators and adiposity signals. Disrupted signaling of these hormones may have detrimental effects on metabolism, but may also promote weight gain. Weight loss is often accompanied by normalizations of long-term adiposity signals, but findings concerning short-term appetite regulators after weight loss vary across interventions (e.g. very low calorie diets vs. exercise). Moreover, it is debated whether such weight-loss-induced hormonal changes may reflect a disposition for weight regain. Here, we investigated changes of long–and short-term appetite signals in response to an intensive 75-week combined lifestyle intervention (CLI) comprising a normocaloric healthy diet, physical activity and psychotherapy to promote improved long-term weight management.
Methods
For 39 patients, data on fasting serum levels of appetite-regulating hormones (leptin, insulin, adiponectin, GIP, PP, PYY, CCK, FGF21) were available. Hormone levels were correlated to BMI and compared across three time points: T0, T1 (after 10 weeks; initial weight loss) and T2 (after 75 weeks; weight loss maintenance).
Results
At T0, hormone levels were not associated with BMI. BMI decreased significantly from T0 (40.13 kg/m^2 ± 5.7) to T1 (38.2 ± 5.4, p < .001) which was maintained at T2 (38.2 kg/m^2 ± 5.9, P < .001). There were no significant changes in GIP, PP, PYY, CCK and FGF21. Leptin decreased from T0 (44.9 ng/nl ± 15.3) to T1 (33 ng/nl ± 14.8, P < .001) and T2 (38.6 ng/nl ± 16.0, P < .01), just like insulin which was significantly decreased at T1 (123 pmol/l ± 65, P < .05) and T2 (128 pmol/l ± 64, P < .05) compared to T0 (160 pmol/l ± 80). Adiponectin did not change between T0 (3.36 mg/ml ± 2.1) and T1 (3.2 mg/ml ± 2.1), but was increased at T2 (3.7 mg/ml ± 2.9, P < .01) compared to T1. T0-T2 BMI decrease correlated positively with T0-T2 decreases in leptin (r = .667, P < .001), insulin (ρ = .535, P < .001) and increases of adiponectin (r = .412, P < .01), but no other hormone. T0-T1 hormone changes did not predict T1-T2 BMI changes.
Conclusion
A 75-week CLI was associated with beneficial changes in the long-term energy regulators adiponectin, leptin and insulin, but no changes in short-term appetite-regulating hormones were observed despite significant weight loss. Initial changes in appetite-regulating hormones were not associated with subsequent weight regain. Overall, our data suggest that a CLI does not lead to adverse changes in appetite regulation, but rather long-term improvements such as e.g. increased leptin and insulin sensitivity.

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OC12.5

Effects of the ghrelin gene-derived peptides on adipose browning and thermogenesis

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White adipose tissue (WAT) stores excess energy as triglycerides, while brown adipose tissue (BAT) dissipates energy through heat, acting as a defence against cold and obesity and as a positive regulator of metabolic functions. BAT thermogenic functions are mainly induced by mitochondrial uncoupling protein-1 (UCP-1), which induces uptake of lipids and glucose to sustain oxidation and thermogenesis in both brown and beige adipocytes. The ghrelin gene-derived peptides, acylated ghrelin (AG), unacylated ghrelin (UAG) and obestatin (Obe), are key regulators of energy homeostasis, as well as glucose and lipid metabolism. *In vivo* studies suggest that AG, via the growth hormone (GH) secretagogue receptor type 1a (GHS-R1a), exerts inhibitory effects on UCP-1 mRNA expression and noradrenaline release in BAT; moreover, ablation of GHS-R in mice increased BAT thermogenic functions. However, the role of the ghrelin peptides in adipose browning and BAT function is yet unknown. Thus, we aimed to assess the role of AG, UAG and Obe in promoting white adipocyte browning and on brown adipocyte thermogenic functions. 3T3-L1 preadipocytes and human mesenchymal stem cells (hMSC) were differentiated to white adipocytes for 9 and 21 days respectively. Browning was induced for 72 h with rosiglitazone and insulin,

in the presence or absence of AG, UAG and Obe. UAG and Obe, but not AG, increased the mRNA levels of BAT genes (Ucp-1, Cidea, Tmem26, Prdm16, Pgc-1α) and lipolytic genes (CPT-1a and Sirt1), while reducing the lipogenic gene C/EBP in 3T3-L1 and human adipocytes. UAG and Obe also increased the number of small lipid droplets, characteristics of brown adipocytes. The thermogenic role of the peptides will be next studied in rat T37i brown adipocytes. Overall, our findings indicate that Obe and UAG, but not AG may promote browning of adipocytes, leading to the identification of new potential therapeutic targets against obesity and metabolic diseases.

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OC12.6

Molecular and functional mapping of POMC neuronal heterogeneity in obesity

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The brain is critically involved in the regulation of energy balance and glucose homeostasis. Depending on the levels of energy available in our body, the activity of a group of hypothalamic neurons expressing the neuropeptidergic marker proopiomelanocortin (POMC) changes and it plays a key role in maintaining energy balance. When POMC neuronal activity is altered, this can lead to impaired energy homeostasis and therefore to obesity. However, POMC neurons are highly diverse, and whether or not such heterogeneity is implicated in the development of diet-induced obesity (DIO) remains unknown. Here, we used a lineage-tracing approach in combination with immunofluorescence, fluorescent in situ hybridization, and ex-vivo hypothalamic slice electrophysiology, to characterize the molecular and functional heterogeneity of POMC neurons in control lean and DIO mice. Thanks to the genetic strategy employed, we have successfully 'traced' with a reporter protein POMC neurons in adult mice, thereby allowing to study these neuronal cells independently from the expression of their main marker POMC. Three subpopulations of POMC neurons could be identified: neurons expressing high levels of POMC (POMC-high), neurons with low POMC expression (POMC-low), and neurons with no POMC expression (POMC-'ghost'). Notably, chronic exposure to a high-fat diet (HFD) led to alterations in the peptidergic and molecular machinery of the POMC-high subpopulation, but did not affect POMC-low or POMC-ghost neurons. Thus, our data suggest that DIO leads to selective functional alterations in specific POMC neuronal clusters. The approach proposed may be used in the future to map the functional relationship between specific subpopulations of POMC neurons and obesity pathogenesis.

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Pituitary and Neuroendocrinology

OC13.1

TP53 mutations in functional corticotroph tumours: prevalence and clinical relevance

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Introduction
TP53 mutations have been rarely reported in pituitary tumours. Recently two exploratory exome sequencing studies have identified somatic TP53 mutations in a small number of functional corticotroph tumours (6/18 and 4/10) with USP8 wild type (wt) status, suggesting that they may be more frequent than previously thought. Nevertheless, the clinical impact of those mutations is still unknown.
Aim
To determine the prevalence of TP53 mutations in a cohort of USP8wt tumours and to identify clinical features associated with TP53 mutations.
Methods
We analysed samples from 54 patients with USP8wt corticotroph tumours, (47 females, 7 males), 43 diagnosed with Cushing's disease (CD) and 11 with corticotroph tumour progression after bilateral adrenalectomy/Nelson syndrome (CTP/NS). An additional cohort of 23 patients with USP8 mutant (mut) tumours was included for comparison (23 females, 14 CD and 9 CTP/NS). In total, 63 tumours were fresh frozen and 14 formalin-fixed paraffin embedded. The complete TP53 coding region was amplified by PCR with specific primers and sequenced using the Sanger method.
Results
8 single-nucleotide variants in 7 samples (prevalence 13% in USP8wt tumours) were annotated in ClinVar database as pathogenic, likely pathogenic, or uncertain significance but evidence of protein function alteration. All of them were predicted as pathogenic in the COSMIC database. Mutations were detected in heterozygosis and were located in exon 5 (c.398T>A, p.Met133Lys), exon 6 (c.644G>A, p.Ser215Asn), exon 7 (c.714T>A, p.Cys238X; c.718A>G, p.Ser240Gly; and c.773A>C, p.Glu258Ala), exon 8 (2 unrelated patients with c.818G>A; p.Arg273His) and exon 10 (c.1009C>G; p.Arg337Gly). One long deletion was found in one case, but no indels. No mutation was found in USP8mut samples. Mutations were more frequent in CTP/NS than in CD (36% vs 7%, P = 0.025). We found association with: older age at diagnosis (TP53mut 52 ± 21 vs. USP8mut 36 ± 12 vs. wt 41 ± 14 years old, P = 0.046; TP53mut vs USP8mut, P = 0.04), lower frequency of total tumour resection (TP53mut 0% vs. USP8mut 83% vs wt 63%, P = 0.015), higher invasion rate (TP53 100% vs USP8mut 44% vs wt 48%, P = 0.012) and lower survival (TP53mut 50% vs. USP8mut 95% vs. wt 94%, P = 0.012). After stratification in CD or CTP/NS Total resection and survival lost statistical significance but CTP/NS patients with TP53 mutations trended towards lower survival rate (25% vs 89% USP8mut, 86% wt, P = 0.069). No differences were found regarding tumour size or hormone levels.
Conclusion
TP53 mutations are more frequent in CTP/NS than in CD and may be related to a more aggressive tumour behaviour.

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OC13.2

In vitro activity of glutamate decarboxylase types, 65 and 67 in GABAergic brain-regions sleeping-process related

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We determined *in vitro* activity of 17β-estradiol and or progesterone on glutamate conversion to GABA in different GABAergic regions from the brain of castrated and non-castrated rats. The glutamate decarboxylase catalyzes this conversion; there are two different isotypes of glutamate decarboxylase, GAD_{65} and GAD_{67}. Whereas GAD_{65} is a membrane enzyme, GAD_{67} is present in the supernatant obtained after centrifuging to 14,000 g. We treated three different groups of ovariectomized rats with increasing week-dose of 17β-estradiol, progesterone, and the combination of both for five weeks. We maintained one group of the ovariectomized rats as a control. After five weeks of treatment, we separated the rat-brain. We dissect the brain regions which have previously been related to the sleep process: mammillary bodies, *locus coeruleus*, *substantia nigra*, and the ascending reticular activating system. After homogenates and centrifuge these tissues, we incubating the membrane fraction and supernatant separately with tritiated-glutamate a pyridoxal phosphate. We assessed the decarboxylation of glutamate for the formation of a Schiff base, which was purified by thin-layer chromatography. We identified this Schiff base by its fluoresces at ş 302 nm. We quantify this conversion by counting the radioactivity present in the fluorescence zone. Results indicated that 17β-estradiol-treatment increased the GAD_{65} and GAD_{67} activity in all the studied brain-regions compared with those of the ovariectomized (vehicle-treated) control. In contrast, progesterone increased GAD_{65} and GAD_{67} activity only in the

ascending reticular activating system and *locus coeruleus*. Furthermore, 17β-estradiol plus progesterone-treatment also increased GABA synthesis in the ascending reticular activating system and *locus coeruleus* compared to the vehicle-treated control. However, the ovariectomized (vehicle-treated) control showed only GAD_{65} and GAD_{67} activity in the mammillary bodies and *substantia nigra*. The brain GABAergic structures studied are involved in the process of sleep. Therefore the increase of the GABA formation induced by 17β-estradiol is responsible for maintaining sleeping in rats. However, the progesterone role seems to be a regulator of this process because the *locus coeruleus* and the ascending reticular activation system are responsible for inducing the sleep-wake rhythm.

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OC13.3

Cardiovascular and metabolic safety of growth hormone treatment in adult patients with growth hormone deficiency: real-world data from two large studies in the USA and Europe

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Introduction
Evidence suggests that adults with growth hormone deficiency (AGHD) exhibit metabolic abnormalities that are typical of the metabolic syndrome and are risk factors for type 2 diabetes (T2D). Concerns about undesirable effects of growth hormone replacement therapy (GHRT) on glucose metabolism have been raised, but the risk of T2D from AGHD has mixed evidence. This analysis aims to evaluate cardiovascular (CV) and metabolic safety of GHRT in these patients in a real-world setting.
Methods
NordiNet IOS (NCT00960128) and ANSWER (NCT01009905) were observational, non-interventional studies that investigated the long-term effectiveness and safety of GHRT. This analysis includes pooled data from the AGHD population from the two studies (n = 1,275; 50.6% female). Baseline characteristics [mean (SD)] were: age at treatment initiation, 48.5 (13.7) years; growth hormone dose, 0.3 (0.2) mg/day; and body mass index, 29.9 (7.1) kg/m^2. We compared the proportion of patients with CV and metabolic risk factors above the clinical threshold at baseline and after 7 years of GHRT.
Results
The overall proportion of patients with increased CV and metabolic risk factors was not different from baseline after 7 years of follow up, except for the decrease in patients with high LDL-cholesterol (P = 0.03) and non-HDL-cholesterol (P = 0.03) (Table 1). The only statistically significant gender-specific result observed was the decrease in proportion of men with high non-HDL-cholesterol (P = 0.007).
Conclusion
GHRT in AGHD did not increase the percentage of patients with increased CV and metabolic risk factors. This analysis provides further insight into the safety of GHRT in AGHD.

Table 1 CV and metabolic risk factor changes from baseline to 7 years' follow-up

Risk factor thresholds	Patients included in this analysis *N*	Baseline *n* (%)	After 7 years *n* (%)	*P*-value*
FPG ≥ 126 mg/dl	58	4 (6.90)	4 (6.90)	1.0000
HbA_{1c} ≥ 6.5%	81	5 (6.17)	6 (7.41)	1.0000
SBP ≥ 130 mm Hg	130	61 (46.92)	65 (50.00)	0.7098
DBP ≥ 80 mm Hg	130	82 (63.08)	68 (52.31)	0.1025
Total cholesterol ≥ 4.0 mmol/l	88	83 (94.32)	82 (93.18)	1.0000
LDL-cholesterol ≥ 3.0 mmol/l	56	40 (71.43)	28 (50.00)	0.0328
HDL-cholesterol < 1.0 mmol/l (men) and < 1.3 (women)	84	21 (25.00)	21 (25.00)	1.0000
Non-HDL-cholesterol ≥ 3.4 mmol/l	82	65 (79.27)	51 (62.20)	0.0251
Waist circumference ≥ 102 cm (men) and ≥ 88 cm (women)	65	35 (53.85)	27 (41.54)	0.2189

*Calculated using Fisher's exact test

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OC13.4

Growth hormone-releasing hormone (GHRH) promotes survival and proliferation of neural stem cells and reduces amyloid-β-induced toxicity

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Neurogenesis, a process by which new neurons are generated from precursors, still persists in discrete regions of the adult hippocampus. The hippocampus is critical for learning and memory and is a main target of AD, which causes massive neuronal death, reduction in neurogenesis and impairment in cognitive functions. Therefore, preventing neuronal loss or increasing the production of new neurons may represent a potential therapeutic strategy to reduce AD-induced cognitive decline. Growth hormone-releasing hormone (GHRH), apart from promoting growth hormone (GH) secretion from the pituitary, exerts many extrapituitary functions, including stimulation of cell survival, cardioprotection and protection against diabetic retinopathy. Furthermore, expression of GHRH, as well as GHRH-receptor (GHRH-R) and its splice variants (SVs), has been demonstrated in different brain regions, including the cerebral cortex, cerebellum and brain stem cells. To date, however, the role of GHRH on neurogenesis and neuroprotection is still unknown. Thus, we aimed to investigate the role of GHRH on survival, proliferation, apoptosis and differentiation of rat hippocampal neural stem cells (NSCs), in stress conditions such as growth factor deprivation and amyloid-β peptide 1–42 ($A\beta_{1-42}$)-induced toxicity, and to define the underlying mechanisms. We found expression of both mRNA and protein for pituitary GHRH-R in NSCs. GHRH dose-dependently increased cell survival and proliferation and reduced apoptosis in NSCs cultured under both growth factor deprivation and exposure to $A\beta_{1-42}$; these effects were blocked by the GHRH antagonist JV-1–36. The underlying mechanisms involved $G\alpha_s$/cAMP/PKA/CREB signaling, as demonstrated the results obtained in the presence of specific inhibitors, and phosphorylation of ERK1/2 and PI3K/Akt. In addition, GHRH counteracted the effect of $A\beta_{1-42}$ on elevation of the proapoptotic protein BAX and inhibition of the antiapoptotic protein Bcl-2. Moreover, GHRH induced GSK-3β phosphorylation and counteracted the $A\beta_{1-42}$-induced inhibition of GSK-3β phosphorylation. Finally, the role of GHRH was examined on differentiation of NSCs into neuronal lineages, such as neurons, oligodendrocytes, and astrocytes. Interestingly, GHRH increased the mRNA levels of the neuronal marker *Tuj1*, while showing no significant effect on *GFAP* and *Ripk1*, specific for astrocytes and oligodendrocytes, respectively. Collectively, these results suggest a role for GHRH in preventing neuronal loss and in promoting neurogenesis, with potential therapeutic application of its agonistic analogs in neurodegenerative diseases, such as AD.

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OC13.5

Potential therapeutic role of somatostatin and cortistatin in prostate cancer

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Somatostatin (SST), Cortistatin (CORT), Neuronostatin (NST) and their receptors [SST/CORT-receptors (sst1–5/sst5TMD4-TMD5) and NST-receptor (GPR107)] comprise a hormonal pleiotropic system involved in the regulation of multiple pathophysiological functions. Certain components of this system are dysregulated in endocrine-related cancers, including prostate cancer (PCa), wherein we have found that alterations in specific components of this regulatory system [i.e. NST-GPR107-circuit/sst1/sst5TMD4 (1–3)] influence their development and progression. However, a comparative, parallel study of the presence and therapeutic role of SST and CORT in PCa has not been reported hitherto. For that reason, we analysed functional parameters (cell proliferation and migration) in response to SST and CORT treatment (10^{-7}M) and to siRNA-induced CORT-silencing in different PCa-derived cell lines [androgen-dependent (AD): LNCaP, and androgen-independent (AI): 22Rv1 and PC-3, which are models of hormone-sensitive and Castration-Resistant PCa (CRPCa), respectively], and in the normal prostate cell-line RWPE-1. Moreover, western-blotting and quantitative real-time-PCR were implemented to determine the mechanisms of action associated to SST/CORT treatment and CORT-silencing in PCa cells. SST and CORT treatment significantly inhibited proliferation and migration capacity in AI-PCa cells, but not in AD-PCa or in normal cells. Mechanistically, the antitumor capacity of these peptides was associated to the modulation of important oncogenic signalling-pathways (i.e. AKT/JNK). Interestingly, among all SST-receptors, only sst5 was significantly overexpressed in AI-PCa cells compared to normal-cells, suggesting that the SST/CORT-actions observed in PCa-cells might be mainly exerted through sst5. Remarkably, CORT was highly expressed, while SST transcripts were not detected, in all prostate cell-lines analysed, suggesting that local endogenous CORT could be exerting antitumor actions in PCa-cells through an autocrine/paracrine mechanism. Supporting this idea, CORT-silencing drastically increased the proliferation rate of AI-PCa cells 22Rv1 and PC-3. Finally, CORT expression was correlated with key clinical parameters (i.e. Gleason Score and metastasis) in two *in silico* cohorts of PCa patients (Grasso/Taylor). Altogether, our results demonstrate that SST/CORT treatment reduced PCa aggressiveness in CRPCa-cells possibly via sst5 and through the alteration of key oncogenic signalling-pathways, suggesting that SST/CORT peptides might be used as therapeutic tool for CRPCa. Moreover, our data revealed that endogenous CORT is highly expressed in PCa cells wherein could exert an auto-regulatory role.

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OC13.6

A Phase 3 Large International Noninferiority Trial (MPOWERED): Assessing Maintenance of Response to Oral Octreotide Capsules in Comparison to Injectable Somatostatin Receptor Ligands

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Background
MPOWERED, a large phase 3 trial, assessed maintenance of response to oral octreotide capsules (OOC; MYCAPSSA) compared to injectable somatostatin receptor ligands (iSRLs) in patients with acromegaly who responded to OOC and iSRLs (octreotide or lanreotide). OOC were recently approved in the US for patients with acromegaly who responded to and tolerated iSRLs.
Methods
Eligibility criteria included age 18 – 75 years at screening, acromegaly diagnosis, disease evidence, biochemical control (insulin-like growth factor I [IGF-I] < 1.3 × upper limit of normal [ULN] and mean integrated growth hormone [GH] < 2.5 ng/ml) at screening, and ≥6 months' iSRL treatment. Effective OOC dose was determined in a 26-week Run-in phase. Eligible patients (IGF-I < 1.3 × ULN and mean integrated GH < 2.5 ng/ml, week 24) were randomized to a 36-week controlled treatment phase (RCT), receiving OOC or iSRLs starting at week 26. The primary end point was a noninferiority assessment of proportion of patients biochemically controlled in the RCT (IGF-I < 1.3 × ULN using time-weighted average). Other end points included nonresponse imputation of the primary end point, landmark analysis using proportion of responders based on average of last 2 IGF-I values at end of RCT, and change from baseline RCT (week 26) IGF-I and GH levels.
Results
Of 146 enrolled patients, 92 entered the RCT (OOC, n = 55; iSRLs, n = 37). Both arms were well balanced for age, sex, and acromegaly duration. OOC demonstrated noninferiority to iSRLs in maintaining biochemical response, with 91% (CI, 80% – 97%) of OOC and 100% (CI, 91% – 100%) of iSRL groups maintaining control during the RCT. Of those responding at end of Run-in, 96% of patients on OOC maintained response during RCT. Using nonresponse imputation, 89% of OOC and 95% of iSRL groups were biochemically controlled in RCT. Landmark analysis of those responding at end of Run-in showed that 94% of patients in each group maintained response at RCT end. In both groups, IGF-I levels were stable in the RCT, average IGF-I at baseline and RCT end being 0.9 × ULN (OOC) and 0.8 × ULN (iSRL). Mean change in GH from RCT start to RCT end was -0.03 ng/ml (OOC) and +0.29 ng/ml (iSRL). Safety data were mostly similar between groups; the OOC group did not experience injection site reactions.
Conclusion
In this noninferiority trial in patients with acromegaly, OOC demonstrated maintenance of biochemical response compared to iSRLs. Results support the efficacy of OOC as a possible iSRL alternative.

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Across Endocrinology

OC14.1

Organoids as a model to study the impact of EDCs on the prostate gland.

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Endocrine disrupting chemicals (EDCs) produce adverse effects associated with numerous pathologies: neurological disorders, metabolic diseases, infertility and cancer for example. How EDCs interfere with the development of hormone-sensitive tissue is a major question in biology. In this study, we propose that the model of prostate organoids can be used to study the effects of EDCs on the development of the prostate gland. Indeed, the differentiation of adult stem cells (ASC) isolated from prostate into organoids recapitulate quite faithfully the development of the gland. We isolated ASC from mouse prostate (7 to 9 weeks) using flow cytometry. We cultured them in matrigel with a specific organoid medium containing dihydrotestosterone (DHT). These culture conditions allowed the proliferation and the differentiation of ASC. This resulted in a 3D cellular structure composed of an external basal cell layer, an internal luminal cell layer and a central cavity containing luminal cell secretions. Once developed, organoids could be stained and imaged using confocal microscopy in order to analyze phenotypes induced by EDCs. DHT is known as the main regulator of the prostate gland differentiation, we first explored the kinetics of DHT regulation. We showed that prostate organoid development was divided in two phases. The first one was a hormone-independent phase from day 0 (D0) to D4, during which a beta-catenin gradient was formed along organoids radius.

This gradient could control early differentiation of adult stem cells into luminal-like cells. The second phase, from D5 to D9, was DHT dependent and induced the late differentiation into secretory luminal cells leading to a lumen formation in the center of organoids. We investigated the effect of anti-androgenic compound DDE on lumen formation in prostate organoid. We used mathematical approaches to increase the robustness of our model and evaluate the actions of EDCs on normal differentiation and development of organoids. Moreover, we hypothesized that luminogenesis may involve ion channels whose expression or functionality are likely to be regulated by hormones, as previously reported in intestinal organoids. The interaction of DHT and DDE and the cystic fibrosis transmembrane conductance regulator (CFTR) is currently studied in prostate organoids. Thus, we present here the organoid model as a new screening platform to study the effects of EDCs on the prostate gland by combining an analysis of organoids morphological features with mathematical modeling.

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OC14.2

Optimisation of a rapid, sensitive and cost-effective rat NIS iodide uptake assay

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Thyroid hormones are evolutionarily conserved iodine-containing regulators of metabolism and development (reviewed by Mullur *et al*. (2014)). A key process in synthesis of the effectors thyroxine and tri-iodothyronine is the uptake of iodide from the bloodstream into thyroid follicular cells by the sodium-iodide symporter channel (NIS) encoded by the solute-carrier gene SLC5A5. Perturbation of NIS activity by environmental chemicals can lead to rapid and potent changes in thyroid hormone signalling with concomitant harmful effects. Accordingly, an assay to assess the impact on iodide symport by small molecules is a valuable tool for identifying potential endocrine disruptors. The FRTL-5 cell line has been used to study NIS function for more than 40 years. They were isolated by growing thyroid explants in low serum media with a defined additive cocktail to maintain thyroid characteristics along with proliferative capability. They depend critically on presence of thyrotropin, without which proliferation and other thyroid functions are lost (Ambesi-Impiombato *et al*. (1980)). In 2010, a non-radioactive method to quantify iodide uptake by FRTL-5 cells in 96-well plate format was published (Waltz *et al*. (2010)). Here, modifications to the published method are presented that improve sensitivity (1.5pmol compared to 10pmol), with an optimized incubation period (7.5 minute uptake instead of 60 minutes) and improved linearity with regard to iodide concentration and uptake time. We observe similar IC_{50} values for the competitive inhibitors sodium perchlorate, sodium tetrafluoroborate and sodium thiocyanate. Finally, we present a modification to the cell culture medium that reduces costs by more than 20-fold through complete elimination of thyrotropin, whilst retaining proliferation and stable thyroid characteristics such as NIS function unchanged for more than 70 passages.

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OC14.3

Is thyroid gland a target of SARS-CoV-2 infection? Results of the analysis of necropsy thyroid specimens from COVID-19 patients

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Background
In the 2002 outbreak of severe acute respiratory syndrome (SARS) a number of patients presented abnormalities in the thyroid functioning, neuroendocrine and calcium homeostasis. It was detected in autopsies from SARS Coronavirus (SARS-CoV) patients that the thyroid gland was significantly affected by the disease, with extensive injury and death of follicular and parafollicular cells. In the present SARS-CoV-2 pandemic some studies start to report acute thyroiditis and alterations in the levels of thyroid hormones [(triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH)]. Thyroid cells present high levels of mRNA expression of angiotensin-converting enzyme 2 (ACE2), the host receptor for SARS-CoV-2. It remains poorly studied the thyroid expression of proteins that predispose to SARS-CoV-2 infection and if thyroid cells can be a direct or indirect target of SARS-CoV-2 infection.
Aims
We aim to establish the expression of ACE-2, Furin and TMPRSS2 in thyroid from infected and uninfected patients. We aim also to investigate if thyroid cells can be directly infected by the SARS-CoV-2 and which are the putative consequences of this infection in the gland morphology.
Material and methods
In collaboration with Centro Hospitalar Universitário de São João and Universidade São Paulo, Brazil, we have access to autopsy thyroid samples (n = 15) and clinical data from patients infected with SARS-CoV-2. We evaluated the expression, in the autopsy thyroid samples and in a series of other thyroid lesions (normal, thyroiditis and tumors; n = 40), of the ACE2, Furin and TMPRSS2. We analyzed the autopsy thyroid samples for cleaved caspase 3 (apoptosis) and the IHC for viral proteins (spike and nucleocapsid).
Results/conclusions
Our results show positivity for cleaved Caspase 3 and extensive morphologic alterations in the necropsy thyroid samples. ACE2 expression was more intense and frequent in thyroid samples from infected individuals than in the control series. We detected signs of acute inflammation, just vasodilatation and no increased number of neutrophils. We are still evaluating the putative correlation of the inflammation with histologic features using digital pathology and immunohistochemistry. The autopsy thyroid samples will be studied with RNAscope for validation of SARS-CoV-2 RNA expression and other parameters: histological features, proliferation and immune response. We expect to disclose the (direct or indirect) effects of SARS-CoV-2 infection in thyroid gland and eventual consequences in thyroid function of recovered COVID-19 patients.

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OC14.4

Evaluation of the hypothalamic-pituitary-adrenal axis suppression in kidney transplant recipients and its association with metabolic parameters

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Introduction
Corticosteroids are included in the maintenance immunosuppressive regimen in most kidney transplant recipients. Studies evaluating the effect of chronic low-dose glucocorticoid treatment on the hypothalamic-pituitary-adrenal (HPA) axis and the metabolic profile of these patients are limited.
Aim
The objective of the study was to evaluate the metabolic effects and the alterations of HPA axis regulation in stable kidney transplant recipients treated with long-term low-dose glucocorticoids.
Methods
A cross-sectional study was conducted including adult kidney transplant recipients on a stable immunosuppressive regimen followed in our center. Selected patients were transplanted for over a year and maintained an estimated glomerular filtration rate (eGFR)>54 ml/min/1.73 m^2 (CKD-EPI equation). Examined metabolic abnormalities included new-onset diabetes mellitus after transplantation (NODAT), central obesity and dyslipidemia as defined by IDF criteria. HPA axis evaluation encompassed measurements of morning (0800 hours) serum cortisol, adrenocorticotropic hormone (ACTH), dehydroepiandrosterone-sulphate (DHEAS) levels; 24-hour urine free cortisol excretion (UFC) and hair cortisol levels (HC). HC samples (2 cm length) were collected according to SoHT guidelines and measured by liquid chromatography tandem–mass spectrometry (LC–MS/MS). All hormonal functional tests were performed in the same laboratory. An intergroup analysis between patients who received glucocorticoids and those who did not was performed.

Results
Sixty-four kidney transplant recipients (males 67.2%) with a mean age of 53 ± 13.4 years and a median time from transplantation of 71 (IQR 25–147) months were included in the study. The mean eGFR was 70.1 ± 15.1 ml/min/1.73 min^2. Most patients (81.3%) were on a tacrolimus-based regimen, while prednisolone was used by 84.4% of subjects with a mean dose of 5 ± 1 mg/d. NODAT was observed in 17.2% of patients, 81.8% of whom were on glucocorticoids. Dyslipidemia was found in 67.2% of patients and central obesity in 62.5% of men and 50% of women. Glucocorticoid-treated patients had significantly lower median serum cortisol ($P < 0.001$), DHEAS ($P = 0.002$) and UFC ($P = 0.012$). ACTH and HC levels were also lower although not statistically significant ($P = 0.644$ and $P = 0.285$, respectively). Markedly suppressed UFC levels (< 6 μg/24 h) were found in 29.4% of glucocorticoid-treated patients correlating with decreased morning serum cortisol < 5 μg/dl) ($P = 0.01$), DHEAS ($P = 0.021$) and HC levels ($P = 0.899$). Among metabolic parameters, NODAT was associated with suppressed levels of UFC ($P = 0.041$) and HC ($P = 0.042$) in glucocorticoid-treated patients.
Conclusions
Chronic low-dose steroid-treated kidney transplant recipients exhibited HPA axis suppression and increased prevalence of NODAT. HC could be a potential adjunctive biomarker of adrenal insufficiency, although more studies are required to establish this marker.

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OC14.5

The use of e-REC for capturing the occurrence of covid-19 infections in people with rare endocrine conditions

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Introduction
Following the onset of the COVID-19 pandemic in early spring 2020, there was a need to identify the burden of this infection on people with rare endocrine conditions. The European Registries For Rare Endocrine Conditions (EuRRECa) was launched in 2018 in collaboration with Endo-ERN, ESPE and ESE to support the needs of the wider endocrine community. The project consists of an e-reporting (e-REC) platform that allows monthly reporting of new clinical encounters.
Methods
The ESE's Rare Disease Committee, formed in April 2020, created a COVID-19 taskforce which disseminated the use of e-REC through broad condition specific study groups. The e-REC platform does not collect personally identifiable information and does not require individual patient consent. The platform was made available to all centres to report a new confirmed or suspected case of COVID-19 in a patient with an existing endocrine or metabolic bone condition.
Results
Since launching the e-REC platform for notification of COVID-19 infections in March 2020, a total of 21 centres from 10 countries have agreed to participate. Of these 21 centres, 10 were reporting patients < 18 yrs (ie children) and 14 were reporting those ≥18 yrs old (adults). Of the 21 centres, 16 (76%) centres from 9 (90%) countries have used e-REC to notify 100 cases of which 55 were confirmed COVID-19 infections and the remainder were suspected. The median number of cases reported per centre was 2 (range 1, 20) and the median number of cases reported per month was 11 (3, 28). Of the 100 cases, 93 were in adults. This total 100 cases can be further categorized as broad thematic categories of pituitary disorders (n, 36), adrenal disorders (n, 32), genetic (neuro)endocrine tumours (n, 12), thyroid disorders (n, 6), calcium/phosphate disorders (n, 6), bone dysplasia (n, 4), glucose and insulin disorders (n, 2), growth and genetic obesity disorders (n, 1) and disorders of sex development and maturation (n, 1).
Conclusion
The use of the e-REC platform for identifying COVID-19 infection in people with rare endocrine conditions has been accepted in several centres and the platform is open for new centres. The majority of cases that have been reported are in adults and a high percentage are confirmed cases. Preliminary data suggest that COVID-19 infections are being reported more often in some endocrine conditions and there is a need to understand the reason for these differences as well as the impact of the infection on these patients.

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OC14.6

Endocrine disorders in patients with Fabry Disease: A comprehensive reference center study

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Fabry Disease (FD) is a rare X–linked metabolic storage disease characterized by a–galactosidase A deficiency and deficient lysosomal function. The patients suffer from diffuse organ manifestations due to the accumulation of the substrate globotriaosylceramide (Gb3), which are only partially reversed by the available enzyme replacement (ERT) therapies. Previous endocrinological studies in patients with FD included small patient numbers or focused on a certain organ. To investigate the function of the endocrine system in patients with FD, we conducted an observational prospective study and included 77 patients with genetically confirmed FD (26 men, 20/26 classic, 6/26 late–onset phenotype, 51 women, 41/51 and 10/51 respectively), who are systematically followed by our reference center. Within this cohort, 3/77 new cases of subclinical and 2/77 of manifest hypothyroidism were identified while no abnormalities in the GH/IGF-1 axis was found. All (77/77) patients had normal baseline ACTH and morning cortisol levels and unrestricted cortisol response upon short time synacthen testing (62/62). Several cases with altered renin–angiotensin–aldosterone system (RAAS) were detected but none of them included clinical or hormonal suspicion of primary aldosteronism and the discrepancies were explained in the context of chronic kidney disease (CKD) or antihypertensive medications. 11/77 patients were suffering from significant hypophosphatemia ($P < 0.80$ mmol/l), likely due to VitD deficiency. 25/77 patients had VitD deficiency (25(0H)VitD < 20 mg/l) and 25/77 had insufficiency (25(0H)VitD between 20 and 30 mg/l) despite the fact that 23/50 were substituted with cholecalciferol. In male patients, normal baseline testosterone, FAI and SHBG levels were documented with no indication of hypogonadism. In 1/33 women, primary infertility and estrogen substitution was reported and further 4/33 achieved pregnancy only following IVF. 5/33 patients had a history of miscarriages but all of them delivered children. One/33 women had clinical and biochemical features of PCOS. To our knowledge, this is the largest endocrine study in patients with FD. Our findings indicate presence of a range of endocrine conditions in patients with FD. Longitudinal and case/control studies will be required to provide indication whether these findings are caused by FD dependent mechanisms on endocrine organs or represent independent co-morbidities similar than in the general population. Overall, our study highlights the importance of actively seeking and diagnosing endocrine disorders in patients with FD with the goal to optimise their health care.

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Late Breaking

OC15.1

Differential steroidomic profiles of human visceral and subcutaneous adipose tissue before and after bariatric surgery-induced weight loss

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Background
Obesity is closely associated with impaired adipose tissue function. Although bariatric surgery is the treatment of choice for severe obesity and its related conditions, there are conflicting data on the reversal of adipose tissue dysfunction after surgery-induced weight loss. We hypothesise that local steroid hormone availability influences fat deposition or mobilisation and that these changes track with weight loss improvements, because plasma steroid concentrations are altered in obesity. For the first time, we characterise markers of visceral (VAT) and subcutaneous (SAT) adipose tissue function including fourteen *in situ* endogenous steroids and their change after surgery-induced weight loss in humans.
Methods
Institutional approval and consent were obtained. SAT and VAT were collected in men (n = 15) and women (n = 23) before and after sleeve gastrectomy. A validated liquid chromatography-tandem mass spectrometry method was developed to determine steroid hormone amounts in adipose tissue. Principal component analysis was performed to establish global trends related to the impact of depot, sex, and time after surgery. Repeated mixed-models were used to investigate associations of steroid hormones measured by ESI-LC-MS/MS (oestrone, oestradiol, androstenedione, testosterone, 5α-DHT, 5α-androstanedione, DHEA, cortisone, cortisol, 11β-hydroxyandrostenedione, 11-ketoandrostenedione, 11β-hydroxytestosterone, 11-ketotestosterone, and 11-ketoDHT) and of several steroid-converting enzyme transcripts.
Results
Post-surgery samples were obtained on average 26 ± 6 months after baseline. Participants had a preoperative mean BMI of 53 kg/m^2 (range 38–65). VAT had higher amounts of glucocorticoids, androgens, and 11-oxy-androgens. Oestrogens were higher in SAT. After weight loss, testosterone and 5α-dihydrotestosterone adipose tissue amounts were increased only in men (P < 0.05). Oestrogen amounts were decreased in both sexes (P < 0.05). Aromatase expression was higher in men before weight loss and then decreased in both sexes (P < 0.01). Expression of *DHRS11*, an enzyme with oestrogenic 17β-HSD activity, was decreased in women after weight loss (P < 0.01). *AKR1C2*, *AKR1C3*, *HSD11B1*, *SRD5A1* and *SRD5A3* expression also decreased significantly in both fat depots (P < 0.05), but not cortisol nor cortisone amounts. The waist-to-hip ratio was positively associated with concentrations of testosterone, 5α-DHT, 11β-hydroxyandrostenedione, 11β-hydroxytestosterone, androstenedione and 11-ketoDHT in VAT, and with testosterone and 11β-hydroxytestosterone in SAT (P < 0.05).
Conclusions
This is the first study reporting extensive intra-adipose steroid profiling before and after weight loss in a sample of men and women with severe obesity, including newly characterised 11-oxy-androgens. We found that intra-adipose oestrogen amounts decreased, active androgens increased, and 11-oxy-androgens were stable following bariatric surgery. None of the steroids studied were directly associated with the degree of weight loss, suggesting other biological mechanisms at play.

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OC15.2

Screening for mutations in isolated central hypothyroidism reveals a novel mutation in insulin receptor substrate 4 (IRS4)

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Background
Central hypothyroidism (CeH) is a rare condition affecting approximately 1:16000 – 100 000 individuals. Congenital forms can harm the normal development if not detected and treated promptly. The clinical and biochemical diagnosis especially of the isolated CeH can be challenging. The cases are not usually detected in the neonatal screening, which, in most countries, are focused on detection of the more prevalent primary hypothyroidism. Until now, five genetic causes for isolated CeH have been identified. Here we aimed to identify the genetic cause in two brothers with impaired growth and diagnosed with CeH at the age of 5 years. Furthermore, we evaluated the candidate gene variants in a large genetic database.
Methods
Clinical and biochemical characterization together with targeted next-generation sequencing (NGS) was used to screen the genetic etiology in a family of two brothers presenting with CeH. Screening of *insulin receptor substrate 4* (*IRS4*) variants was carried out in the FinnGen-database.
Results
A novel monoallelic frameshift mutation c.1712_1713insT, p.Gly572Trp fs*32 in an X-linked *IRS4* gene was identified in NGS analysis in both affected males and confirmed using Sanger sequencing. Their mother was an unaffected carrier. In addition to the declined growth at the presentation, central hypothyroidism and blunted TRH test, no other phenotypic alterations were found. The diagnostic tests included head MRI, thyroid imaging, bone age, and laboratory tests for thyroid autoantibodies, glucose, insulin and glycosylated hemoglobin levels. Examination of the *IRS4* locus in FinnGen (R5) database revealed the strongest associations to a rare Finnish haplotype associated with thyroid disorders (P = 1.3e-7) and hypothyroidism (P = 8.3e-7).
Conclusions
Here, we identified a novel frameshift mutation in an X-linked *IRS4* gene in two brothers with isolated CeH. Furthermore, we demonstrate an association of *IRS4* gene locus to a general thyroid disease risk in the FinnGen-database. These findings together confirm the role of *IRS4* in isolated central hypothyroidism.

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OC15.3

Targeting PI3K and CDKs as effective therapeutic option for PPGLs in vitro and in vivo

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Pheochromocytoma and Paraganglioma, collectively referred to as PPGLs, are rare, mostly benign neuroendocrine tumors arising from chromaffin cells of the adrenal gland or of extra-adrenal sites, respectively. Surgery is the first-line therapy for localized PPGLs. However, up to 17% of PPGLs show metastatic spread, and for these cases there is no curative treatment. Therefore, the identification of novel therapeutic approaches for advanced PPGLs is highly clinically relevant. We aimed to find a new targeted therapy option for PPGLs based on their molecular profile. We set out to target two of the most dysregulated pathways in PPGLs, i.e. the PI3K and the CDK4/6 pathways, using BKM120 (pan-PI3K inhibitor) and LEE011 (CDK4/6 inhibitor). We analyzed the effect of these two drugs, as single agents or in combination, on PPGL cell lines and on primary rat and human PPGL cells in vitro and in xenograft experiments *in vivo*. Our results showed a clear reduction in the viability of PPGL cell lines upon treatment with the two drugs used as single agents. More importantly, a beneficial effect of the drug combination was observed in both 2D and 3D culture conditions. Moreover, we saw reduced migration as well as inhibited clonogenic potential of PPGL cell lines treated with both BKM120 and LEE011 compared to the single treatments. Interestingly, also primary PPGL cells (from an endogenous rat model and from human patients) responded to the single treatments with BKM120 or LEE011, and showed a beneficial combinatorial effect of the

two drugs. Based on these promising in vitro effects, we engrafted PC12 cells in immunodeficient mice and treated them for 21 days with BKM, LEE and their combination. We observed a clear reduction of tumor growth in the groups treated with the single drugs, and even tumor shrinkage in mice treated with the drug combination. Overall, our novel approach to combine a PI3K with a CDK4/6 inhibitor emerged as a new effective therapeutic option for PPGLs, especially interesting for inoperable and metastatic cases.

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OC15.4

Identification of a dose range for once daily oral paltusotine in patients with acromegaly that maintains IGF-1 levels when switching from long-acting somatostatin receptor ligand therapy

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Long-acting somatostatin receptor ligands (LA-SRLs) are a first line medical treatment for acromegaly but require monthly parenteral administration. Paltusotine (CRN00808) is a nonpeptide, small molecule somatostatin type 2 (SST2) receptor agonist with high oral bioavailability (70%), suitable for once daily, oral dosing. The recently reported results of the ACROBAT Edge study (NCT03789656) suggest that patients with acromegaly treated with injected SRLs can switch to once daily oral paltusotine while maintaining IGF-1 and that paltusotine appeared to be well tolerated. The dose-response relationship for paltusotine was explored using pooled data from patients with acromegaly who participated in the ACROBAT Phase 2 Edge and Evolve (NCT03792555) studies. Both studies were designed to evaluate the safety and efficacy of switching acromegaly patients receiving LA-SRLs to once-daily, oral paltusotine (n = 60). The switch to paltusotine occurred 4 weeks after last LA-SRL injection. Patients were treated with paltusotine at doses titrated upward based on target IGF-1 starting at 10 mg to a maximum of 40 mg per day for up to 13 weeks, followed by a 4-week paltusotine wash-out period. The change from baseline in IGF-1 during the treatment period and the rise in IGF-1 after paltusotine wash-out were used to measure the magnitude of paltusotine-related IGF-1 suppression. An evaluation of steady state IGF-1 changes as a function of paltusotine dose showed that 10 and 20 mg per day resulted in IGF-1 levels that were above baseline, whereas doses of 30 and 40 mg result in changes from baseline of near zero, indicating the 30 and 40 mg doses were equally effective in suppressing IGF-1 as prior monotherapy with injected LA-SRLs. A dose-response relationship was also observed when evaluating the magnitude of the rise of IGF-1 during paltusotine washout. Exposure-response modeling estimated the paltusotine concentration at which 80% of maximal pharmacological response (EC_{80}) is achieved. Simulations of 3 doses (20, 40 and 60 mg/day) of an improved formulation were performed to evaluate the likelihood of achieving this trough concentration of paltusotine in a population of patients. These simulations suggest that a dose range of 40 to 60 mg/day would result in daily trough concentrations that exceed EC_{80} and result in consistent IGF-1 suppression in patients with acromegaly. In summary, dose and exposure response analyses of clinical trial data in patients with acromegaly has identified a dose range of oral paltusotine expected to result in IGF-1 suppression similar to that of injected LA-SRLs.

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OC15.5

The Importance of maternal thyroid hormone for programming the cardiovascular system in the male offspring

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Thyroid hormones play an essential role for the embryonal development of the cardiovascular system including its central control mechanisms. Particularly the latter critically depends on maternal thyroid hormone, as the embryo doesn't produce own thyroid hormone until late in pregnancy. However, the precise window of action has remained undetermined, and it is therefore unclear whether alterations in maternal thyroid hormone directly affect the offspring's cardiac function. To address this question, we used mice heterozygous for a mutant thyroid hormone receptor α1 (TRα1), which exhibit resistance to thyroid hormone in tissues relying on TRα1 such as the heart. This was combined with maternal thyroid hormone treatments, which reactivated the mutant receptor for defined periods of time, either in the first or the second half of pregnancy. Phenotyping the offspring animals, we observed a significant increase in heart weight of male and female wildtype mice born by mothers that received thyroid hormone during the first or second half of pregnancy. Interestingly, TRα1 mutants were protected from this effect suggesting an important role of the receptor for embryonal heart development. Most remarkably, we also found a significant increase in heart rate in male mice that were exposed to elevated maternal thyroid hormone in the second half of the pregnancy independently of their own genotype, while female mice were not affected. Taken together our findings demonstrate that maternal thyroid hormone is of particular relevance during the second half of pregnancy for establishing cardiac properties, with specific effects depending on TRα1 or gender. The data therefore advocate routine monitoring of thyroid hormone levels during pregnancy to avoid adverse cardiac effects in the offspring.

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OC15.6

Genetic polymorphism (IP-10/CXCL10) and diabetes mellitus type 1

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Introduction
The development of Diabetes mellitus type 1 (DMT1) is considered as an autoimmune pro-inflammatory process. Human enteroviruses are thought to be also a cause. These viruses influence beta cells and cause expression of immunological factors. The affected cells destroy the related beta cells. The aim of the work is to study the genetic polymorphisms in IP-10/CXCL10 and its receptors CXCR3 and TLR4 in order to predict expression of DMT1.
Related work
There has been increasing evidence of elevated serum levels and increased expression of IP-10/CXCL10 in the pancreatic islets before and during the early stages of DMT1. A strong expression of IP-10 was detected in the Langerhans islets of NOD mice. They spontaneously develop DMT1, what is also observed in newly diagnosed patients with DMT1.
Problem description and hypothesis
Major assumption is based on the hypothesis and experimental evidence that DMT1 is a result of a pro-inflammatory process mainly through IP-10/CXCL10 polymorphism, which interacts with the CXCR3 receptor on immune cells. Viral infections induce the expression of cytokines and CXCL10. They attract immune cells through the CXCR3 receptor and cause beta cell destruction and subsequently DMT1. By blocking of CXCL10 receptors in early stage emerges as an opportunity to prevent the beta cells destruction. The potential reasons for cell destruction, are hypothesized with some differences in gene encoding. This process is related to the receptor or to the ligand and leads to a different way of their interaction and stimulation.
Material and methods
The sources of our study are based on genetic polymorphisms which encode IP-10/CXCL10 and its receptors CXCR3 and TLR4 on the surface of immune cells. We isolate and cut genomic DNA from two patients' cohorts: with DMT1 and with healthy controls. We used different restriction enzymes of genes encoding different chemokines, and we came across to a difference in the gene encoding IP-10/CXCL10.
Results and discussion
The identification of this polymorphism reveals the possible mechanism and causes for the manifestation of DMT1. Based on the obtained results, we can contribute to a potential prognostic test for predisposition to DMT1. Chemokines are important participants in the attraction of specific subpopulations of inflammatory cells in the pancreas. The identification of this polymorphism would contribute to further progress in discovering of triggering mechanisms of the DMT1. Advances in the study of genetic

polymorphism of chemokines and their receptors is useful in predicting the onset of diabetes and preventing it.

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Young Investigator Awards

YI1

Circulating myomiRNAs as biomarkers of Cushing's syndrome

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Cushing's syndrome (CS) is a rare endocrine disease caused by a chronic exposure to endogenous cortisol or exogenous glucocorticoids (GCs). Among multiple comorbidities, impairment of skeletal muscle mass and strength affects 40–70% of patients with active CS and persist even after long-term disease remission. In pathological conditions, GCs excess sustain muscle atrophy and weakness affecting type II muscle fibers. Muscle-specific microRNAs, defined myomiRs, are involved in myoblast proliferation, differentiation and regeneration, and changes in myomiR levels were reported in several pathological conditions associated with muscle organization and function perturbations. The current study aims to explore changes in circulating myomiRs in patients with CS, characterized by muscle atrophy and weakness compared to heathy controls. To focus the clinical study on a specific myomiRs subset, C2C12, mouse myoblast cell line, differentiated into myocytes, was exposed to 1.4×10^{-6} M of hydrocortisone (HC), resembling high cortisol serum level (500 ng/ml) observed in CS patients, for 4,6,8 and 12 hrs and gene and protein expression of the atrophy-related genes Atrogin and Murf were investigated by RT-qPCR, Western Blot and immunofluorescence to assess the HC-mediated atrophic signaling. The myomiRs levels were evaluated in treated C2C12 and controls by miScript miRNA PCR array. Circulating myomiRs significantly overexpressed in HC-treated C2C12 were then investigated by RT-qPCR in 33 patients affected by CS and 12 sex–and age-matched healthy controls. HC induced muscle atrophic signals significantly increasing Atrogin and Murf gene and protein expression and a concomitant higher expression of miR-133a-3p, miR-122–5p and miR-200b-3p in C2C12 after 12 hrs of treatment. The evaluation of these myomiRs in CS patients revealed higher circulating levels of miR-133a-3p ($P < 0.0001$), miR-122–5p ($P = 0.0135$) and miR-200b-3p ($P < 0.0001$) compared to controls. ROC curves for miR-133a-3p (AUC 0.866 (95% CI 0.756–0.976, $P = 0.0002$) and miR-200b-3p (AUC 0.976 (95% CI 0.930–1.023, $P < 0.0001$) demonstrated that both myomiRs represent potential biomarkers to discriminate between CS and healthy subjects. Interestingly, linear regression analysis revealed that circulating levels of miR-133a-3p are directly correlated with 24h urinary free cortisol level ($r = 0.428$, $P = 0.026$) in the CS patients. In conclusion, this study confirmed that HC induces atrophic signals and myomiR overexpression in mouse muscle cells, and in humans, circulating miR-200b-3p and mainly miR-133a-3p levels are promising molecular markers of hypercortisolism.

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YI2

Efficacy of the Anti-BAFF monoclonal antibody belimumab vs methylprednisolone in active moderate-severe graves' orbitopathy: Preliminary analysis of a randomized controlled trial

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Background

Serum B cell stimulating factor (BAFF) has been shown to be elevated in Graves' disease (Vannucchi 2012). In addition, BAFF and its receptor have been shown to be expressed on lymphocytes infiltrating the thyroid in Graves' disease and also on thyrocytes (Campi 2015).

Aims

We tested in a single-blind randomized controlled trial (EudraCT 2015–002127–26) whether the administration of the anti-BAFF monoclonal antibody belimumab (BMB), approved for therapy of SLE, is effective in active moderate-severe Graves' Orbitopathy (GO) as compared to first line treatment iv methylprednisolone (MP).

Methods

We randomized 27 patients with active, moderate severe GO and detectable serum TSH receptor antibodies (TRAb), euthyroid for at least 3 months, whether untreated or previously treated with iv steroids (relapsing GO). 14 received iv belimumab at 0,14, 28 days and then every four weeks for five cycles of infusion and 13 iv MP, 833 mg/ weekly for 6 cycles, followed by one cycle of 425 mg/week. The first dose of belimumab was associated to a full dose (833 mg) of MP (inception dose). Patient were studied at 12, 24 weeks (primary end point) and followed-up for 48 weeks. In addition to assessment of the CAS (primary end point), proptosis and the titers of TRAb (secondary end points) were also measured.

Results

In both groups of patients the CAS decreased significantly at 24 weeks ($P < 0.0001$). At 12 weeks patients on MP had a significantly lower CAS than those on BMB (4.75 ± 0.3 1.5 ± 0.5 vs 4.15 ± 0.2 2.54 ± 0.5, $P < 0.009$). At 24 weeks 12/13 patients on MP (CAS 1.00 ± 0.4) and 13/14 on BMB (CAS 1.38 ± 0.3) had inactive disease. Proptosis improved in all patients ($P < 0.05$) and in MP patients more significantly than BMB ($P < 0.04$). Serum TRAb levels decreased significantly ($P < 0.01$) in both groups of patients. Two patients in each arm developed optic neuropathy. BMB treatment was very well tolerated, with 1 major and 4 minor side effects vs 2 and 3, when compared to MP.

Conclusions

BMB is as effective as iv MP in the treatment of active GO, inducing inactivation in more than 92% of subjects. While its effect is somewhat slower than that of MP, its tolerability is very good. BMB is suggested to be an excellent alternative to MP when this is contraindicated or not effective.

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YI3

The american lifestyle induced obesity syndrome (ALIOS) diet induces an increase in intestinal permeability and exacerbates inflammation in female and male mice via the TLR4 signalling pathway

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Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disease spanning from simple steatosis to non-alcoholic steatohepatitis (NASH) with risk of progression to fibrosis and eventually cirrhosis. Dysfunction of the gut-liver axis plays a role the progression to NASH. Intestinal damage and increased permeability can increase the delivery of pathogen-associated molecular patterns (PAMPs), such as LPS and intact bacteria, to the liver where they can activate the TLR4 signalling pathway, and drive hepatic inflammation. Previously, we have shown that the ALIOS diet (high fat/high fructose) causes hepatic steatosis, inflammation and fibrosis in both female and male mice. Here, we examine whether intestinal damage and increased permeability contribute to hepatic inflammation in ALIOS female and male mice. Female and male C57BL/6 mice were fed either normal chow (NC) or ALIOS (45% fat [30% trans-fat], 55% fructose: 45% glucose in H2O; $n = 10 - 17$ in each group) until 52-weeks of age. The TLR4 signalling pathway was upregulated in the ALIOS mice. In detail,

hepatic protein levels of TLR4, total and phosphorylated NF-κB were increased, as was mRNA expression of the NF-κB target genes *Tnfa, Il-1*β and *Ccl2*. Marker of macrophage infiltration, F4/80, was also increased at mRNA and protein level. Increased intestinal permeability can be caused by loss of intestinal integrity and failure of antimicrobial response of the epithelial barrier. Consistent with intestinal damage, ALIOS diet altered the structure of the intestinal mucosa. Crypt depth was decreased in the ileum and, in females only, in the colon. Villus length was unchanged in both sexes. Suggesting increased permeability, expression of key tight junction genes *occludin* and *ZO-1* were decreased in the colon of female, but not male, ALIOS fed mice. In addition, the antimicrobial and immune supporting genes *Reg3g*, *Defa5* and *Muc2* were decreased in the ileum of the female mice and colonic *Reg3g* and *Muc2* were decreased in both sexes. Suggesting increased bacterial translocation and reduced barrier function, the amount of hepatic bacterial DNA was increased in both female and male ALIOS fed mice, although LPS levels were comparable to controls. Collectively, ALIOS diet represents a robust model for investigating the pathogenesis of NAFLD and its progression to NASH as it recapitulates the majority of the molecular features of NASH, with increased intestinal permeability, increased bacterial translocation and increased hepatic TLR4 pathway activation.

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YI4

Use of ^{11}C-methionine PET-CT scanning to guide management of acromegaly following primary therapy – A pragmatic prioritisation strategy to achieve maximal cost effectiveness

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Background
^{11}C-methionine (11C-Met) positron emission tomography co-registered with MRI is a new imaging technique used for functioning pituitary adenomas, permitting targeted intervention (Transphenoidal Surgery (TSS) or Radiotherapy)[1]. The ^{11}C-Met PET-CT scan has been available in our centre since Dec 2016. With limited availability in 2019/2020 (due to cyclotron refurbishment) we re-audited our patients to prioritise those most likely to benefit.
Methods/Results
Retrospective study of patients with acromegaly under active follow-up in a tertiary hospital. Fifty-one patients included (61% female, mean age 59 years) with median follow-up of 13 years with 23 on active treatment. Patients were categorised into groups according to acromegaly treatment status as outlined in the below table. Poor control defined as IGF1> 1.3 × ULN, suboptimal control defined as IGF1 1.1–1.3 × ULN. Eighteen patients from Groups 1, 2 and 3 (2017) were initially considered suitable for ^{11}C-Met PET-CT. Progress to date: five scanned; two declined; eleven pending. Of the five patients scanned, two underwent TSS and have been cured (cost saving of £46822 per annum). One patient awaits surgery and no surgical target was identified in two patients (both in Group 3). We have subsequently reassessed our prioritisation criteria for Group 3 and will now predominantly offer 11C-Met PET-CT if adverse effects to SSA therapy are experienced.

Group	Acromegaly Treatment Status	2017	2020
1a	Poor control on SSA/pegvisomant	7*	0*
1b	Poor control, SSA intolerant/unsuitable (may have tried DA)	0	2
1c	Suboptimal control on SSA	2	2
2	Good control, very high-cost medication pegvisomant/pasireotide	1	1
3	Good control, high-cost medication SSA	8	12
4	Poor control DA – switch to SSA	4	0
5	Good control on DA	2	3
6	Good control on no medication	27	29
7	Deceased/Lost to follow-up	0	2
	Total	51	51

*Comparing 2017 with 2020: 2 operated and cured, 1 moved to category 1b, 2 moved to category 1c, 2 moved to category 3
SSA–somatostatin analogue, DA–dopamine agonist.
Conclusion
^{11}C-Met PET-CT can help localise residual functioning pituitary adenomas in patients with uncontrolled acromegaly but no visible tumour on MRI. However, its availability is currently limited. We present a pragmatic prioritisation strategy targeting those with poor control, ideally prior at the point of consideration of expensive medication such as pegvisomant and pasireotide. There is potential to extend this strategy nationwide.
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YI5

Atlas of G protein-coupled receptors in radioiodine-refractory thyroid cancer: Novel therapeutic targets for drug repositioning?

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Introduction
Progressive and radioiodine-refractory thyroid cancer has poor outcomes and limited therapeutic options (i.e tyrosine kinase inhibitors) due to the transient efficacy of treatment and toxic effects. Therefore, combinatorial treatment with new therapeutic approaches are needed. Many studies link G Protein-Coupled Receptors (GPCRs) to cancer. The aim of this study is to present the first specific atlas of GPCRs expression in progressive and refractory thyroid cancer and identify new potential targets among theses GPCRs aiming at drug repositioning.
Methods
We analyzed samples from tumor and normal thyroid tissue from 17 patients with refractory thyroid cancer (twelve papillary thyroid cancers (PTC) and five follicular thyroid cancers (FTC)). We assessed the GPCR mRNA expression by using the NanoString technology with a custom panel of 371 GPCRs and we selected GPCRs differentially-expressed between normal and tumoral tissues. The data were compared with public repositories by bioinformatics analyses (GEO and TCGA data sets) and pharmacological databases. Finally, we screened approved drugs that target differentially-expressed GPCRs. Experiments were performed with primary human refractory thyroid cancer cells isolated from tumoral ascites by measuring cell viability (Cell Titer-Glo Luminescent Cell Viability Assay kit) and cell migration (IncuCyte S3 live cell imaging system).
Results
With our transcriptomic analysis, 4 receptors were down regulated in FTC (VIPR1, ADGRL2, ADGRA3 and ADGRV1). In PTC, 24 receptors were deregulated, seven of which identified also by bioinformatics analyses of published studies on primary thyroid cancers (VIPR1, ADORA1, GPRC5B, P2RY8, GABBR2, CYSLTR2 and LPAR5). Among all the differentially-expressed genes, 25 GPCRs are the target of approved drugs and some receptor feature was also associated with overall survival or progression-free survival. Drug screening in ascites-derived primary refractory thyroid cancer cells found three agents with antiproliferative effect and anti-migratory effect in the micromolar range.
Conclusions
For the first time, we performed GPCR mRNA expression profiling in progressive and refractory thyroid cancers. A preliminary drug screening identified candidate drugs that target GPCRs. These findings provide an opportunity to the identification of new therapeutic targets for drug repositioning and precision medicine in radioiodine-refractory thyroid cancer.

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YI6

Unveiling the pathophysiological relationship between prostate cancer and obesity: miR-107 as a novel personalized diagnostic and therapeutic tool

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Prostate cancer (PCa) is one of the most common causes of cancer-related deaths in men worldwide. Therefore, more specific and non-invasive diagnostic biomarkers as well as novel therapeutic targets are urgently needed. As miRNAs have been proposed as promising elements for the identification of novel diagnostic and therapeutic tools for different pathologies, including cancer, we investigated the miRNA landscape in PCa 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. The main changes were validated in two independent cohorts (n = 296 and n = 84) by quantitative real-time PCR. Additionally, *in silico* and *in vitro* assays in normal and tumor prostate cell lines were performed. Results from the array revealed that the expression of 104 miRNAs was significantly altered (P < 0.01) in plasma samples from PCa patients compared with healthy controls. Of note, 6 of these miRNAs also exhibited a significant ROC curve to distinguish between healthy and PCa patients with an AUC equal to 1. A systematic validation using two independent cohorts of patients demonstrated that miR-107 was the most profoundly altered miRNA in PCa (P < 0.0001) exhibiting an AUC equal to 0.75. Interestingly, miR-107 significantly outperformed the ability of PSA to distinguish between control and PCa patients, as well as between non-significant (Gleason Score = 6) and significant (Gleason Score ≥∈7) PCa patients, being its expression correlated with relevant clinical parameters (e.g. PSA and testosterone levels, tumor volume). Remarkably, all these comparisons were even stronger in obese patients (BMI > 30). Interestingly, we found that miR-107 levels were also dysregulated in PCa tissues (compared to non-tumor tissues) and in PCa cells (compared to non-tumor cells). Moreover, *in vitro* overexpression of miR-107 significantly reduced cell proliferation, migration and tumorsphere formation in PCa cells, and altered the expression of several genes critical in PCa pathophysiology, such as *FASN* and *CPT2* (implicated in cellular lipid metabolism), *SRRM1*, *SRSF2* and *TIA1* (involved in splicing process). Altogether, our data demonstrate that miR-107 might represent a new diagnostic and potential therapeutic tool in PCa, especially in patients under obesity condition.

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YI7

Alterations in clock genes expression in eutopic and ectopic endometrial tissue

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Introduction
Endometriosis is a dysplastic disease affecting approximately 7–10% of reproductive–aged women. It is defined as the presence of endometrial-like tissue outside the uterine cavity. Disruption of circadian rhythm in night shift worker has been associated with menstrual irregularity and increased chance of developing endometriosis and ovarian tumors. The central circadian clock system located in hypothalamic suprachiasmatic nucleus (SCN) along with the peripheral clock system located in the reproductive tissues (endometrium) control the timing and length of the ovulatory cycle by regulating the expression of various hormones (i.e.gonadotropins, estradiol) which in turn regulate the expression of clock related genes and vise-versa. To best of our knowledge, no studies related to the alterations in expression profile of the core clock -genes in human endometriosis have been published to date.
Aim
Herein, we aimed to investigate the expression of the core clock related genes in paired eutopic and ectopic endometrial tissues.
Methods
27 patients with confirmed ovarian endometriosis were included in this study. 11 paired samples were collected from ovarian cysts (ectopic endometrial tissues) and normal endometrium (eutopic tissues) while further 8 ectopic and 8 eutopic endometrial tissues were collected from 16 different patients with the same diagnosis. The mRNA expression of Clock-genes (CLOCK, BMAL1,CRY-1, PER-2, ROR-α and REV-ERBb) was evaluated by qPCR in ectopic tissues and was compared with the eutopic tissues.
Results
The mRNA expression of PER-2 and CRY-1 genes was decreased in the total of ectopic tissues (n = 19) compared to the total eutopic tissues (n = 19) (P = 0.02,P = 0.02 respectively). A marginal reduction in the expression of CLOCK along with a marginal increase in REV-ERBb expression was noted (P = 0.06 and P = 0.09 respectively) in ectopic (n = 19) compared to eutopic tissues (n = 19). The mRNA expression of clock-genes in the ectopic (n = 11) compared to their paired eutopic tissues (n = 11) revealed that the expression of PER-2 and CRY-1 genes were significantly lower (P = 0.04,P = 0.04, respectively), whereas REV-ERBb levels was significantly elevated (P = 0.02). Additionally, a marginal decrease in the expression of clock gene in ectopic as compared to paired eutopic tissues was observed (P = 0.09). Of note, the mRNA levels of BMAL1 and ROR-α were not altered between our studied groups.
Conclusions
Our study demonstrates for the first time an altered expression of CLOCK,CRY1,PER-2,and Rev-ERBb in eutopic as compared to ectopic endometrial tissues indicating circadian clock disruption. However, the causal relationship of the altered expression pattern of these genes with the development of endometriosis needs further investigation.

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YI8

Metformin and simvastatin in combination: drugs repositioning to impair high-grade astrocytomas progression

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Astrocytomas are a subtype of malignant gliomas characterized by rapid growth and high diffusion through the brain. Based on the agresiveness features, they are stratified from low grades (I and II) to high grades (HGAs; III and IV), being grade-IV [glioblastoma multiforme (GBM)] the most aggressive and one of the most common malignant cancers in the brain, with an overall survival from diagnosis of ~14 months. Current standard therapies to treat HGAs are not efficient and therefore, identification of new therapeutic tools to tackle HGAs is urgently needed. In this sense, many metabolic drugs have emerged as antitumor agents for several endocrine-related cancers demostrating different pleiotropic anti-tumoral effects. Among them, metformin and simvastatin are currently prescribed to treat T2D patients and hypercholesterolemia, respectively. Thus, our aims were to evaluate: i) the putative *in vivo* association between metformin and/or simvastatin treatment and key clinical parameters in HGA patients, and ii) the direct effects of metformin, simvastatin and their combination, on key functional endpoints and associated signaling mechanisms in GBM-cells. Specifically, an exploratory/observational retrospective cohort of patients with HGAs (n = 61; mean age: 63.9 ± 5.5) was analyzed, and human GBM-

cells (U-87 MG/U-118 MG cell lines and patient derived-HGA cell cultures) were used to measure a set of key functional parameters and signaling-pathways in response to metformin, simvastatin and their combination. We found that metformin/simvastatin combination showed an association to longer overall survival *in vivo*. Moreover, metformin and simvastatin exerted strong antitumor actions being able to inhibit proliferation, migration, tumorsphere/colony-formation, VEGF secretion and to induce apoptosis on HGA-cells *in vitro*. Notably, their combination further decreased, additively, these functional parameters compared with the individual treatments. These individual or combined actions were mediated through modulation of key oncogenic signaling-pathways (i.e. AKT/JAK-STAT/NFkB/TGFß pathways). Interestingly, an enrichment analysis uncovered an activation of TGFß pathway together with the AKT inactivation when metformin and simvastatin were administered in combination, which might promote to a senescence-associated secretory phenotype and then a senescence state transition. Altogether, our results demonstrate that metformin and simvastatin significantly reduce tumor aggressiveness features in HGAs, being this effect more potent (*in vitro* and *in vivo*) when both drugs are combined. Therefore, given the demonstrated clinical safety of biguanides (metformin) and statins (simvastatin), our results suggest a potential therapeutic role of these compounds, especially their combination, for the treatment and management of this devastating brain cancer.

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YI9

The value of liquid and solid mixed meal tests to diagnose postprandial reactive hypoglycaemic syndrome

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Background
Precise diagnostics for postprandial reactive hypoglycaemic syndrome (PRHS) after gastric bypass surgery (GBS) are lacking. Oral glucose tolerance tests are advocated but might cause early dumping in this population and often cause hypoglycaemic values in a normal population.
Aim
To evaluate glycaemic responses during liquid and solid mixed meal tolerance tests (LMMTT and SMMTT) in a post-GBS population.
Subjects and methods
Twenty-two subjects (age 49 ± 10 years, BMI 29.8 ± 4.9 kg/m^2) who were at least one year after GBS, with or without subjective complaints of PRHS, and 14 age-matched control subjects (6 normal-weight, 8 obese) participated. With a 1-week interval, all underwent a 3-hour LMMTT and SMMTT (with equal caloric and macronutrient content). Serum glucose concentration was determined using hexokinase method, insulin with immunoassays (COBAS, Roche Diagnostics). Hypoglycaemic symptoms during testing were evaluated using a 4-point Likert scale for the Edinburgh Hypoglycaemia Scale (EHS) and divided into three EHS subcategories (autonomic, neuroglycopenic, malaise symptoms).
Results
In the GBS group, mean nadir glucose levels did not differ between LMMTT and SMMTT (70 ± 16 mg/dl vs 71 ± 15 mg/dl, $P > 0.05$). During LMMTT, three and 10 subjects had glucose levels < 54 mg/dl and < 70 mg/dl, respectively which did not differ from the SMMTT where this was two and 10 subjects, respectively ($P > 0.05$). During LMMTT, markedly higher maximal glucose and insulin levels were observed than during SMMTT (glucose: 186 ± 27 mg/dl vs 156 ± 27 mg/dl, $P < 0.001$; insulin: 169 (107– 240) mU/l vs 92 (71 – 146) mU/l, $P = 0.002$; respectively). Rates of increase and decrease were greater during LMMTT for both glucose ($P < 0.001$ and $P = 0.001$, respectively) and insulin ($P = 0.001$ and $P = 0.006$, respectively) levels. Short after ingestion (15' and 30'), there were more autonomic, neuroglycopenic and malaise symptoms and at 150' and 180' there were more autonomic symptoms during LMMTT vs SMMTT (all $P < 0.05$). No-one from the control group developed glucose levels < 54 mg/dl during either test whereas three and one developed glycaemia < 70 mg/dl during LMMTT and SMMTT, respectively. The control group had more autonomic symptoms during LMMTT (at 120' and 150') in comparison to the post-GBS group (all, $P < 0.05$).
Discussion
In a post-GBS population, although a LMMTT causes greater variability in glycaemic and insulinemic responses and development of PRHS symptoms (but also symptoms of early dumping) than a SMMTT, both tests do not differ in nadir glucose levels or frequency of hypoglycaemia. In addition, neither tests cause hypoglycaemic values in control subjects making them possible diagnostic tools for PHRS in post-GBS subjects.

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YI10

Placental expression of neurokinin B and its receptor NK3R is increased in women with polycystic ovary syndrome: results of a preliminary study

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Background
Women with polycystic ovary syndrome (PCOS) are at increased risk of pregnancy complications and poor pregnancy outcomes. Defective placentation is among the proposed mechanisms involved. Altered neurokinin B (NKB) placental expression has been associated with several conditions characterized by placental dysfunction, such as pre-eclampsia and intra-uterine growth retardation. However, the expression of NKB and its receptors has not been studied in placental tissue of women with PCOS.
Objective
To compare the placental mRNA expression of NKB and its receptors NK1R, NK2R and NK3R in women with PCOS and controls.
Methods
This was a single-center, prospective, case-control study. Women with PCOS according to the Rotterdam criteria (cases) and healthy pregnant women (controls) were enrolled at first prenatal visit and followed until delivery. Only women with spontaneous conception and singleton, uncomplicated, term pregnancies (10 PCOS and 10 controls) were included in the final analysis. All participants provided informed consent. At delivery, placental specimens were collected and immediately submerged in RNAlater solution. Samples were stored at -20ºC until analysis. The mRNA expression of NKB, NK1R, NK2R and NK3R was quantified by real-time PCR (RT-PCR). The relative mRNA expression was estimated by the ΔΔCT method, using β-actin as reference (housekeeping gene). Statistical analysis was performed using SPSS 25.0, and the level of statistical significance was set at 0.05 (two-sided).
Results
The placental mRNA expression of NKB and NK3R was significantly higher in PCOS women vs controls (2.4-fold, $P < 0.05$ for NKB and 7-fold, $P < 0.05$ for NK3R). No significant alterations were observed in the mRNA expression of NK1R and NK2R between the two groups. There was no statistically significant difference regarding age, BMI, caesarian section frequency, offspring sex and birth weight between women with PCOS and controls. The placental expression of NKB and its receptors was correlated neither with maternal age and BMI, nor with offspring birth weight.
Conclusions
The present study is the first to demonstrate increased placental expression of NKB and its receptor NK3R in women with PCOS. These findings support a potential role for NKB as a mediator of placental alterations characterizing PCOS. Expanding the number of participants is the necessary next step, in order to corroborate these preliminary findings. Furthermore, correlations between the placental expression of NKB, NK1R, NK2R, NK3R and PCOS phenotype, maternal sex steroids, glucose and insulin levels should be sought.
Keywords: polycystic ovary syndrome (PCOS), placenta, neurokinin B (NKB), NK3R.

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YI11

Gβγ-mediated signaling regulates NIS abundance at the plasma membrane

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Introduction
The Sodium Iodide Symporter (NIS) is responsible for the active transport of iodide into thyroid cells. Most of differentiated thyroid carcinomas (TC) retain the functional expression of NIS, which allows the use of radioiodide (RAI) as the systemic treatment of choice for metastatic disease. Still, a significant proportion of patients with advanced thyroid cancer fail to respond to RAI therapy (refractory-TC), which makes their management very challenging. In addition to reduced NIS expression, the limited iodide uptake observed in cancer tissue is also a consequence of an impairment of plasma membrane (PM) targeting and retention of NIS. However, signaling cues potentially mediating the activation of pathway components leading to NIS functional expression at the PM, remain elusive. Using a proteomic approach, we have recently identified a set of proteins that interact with NIS selectively at the PM, potentially modulating its abundance and stability at the surface of TC cells. The G protein subunit gamma 12 (GNG12) was detected as a specific PM-interactor of NIS. This is one of twelve Gşsubunits in the human genome that can pair with Gβ subunits to form unique Gβγ complex combinations. Along with Gα, Gβγ are key regulators of G protein-coupled receptor (GPCR) signaling, having the ability to activate several signaling mediators such as kinases, GTPases or lipases.
Objective
To evaluate whether modulation of Gγ12 subunit would have an impact on NIS PM abundance.
Methods
The TPC1 thyroid cancer cell line stably expressing a full-length NIS construct containing an extracellular triple HA tag (NIS-HA-TPC1) was used to assess the PM levels of NIS upon siRNA-mediated knockdown of GNG12 expression. NIS PM levels were assessed using surface protein biotinylation assays coupled to WB detection of NIS-HA using anti-HA primary antibody. A non-radioactive iodide influx assay was used to further analyze the impact of GNG12 on NIS function by assessing the rate of iodide uptake.
Results
siRNA-mediated GNG12 depletion, although partial (ş30% reduction), was able to induce a 1.6-fold decrease in NIS cell surface levels and also impair iodide uptake efficiency, halving the influx rates in HA-NIS-TPC1 cells.
Conclusion
Our findings suggest that signaling cues that lead to the release and activation of Gβγ may act upstream of signaling pathways that enhance NIS expression in the PM. This supports the relevance of further studying the impact of modulating Gβγ-mediated signaling on NIS functional expression, as a potential approach to enhance the efficiency of iodide uptake.

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YI12

Preoperative predictors and prognostic factors of recurrence of the parathyroid carcinoma – Data of a multi-center study

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Background
There are no specific markers for parathyroid carcinoma (PC) therefore, the development of algorithms for identifying high-risk patients is an urgent task.
Aims
To determine clinical and laboratory predictors of PC and identify the factors of a poor prognosis.
Materials and methods
A multi-center retrospective study included 242 patients with primary hyperparathyroidism (PHPT) who were divided into these groups: 50 patients with PC, 30 with atypical adenoma (AA), and 162 with adenoma of the parathyroid glands (PG). We compared clinical, histopathological, immunohistochemical (IHC), and genetic characteristics. Overall survival was assessed using the Kaplan-Mayer estimator. Cut-off for Ki-67 proliferation index was determined by ROC-analysis.
Results
The group of patients with increased risk of the PC included individuals with the levels of intact PTH >€443 pg/ml, Ca++ > 1.5 mmol/l, albumin corrected calcium > 3.2 mmol/l, alkaline phosphatase > 176 IU/l, size of the tumor > 22.5 mm and volume of the tumor > 2.6 cm^3, (P < 0.001). Heterogeneous structure is more typical to PC compared to the AA (P = 0,004 and P = 0,011), the same applies to indefinite contour (P = 0,001 и P = 0,011). The incidence of nuclear atypia was more common in PC and AA compared to benign adenomas (P < 0.001). There difference appeared to show in the frequency of pathological mitoses (P = 0.007) in patients with recurrent PC. The sensitivity of the IHC study of parafibromin expression as a marker of the *CDC73* germline mutation is 100% (95% CI: 59%–100%), specificity 86% (95% CI: 73%–95%). The overall five-year survival rate for patients with PC is 87%, ten-year survival rate is 80%, disease-free five-year survival–56%, ten-year–50%. Cut-off for Ki-67 proliferation index as a predictor as increased risk of recurrent PC is 14.5% with PPV = 100% (63 %; 100%), and NPV = 81% (64%; 93%).
Conclusions
We have identified clinical and laboratory predictors of malignant neoplasms of the PG and identified factors of poor prognosis. Genetic study of the *CDC73* gene is shown patients with a loss of parafibromin expression in the primary tumor or in metastases of PC according to the results of the IHC study. Patients with a Ki-67 proliferation index above 14.5% require closer follow-up due to the increased risk of PC recurrence. The patients with suspected PC should be timely referred to specialized centers with extensive experience in managing this pathology and thereby improve the patient's prognosis.

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Presented ePosters

Adrenal and Cardiovascular Endocrinology

PEP1.1

Salivary steroid and 11-oxygenated androgen profiles in patients with congenital adrenal hyperplasia on various glucocorticoid replacement regimens

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Context
11-oxygenated C19 steroids have recently gained attention as markers of androgen control in congenital adrenal hyperplasia (CAH) due to 21hydroxylase deficiency (21OHD). However, they have not yet been systematically investigated in the context of different glucocorticoid (GC) replacement regimens and in particular not in patients receiving new modified-release formulations.
Methods
Cross-sectional single center study including 26 men and 48 women with CAH and 14 male and 9 female controls. Saliva samples were collected at four times during the day starting with a morning sample after awakening. 24 patients were receiving conventional hydrocortisone three times a day, 15 patients Plenadren once in the morning, 19 patients twice-daily prednisolone and 16 patients twice-daily Chronocort. Salivary concentrations of 17hydroxyprogesterone (17OHP), androstenedione (A4), testosterone (T), 11βhydroxyandrostenedione (11OHA4) and 11ketotestosterone (11KT) were analyzed by LC–MS/MS. Sex-specific linear mixed-effects models corrected for hydrocortisone (HC) equivalence dosage and age were calculated to compare steroid profiles between groups.
Results
Once daily plenadren resulted in poor androgen control in both sexes in comparison to other GC replacement regimens as it was not able to suppress nightly rise of adrenal androgens. All investigated steroids in the Plenadren group were higher in the morning than in any other group. Mean overall salivary T levels in women on Plenadren (102.0 ng/ml; 95% CI 82.0–126.9) were actually as high as in control men (111.1 ng/ml; 95% CI 81.9–150.5) whereas on Chronocort they were comparable to controls and on prednisolone even lower. 11-oxygenated C19 steroids were only elevated on plenadren, where 11KT levels were greatly increased in both sexes. Females on chronocort and HC had lower 11KT levels compared to controls and 11KT was similar to controls on prednisolone. There was a strong natural diurnal rhythm in 11OHA4 and 11KT in healthy controls that was independent of 17OHP. Diurnal variance for 11-oxygenated C19 steroids was lowest in patients receiving chronocort. In accordance with the half-life of prednisolone and HC, most steroids showed a small peak around lunchtime in these groups, an effect that was limited to men.
Conclusions
Once daily Plenadren cannot mimic physiological cortisol secretion in CAH and therefore fails in suppressing the nocturnal androgen surge. Chronocort in contrast controls the overnight rise in 17OHP and the subsequent pathological generation of 11OHA4 and 11KT seen in CAH.

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PEP1.2

Tildacerfont for the treatment of patients with classic congenital adrenal hyperplasia: results from a 12-week phase 2 clinical trial in adults with classic CAH

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Background
Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is an autosomal recessive disorder characterized by insufficient cortisol production resulting in excess adrenocorticotropic hormone (ACTH) and adrenal androgen production. Standard-of-care therapy with glucocorticoids (GC) is suboptimal due to the difficulty of balancing control of the ACTH-driven androgen excess against the serious long-term side effects associated with chronic supraphysiologic GC exposure. Tildacerfont, a second-generation corticotropin-releasing factor type-1 (CRF_1) receptor antagonist, lowers excess ACTH, and thus has the potential to reduce adrenal androgen production and to allow for GC dosing closer to physiologic doses. A prior study demonstrated that tildacerfont was effective in reducing ACTH, 17-hydroxyprogesterone (17-OHP) and androstenedione (A4) after 2 weeks of therapy. Here we report results from an open-label 12-week extension study.
Methods
Subjects met either of the following criteria: 1) completion of prior study or 2) treatment naïve to tildacerfont with 17-OHP >800 ng/dl while on a stable GC regimen (excluding dexamethasone). Subjects were treated with oral tildacerfont at 400 mg once daily for 12 weeks. Efficacy and safety parameters were assessed at baseline through Week 12.
Results
Subject characteristics (n = 8) are as follows: median (range) age was 44.5 years (26–67 years; 5 females), median (range) body mass index 30.8 kg/m^2 (22–41 kg/m^2). In month 3, in the participants with poor control of disease at baseline (elevations in all key biomarkers: ACTH, 17-OHP, and A4) (n = 5), maximum mean percentage reductions for ACTH, 17-OHP and A4 were 84%, 82%, and 79%, respectively. In this subgroup, 60% of subjects achieved ACTH normalization and 40% achieved A4 normalization during treatment. Tildacerfont treatment maintained, and did not suppress, biomarkers in participants with good control of disease at baseline (A4 below upper limit of normal) (n = 3). Overall, tildacerfont was well tolerated with no serious adverse events.
Conclusions
This is the first study of 12 weeks' duration for a novel, non-steroidal mechanism-of-action agent for the treatment of 21-OHD. Results of this study show that tildacerfont was generally well-tolerated and effective in achieving meaningful reductions in ACTH and A4 in poorly controlled patients over 12 weeks. In addition, this is the first, non-steroidal therapeutic to show evidence of ACTH and A4 normalization over 12 weeks of therapy. Longer term future studies will evaluate whether treatment with tildacerfont can achieve further clinical benefits and allow reduction of GC doses while controlling relevant disease biomarkers.

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PEP1.3

Rationale for a reduced dexamethasone dosis in prenatal CAH therapy based on pharmacokinetic modelling

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Context
Prenatal dexamethasone (Dex) therapy is used in female foetuses with congenital adrenal hyperplasia (CAH) to suppress adrenal androgen excess and prevent virilisation of the external genitalia. The prenatal dexamethasone dose of 20 µg/kg per day has been used for decades in prenatal CAH and is associated with risks for the treated mother and potentially for the unborn child. Despite the high medical need, no prospective, clinical studies had been conducted in order to determine a Dex dose with a scientific rationale.
Objective
We aimed to investigate a rationale of a reduced Dex dose in prenatal CAH therapy based on a pharmacokinetics-based modelling and simulation framework.
Design and methods
Population modelling was applied on a published dexamethasone study to develop a maternal dexamethasone pharmacokinetic model. By simulations, a typical pregnant population was separated into to receive either the 20 µg/kg per day Dex dose or reduced doses. Target maternal dexamethasone concentrations, identified from literature, served as threshold to be exceeded by 90% of patients at steady state to ensure foetal hypothalamic-pituitary-adrenal axis suppression.

Results
A two-compartment dexamethasone pharmacokinetic model was successfully developed. The simulations resulted in 7.5 µg/kg per day to be the minimum effective dose and thus our recommended optimised dose.
Conclusions
Based on our modelling and simulation results, the current experimentally used Dex dose seems 3-fold higher than needed, possibly causing harm in treated foetuses and mothers. The clinical relevance and appropriateness of this reduced dose should be tested in a prospective international clinical trial.
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PEP1.4

Adrenocortical oncocytoma in a patient with classic congenital adrenal hyperplasia

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Introduction
Oncocytic neoplasms arising in adrenal tissue are extremely rare with nearly 150 cases being reported in literature. They are mostly nonfunctioning benign tumors, incidentally discovered, but 20% of them demonstrate elements of malignancy and up to 30% appear to affect hormone production.
Case report
A 35 years old female with primary amenorrhea, diagnosed with Congenital Adrenal Hyperplasia due to 21-hydroxylase deficiency at age of 2, who underwent feminizing genitoplasty 5 years after diagnosis, presented in our clinic complaining of abdominal pain, nausea, vomiting and hypotension. She was on treatment with 1 mg Dexamethasone daily with poor medication adherence. Clinical findings included: altered general condition, dry skin and mucosae, hirsutism, BP = 70/50 mmHg with orthostatic hypotension, HR = 100 bpm, intense spontaneous and on palpation pain located in the left iliac fossa and moderate abdominal dystension. Lab tests revealed an important inflammatory syndrome, normocytic normochromic anemia, hypoglycemia (65 mg/dl), high-normal potassium level (5 mmol/l), hyponatremia (131 mmol/l), hypocalcemia (8.3 mg/dl). She started IV hydrocortisone and oral fludrocortisone. Hormonal workup showed high 17-OH progesterone (> 20 ng/ml), low 0800 h cortisol (1.58 µg/dl), high ACTH (1362 pg/ml), high renin (170 pg/ml), normal aldosterone (243 pg/ml). Abdominal and pelvic MRI revealed on the superior pole of left adrenal gland a 55/60 mm tumoral mass with polycyclic contour and at the level of the left anexa another tumoral mass with cystic components, thick walls, with maximum diameters of 47/75 mm. After the acute episode remission, the patient was transferred to surgery unit where was performed left adrenalectomy with left anexectomy. Hystopatological exam established the diagnosis of adrenocortical oncocytic neoplasm with uncertain malignant potential and immunochemestry was positive in tumoral cells for inhibin A, Melan A, Calretinin, Synapto and negative for Chromogranin A, Ki67~ 2%.
Conclusion
Oncocytic adrenocortical neoplasm is a rare tumor of the adrenal gland which origin, biological behavior, diagnostic criteria and prognosis are controversial. To our knowledge, only one case of adrenocortical oncocytoma in a patient with congenital adrenal hyperplasia was previously reported in the literature. More data are needed for better management of these patients.
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PEP1.5

Modified-release hydrocortisone improves androgen excess and facilitates glucocorticoid dose reduction in patients with classic congenital adrenal hyperplasia: non-invasive monitoring in saliva and urine

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Background
Standard glucocorticoid (GC) therapy in classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21-OHD-CAH) is often inadequate in controlling adrenal androgen excess, leading to GC over-exposure and poor health outcomes. A novel modified-release formulation of hydrocortisone (MR-HC, Chronocort® Diurnal Ltd. UK) has been shown to improve circulating adrenal androgen excess in 21-OHD-CAH. We investigated whether saliva and 24-h urine could be used as non-invasive tools to monitor disease control by MR-HC.
Methods
This is a sub-study of the EudraCT 2015-000711-40 and 2015-005448-32 clinical trials. Patients with 21-OHD-CAH were randomised to either MR-HC or their standard GC treatment; at 6 months all were offered MR-HC. Throughout the study, GC replacement was titrated according to serum 17OHP and A4. 24-h urine and saliva day profiles were collected at baseline (standard GC), 6 months (standard GC vs. MR-HC), and 12 months (all on MR-HC). Saliva was collected by passive drool every 2 h between 0700 h and 2300 h. Samples were analysed by LC-MS/MS (saliva) and GC-MS (24-h urine) to measure the 21-OHD-CAH marker 17-hydroxyprogesterone (17OHP in saliva; 17HP, PT, and PTONE in urine), steroids of the classic androgen pathway (A4 in saliva; An and Et in urine), the 11-oxygenated androgen pathway (11OHA4 and 11KT in saliva; 11βOHAn in urine), and the alternative pathway to dihydrotestosterone (3α5α17HP in urine).
Results
12 patients (9 women; median age 42 years, range 21–68) were randomised to MR-HC (n = 4) or standard GC (n = 8). After six months, MR-HC led to a 97% decrease in salivary 17OHP (area under the curve, AUC, P 0.006), A4 (AUC -99%, P 0.029), 11OHA4 (AUC -97%, P 0.001), 11KT (AUC -100%, P 0.004), and urinary 3α5α17HP (97% median reduction, P 0.05) as compared to standard GC. A significant decrease in the 11KT/T ratio also indicated improved control of adrenal androgen excess. Urinary excretion of 17OHP and androgen metabolites also decreased on MR-HC, albeit non-significantly. This improvement in biochemical control was achieved on a lower daily GC dose of MR-HC compared to standard treatment at 6 months (MR-HC 23 mg (15–35 mg); standard GC 32 mg (25–38 mg)). At 12 months, MR-HC maintained excellent biochemical control, despite a further reduction of the median GC dose to 18 mg (10–40 mg).
Conclusions
MR-HC treatment facilitated a significant reduction of GC dose, with non-invasive steroid monitoring comprehensively reflecting biochemical disease control.
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PEP1.6

ARMC5 modifies cell redox state to regulate steroidogenesis and lipid metabolism in the adrenal cortex

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Background
ARMC5 is a putative tumor suppressor gene that is frequently mutated in primary bilateral macronodular adrenal hyperplasia (PBMAH), a rare cause of Cushing's syndrome. The function of ARMC5 is poorly known, aside the fact that it regulates cell apoptosis and adrenal steroidogenesis in by mechanisms still unknown. Tumor suppressor genes play an important role in oxidative stress.
Methods
In this study we used as model the adrenocortical carcinoma cell line H295R. In order to investigate ARMC5 response to stress, cells were treated with Menadione and reactive oxygen species (ROS) production was measured by Cellrox assays with flow cytometry. Oxidative response genes and steroidogenic enzymes expression were investigated by qPCR, whereas p38 phosphorylation was investigated by western blotting.
Results
ARMC5 protein is differentially regulated in response to menadione-induced stress in H295R adrenocortical cells. Moreover, ARMC5 depletion

increases total intracellular ROS production (P <0.05) and causes an imbalanced transcription of pro and anti-oxidant genes leading to increased phosphorylation of p38 (P <0.05). ROS production and p38 pathway activation alter steroidogenesis. These effects are partially reversed by the anti-oxidant compound N-acetylcysteine (NAC) or the p38 inhibitor (SB203580). Finally, ARMC5 depletion leads to lipid droplets accumulation in the cell cytoplasm, associated to increased expression of APOE gene, important for cholesterol esterification.

Conclusion

Altogether, this study describes a new function of ARMC5 as regulator of the redox homeostasis and lipid metabolism in adrenocortical cells.

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PEP1.7

Adverse events of mitotane treatment in patients with adrenocortical carcinoma

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Background

Mitotane represents the first-line medical treatment in most patients with adrenocortical carcinoma (ACC). Although adverse effects (AEs) due to mitotane are known to be frequent and may limit treatment, few systematic data are available. Aim of the study was to evaluate the AEs in ACC patients treated with mitotane monotherapy.

Methods

A retrospective multicenter study including 311 ACC patients (M:F = 111:200, median age 49 years) treated with mitotane as adjuvant therapy (n = 214, 68.8%) or in advanced disease (n = 97, 31.2%), was performed. Presence and grade of AEs were collected from medical records, retrospectively classified according to the CTCAE 5.0 criteria and correlated with duration of treatment, dosage administered and plasma concentrations of mitotane.

Results

Median duration of mitotane monotherapy was 20 (1–203) months, during which we observed a total of 3004 AEs with a rate *per* patients of 9.6 (0–30). The number of AEs significantly correlated with AUC of mitotane levels (P = *0.0001*, r_s = 0.23) and duration of treatment (P = *0.0002*, r_s = 0.21). Beside glucocorticoid insufficiency, the most frequent AEs were increase of gamma-glutamyl transferase (GGT, 88%), asthenia (68%), nausea (53%), hypercholesterolemia (54%), diarrhea (45%), increased transaminases, anorexia, and vertigo (36%, respectively). Apart from glucocorticoids, specific hormone replace therapy was administrated in 121/172 (70%) patients with hypothyroidism, 44/90 (49%) patients with hypomineralcortisolism, and 20/47 (42.5%) men with hypogonadism secondary to mitotane treatment. Statins and fenofibrate were used in 83/219 (37.9%) and 8/127 (6.3%) of patients with hypercholesterolemia and hypertrygliceridemia. Patients with short-term treatment (≤3 months) had a significantly lower probability to present asthenia (OR = 0.5, P = *0.01*), concentration impairment (OR = 0.2, P *<0.001*), ataxia (OR = 0.1, P = *0.007*), increased GGT (OR = 0.4, P = *0.004*) and SHBG (OR = 0.2, P *<0.001*), hypertriglyceridemia (OR = 0.3, P = *0.003*), hypothyroidism (OR = 0.4, P = *0.007*), hypomineralcortisolism (OR = 0.1, P = *0.01*) and gynecomastia (OR = 0.1, P = *0.008*) compared to those who received longer treatment (>3 months). Patients with advanced disease were treated for shorter time compared to those adjuvantly treated (median 9 vs 23 months, respectively, P *<0.0001*) and had a lower risk of aphasia (OR = 0.2, P = *0.04*) and dysarthria (OR = 0.5, P = *0.03*). Grade 4 AEs were reported in 24 cases (7.7%), including one case of peripheral neuropathy, leukopenia, and sepsis, 3 cases of severe adrenal crisis, and 4, 5, and 9 cases of hypertrygliceridemia, hypercholesterolemia and GTT increase, respectively. Mitotane was permanently discontinued due to AEs in 45 (14.5%) patients.

Conclusion

This is the first comprehensive overview of AEs by mitotane, which will be helpful in the daily clinical practice to prevent and manage toxicity, improving the patient's quality of life.

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PEP1.8

Adrenal insufficiency with chronic hyponatraemia and normal basal cortisol level: time to review the investigation of hyponatraemia

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Adrenal insufficiency is serious, life-threatening condition. Classical features include nausea, malaise, weight loss and hypotension. It is usually diagnosed at a late stage only when it presents as adrenal crisis. We report a patient with autoimmune adrenal insufficiency who presented with chronic hyponatremia and a repeatedly normal serum cortisol level. A 66-year-old female was referred to endocrinology with a 12-month history of hyponatraemia (Na 125–131 mmol/l). She was feeling tired and sometimes dizzy. There was no weight loss. She was not taking any steroid or opioid therapy. On examination, she was euvolemic with no postural hypotension. Other systemic examination was normal. Investigations showed Na 125 mmol/l, K 4.3 mmol/l, with normal renal function, serum osmolality: 265 mmol/kg, urinary osmolality 375 mmol/kg, urinary sodium: 50 mmol/l, TSH: 1.51 mU/l, 0900 h cortisol 378 nmol/l (RR: 185–624 nmol/l). CT head and CT chest, abdomen and pelvis were normal. She was diagnosed with Idiopathic SIADH; she was treated with fluid restriction and briefly with demeclocycline. She travelled to Australia on holiday, where she was admitted for a saline infusion. A year later she re-presented with hyponatraemia. Further investigation showed Na 122 mmol/l, 0900 h cortisol 312 nmol/l, with no significant response in a short Synacthen test (basal cortisol 237 nmol/l, 30 min 245 nmol/l and 60 min 242 nmol/l), with ACTH 612 ng/l (RR: <50 ng/l), indicating adrenal insufficiency. Adrenal antibodies were detected. Addison's disease was diagnosed. She was treated with hydrocortisone and fludrocortisone. She felt much better after starting treatment; the sodium level rose to 142 mmol/l after treatment. This patient demonstrates that adrenal insufficiency may occur as a chronic condition, with hyponatremia and malaise but without weight loss or hypotension, and with no progression or crisis. ACTH responsiveness was significantly impaired without any change in the basal cortisol level. Clinicians should not rely on a normal basal cortisol level for excluding adrenal insufficiency in hyponatraemia, but should also consider the ACTH level or a short Synacthen test. It is not clear why autoimmune disease should damage ACTH-responsiveness before it affects basal cortisol secretion; a similar finding has been made in the context of adrenal metastasis.

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Diabetes, Obesity, Metabolism and Nutrition

PEP2.1

MODY 5: a rare cause of diabetes and chronic kidney disease – a report of 10 cases

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Introduction

Maturity Onset Diabetes of the Young (MODY) affects 1–2% of diabetic patients. Subtype 5 (*HNF1*β mutation) is rare (~1% of all MODY subtypes) and extra-pancreatic manifestations are often present (chronic kidney disease (CKD), liver disease and/or genitourinary malformations).

Aim

To report and review confirmed MODY 5 cases in an Endocrinology Department.

Methods

Retrospective study of patients with *HNF1*β mutation followed between 2013 and 2020.

Results

We found 10 patients (6 female) with HNF1β mutation (7 index cases). The median age at MODY 5 diagnosis was 40.5 (IQR 35–58) years old.

Six patients were first classified as having type 1 diabetes and 4 as type 2. Diabetes was the first manifestation of MODY 5 in 50% of cases. The median age of diabetes diagnosis was 28 (IQR 16–40) years old. The average time between diabetes and MODY 5 diagnosis was 16.5 years old. Insulin therapy was prescribed in 8 patients (started at diabetes diagnosis in 75% of cases). The average diabetes evolution time was 19.4 years old. In 50% of the cases CKD in pediatric age was the first manifestation of MODY 5. These patients not only had progressive renal failure but also renal malformations: unilateral kidney hypoplasia (n = 1), bilateral kidney hypoplasia (n = 1) and solitary kidney (n = 1). Two patients were submitted to kidney, one to combined kidney and pancreas, and one to combined kidney and liver transplantations. All patients have functioning kidney graft. CKD was present in 7 patients. Additional long-term complications of diabetes include retinopathy (n = 3), peripheral neuropathy (n = 1) and ischemic cardiomyopathy (n = 1). Regarding other extra-pancreatic manifestations: cholestatic liver disease (n = 4) and genital malformation (bicornuate uterus) (n = 1). History of a first-degree relative with diabetes and/or nephropathy diagnosed at a young age was present in 71.4% (n = 5) of the index-cases.
Conclusions
Despite being a rare disease, MODY 5 is underdiagnosed and often classified as another type of diabetes. It should be considered in patients with diabetes and CKD especially at a young age, if family history is suggestive and nephropathy appears before/shortly after the diagnosis of diabetes. Presence of liver disease increases the degree of suspicion. Early diagnosis allows the risk of complications to be minimized and to carry out pre-conception genetic counseling.

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PEP2.2

Type 2 diabetes clusters indicate diabetes duration key in fracture risk

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Introduction
Individuals with type 2 diabetes mellitus (T2DM) are at an increased risk of developing fractures, despite higher mean BMI and BMD. Recently, clinically relevant sub-groups of T2DM have been characterised using biomarkers of glycemic metabolism.
Aim
Characterise T2DM sub-groups in a population-based setting and test for differences in fracture risk.
Methods
A total of 10019 Rotterdam Study participants were available with glycemic and (incident) fracture follow-up. Participants with T2DM (n = 1678) were partitioned in subgroups using K-means clustering based on: HOMA-B, HOMA-IR, age of diabetes onset, BMI and waist circumference measurements. Non-vertebral fracture risk was estimated across T2D subgroups using Cox proportional hazard models, adjusted for sex, age, BMI, collection cohort and prevalent T2DM.
Results
Four T2D clusters were defined each with relatively unique clinical characteristics namely, 1) advanced age of onset; 2) decreased insulin sensitivity; 3) beta-cell disfunction; 4) Obesity/high BMI. Individuals with prevalent and incident T2DM (independent of cluster) had lower risk of fracture than non-diabetics (see Forest plot). In contrast, individuals with prevalent T2DM (n = 1152) had increased risk of non-vertebral fracture (HR: 2.1, 95%CI: 1.65–2.76), than individuals without T2DM.
Conclusion
Despite that partitioning the heterogeneity of T2DM in clinically meaningful clusters opens the road to tailored prevention and care, our findings with prevalent T2DM indicate that disease duration (likely with inadequate glycemic control) is the main determinant of fracture risk. In line with this contention, the association between T2DM and fracture risk is not causal, as causality requires association with incident cases, as also confirmed by earlier Mendelian randomization studies. Future work, using genetically determined disease definitions and biomarkers will help unveil clusters of individuals with T2DM at increased risk of fracture.

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PEP2.3

The rs10830963 polymorphism of the MTNR1B gene is associated with glucose metabolism in the Czech population

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Introduction
The *MTNR1B* gene encodes a receptor for melatonin, a hormone that controls biorhythms. The gene is expressed primarily in the brain, but also in human pancreatic cells. Genetic studies suggest that variability in the *MTNR1B* gene is one of the factors sought to influence the pathophysiology of type 2 diabetes mellitus (T2DM). The single nucleotide polymorphism rs10830963 shows the strongest association. Our aim was to compare the distribution of the genetic variant rs10830963 among persons with different glucose tolerance. Subjects with impaired fasting blood glucose (IFG) and impaired glucose tolerance (IGT) during the oral glucose tolerance test (OGTT) were compared with controls. Another goal was to evaluate the possible associations of the polymorphism with insulin sensitivity (IS). Indices of IS, beta cell function and hepatic extraction were calculated and shape of glucose, insulin and C-peptide trajectories during the OGTT (monophasic, biphasic or more complex) were analysed.
Methods
A total of 1206 volunteers were examined biochemically, anthropometrically and underwent a 3 h OGTT (75 g glucose). Genotyping was performed on a TaqMan (LC480, Roche), the NCSS 2004 program was used for statistical evaluation.
Results
13 persons were diagnosed with T2DM, 119 had IFG or IGT and 1074 showed normal results. Higher frequency of minor and in relation to T2DM risk allele G was found in the IFG/IGT group (40.7% vs. 32.4% in controls, P = 0.01), OR = 1.57, CI 95% [1.06; 2.33], P = 0.03). The GG constellation was present in 23% of diabetics, in 17% of the IFG/IGT probands and in 11% of controls (Chi^2 = 11.2, P = 0.02). GG homozygotes showed slightly higher basal glycemia compared to CC homozygotes (P = 0.01) and also higher stimulated glycemia (AUCgly) in comparison with CC homozygotes (P = 0.002) and with heterozygotes (P = 0.004). GG genotype showed lower OGIS index of IS and lower HOMA-B and IGI indices of beta cell function. No association of the genotype with hepatic extraction or with the shape of glucose, insulin and C-peptide trajectories was observed.
Conclusion
In the sample of the Czech population we confirm the association of the G allele of the rs10830963 polymorphism in the *MTNR1B* gene with glucose metabolism. The risk allele G is more frequent in people with impaired glycoregulation and homozygous carriers of this allele show higher blood glucose levels during the OGTT and lower indices of IS and beta cell function.
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PEP2.4

Long-term clinical benefits with early combination therapy in patients with newly diagnosed type 2 diabetes from Europe: insights from the VERIFY study

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Objective
VERIFY demonstrated the long-term benefits of an early combination (EC) treatment strategy compared with initial metformin monotherapy (MET) followed by sequential intensification in a multiethnic population with

newly diagnosed type 2 diabetes mellitus (T2DM). The results for European patients enrolled in VERIFY are presented.
Methods
Adult patients with T2DM (≤2 years) and mild hyperglycaemia (glycated haemoglobin [HbA1c] 6.5–7.5%) were randomised 1:1 to either EC (vildagliptin plus metformin) or MET. The primary endpoint was time to initial treatment failure (TF), defined as HbA1c ≥7% at two consecutive scheduled visits after randomisation. If initial treatment did not maintain HbA1c <7%, patients on MET received vildagliptin. Time to second TF was when patients in both groups were receiving and failing on combination.
Results
Eligible patients from Europe (N = 1048) were assigned to EC (n = 523) or MET (n = 525). The 5-year incidence of initial TF was 45.3% with EC and 61.2% with MET. The median time to TF with MET was 36.6 (interquartile range 18.0–not reached [NE]) months; while for EC it was, 61.9 (29.9–NE) months. Risk of initial and secondary TF was reduced with EC when compared to MET (hazard ratio [HR] 0.59 [95% confidence interval {CI}: 0.50–0.70]; P <0.0001 and HR 0.84 [95% CI: 0.68–1.03]; P = 0.0898, respectively). A greater proportion of patients in the EC group had consistently lower HbA1c levels compared with MET group. Time to initial TF with EC was also lower for predefined subgroups of HbA1c, BMI, age, gender, smoking status, and estimated glomerular filtration rate. Overall safety and tolerability profile was similar between treatment groups; incidence of hypoglycaemic events was 0.3% with EC and 0.2% with MET.
Conclusion
Consistent with the global population, EC therapy provided greater and durable long-term benefits compared with the standard-of-care metformin monotherapy in patients with newly diagnosed T2DM from Europe.

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PEP2.5

Factors predicting insulin requirement in gestational diabetes mellitus

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Aim of the study
To identify the factors predicting insulin need in women with Gestational Diabetes Mellitus (GDM).
Methods
It was a retrospective study conducted in the National Institute of Nutrition between January 2018 and January 2019. Pregnant women referred for the management of GDM were included (n = 1000).GDM was defined according to the World Health Organisation as a glucose intolerance of variable severity with onset or first recognition during pregnancy. ANOVA and Pearson's chi-square tests were performed to compare clinical and biological characteristics of women with insulin therapy (IT) and those with nutrition therapy (NT).
Results
IT was initiated for 291 patients while the rest were maintained on NT (70.90%). Older women were significantly more likely to need IT (33.1±5.3 vs 32.6±5.1 years; P = 0.028).We found a significant association between educational attainment and the need for IT (P = 0.004). Family history of type 2 diabetes as well as personal history of GDM or foetal macrosomia increases the need for IT (P = 0.001, P = 0.002 and P = 0.025 respectively). Women with IT had more risk factors of GDM (P <0.001). All women having five risk factors had required IT.NT's failure was higher in obese women (36.60% vs 25.30%; P = 0.011). For women with IT, GDM was diagnosed at an earlier term (23.33 ± 6.8 vs 24.52 ± 7.1 weeks of gestation; P = 0.017). Fasting plasma glucose was higher in women with IT (5.25±1.07 mmol/l vs 4.67±0.60 mmol/l; P <0.001) as was Glycated hemoglobin (5.48±0.52% vs 5.23±0.38%; P <0.001).
Conclusion
Factors predicting insulin need may allow physicians to establish a concise scoring method for early identification of those women.

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PEP2.6

The relationship between calibration accuracy and glycemic variability on CGM

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The mean absolute relative difference (MARD) on CGM was reported with the various values approximately from 5% to 10%. The MARD in patients with type 1 diabetes was reported to be higher than that in patients with type 2 diabetes. Therefore, as one of the reasons why the reported MARD values varied, it cannot be denied that glycemic variability affects calibration accuracy. We examined relationships between calibration accuracy and glycemic variability on CGM. This is a prospective study where personal-CGM (GUARDIAN CONNECT) and professional-CGM (iPro2) were worn in parallel for 6 days (CGM attachment: day 1) and "blood glucose levels used to calibrate" (BGc) were obtained using "glucometers that were compliant with ISO15197:2013" (ISO) or "those not compliant with ISO15197:2013" (not-ISO) using a randomized crossover design. 25 type 2 diabetic inpatients were almost equally allocated to 2 groups (n = 13 and n = 12). ISO provided 11 BGc during days 2–3 and non-ISO provided those during days 4–5 in group 1 and vice versa in group 2. Every pre- and post-prandial and bedtime (7 times) BGc were obtained on days 2 and 5, and every pre-prandial and bedtime (4 times) BGc were obtained on days 3 and 4. Over days 2–3 and days 4–5, correlations between mean of 11 MARDs (Mean-MARD) and mean of two 24-h coefficient of variation [CV] (Mean-CV) were analyzed, on personal-CGM and professional-CGM. For ISO measurement, Mean-MARD correlated to Mean-CV on professional-CGM (r = 0.47 P = 0.02); however, Mean-MARD did not correlate to Mean-CV on personal-CGM. For not-ISO measurement, Mean-MARD did not correlate to Mean-CV on personal-CGM and professional-CGM. The results for ISO measurement show that inter-individual variability of accuracy for real-time calibrations may weaken the relationship between calibration accuracy and glycemic variability. The results for not-ISO measurement show that low calibration accuracy may lead to larger inter-individual variability of accuracy for calibrations, weakening the relationship between calibration accuracy and glycemic variability. In this study, professional-CGM calibrated using ISO may have revealed the relationship between calibration accuracy and glycemic variability. Patients using personal-CGM should consider possibility of having low calibration accuracy caused by high glycemic variability, that may be masked by real-time calibration.

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PEP2.7

The possibility of inter-individual variability of accuracy for CGM and FGM sensors

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There is little information regarding inter-individual variability of accuracy for CGM and flash glucose monitor (FGM) sensors. We studied the possibility of inter-individual variability of accuracy for CGM and FGM sensors. This is a prospective study. During hospitalization, 10 patients with type 2 diabetes wore a CGM [iPro2] and FGM [FreeStyle Libre Pro] in parallel over 24 h while every pre- and post-prandial "venous blood glucose levels" (VBG) were measured and used to calibrate CGM (n of VBG measurement = 60). We evaluated mean absolute difference (MAD) and mean absolute relative difference (MARD), derived from sensor glucose levels (SG) for CGM, measured every 5 min (MAD "5 min" and MARD "5 min") and extracted every 15 min (MAD "15 min" and MARD "15 min"), and derived from SG for FGM, measured every 15 min (MAD "FGM" and MARD "FGM"). The study participants correlated to the distribution of VBG (correlation ratio: η^2 = 0.38 P = 0.003). The study participants correlated to the distribution of MAD "5 min" and that of MAD "15 min" (η^2 = 0.27 P = 0.04998, η^2 = 0.27 P = 0.047, respectively); however, the study participants did not correlate to the distribution of MARD "5 min" and that of MARD "15 min". However, the study participants correlated to the distribution of MAD "FGM" and that of MARD "FGM" (η^2 = 0.57 P < 0.001, η^2 = 0.52 P < 0.001, respectively). The result of VBG may have been caused by patient-to-patient differences in glycemic control. The results of MAD for CGM may have been caused by the fact that higher VBG may lead to higher MAD. The results of MARD for CGM may have been caused by the fact that VBG are not associated with MARD because MARD is percentage of MAD to VBG. Compared of the result of MARD for FGM to the result of MARD for CGM, the correlation between the study participants and distribution of MARD "FGM" may suggest the inter-individual variability of accuracy for FGM sensors.

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PEP2.8

Association of serum uric acid concentration with diabetic retinopathy and its severity

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Background and aim
Diabetes is the leading cause of adult blindness due to retinopathy. Serum uric acid levels independently predict the development of micro vascular complications. In this study, we analyze the relationship between serum uric acid (SUA) levels with the development and the severity of diabetic retinopathy(DR) in patients with type 2 diabetes mellitus (T2DM).
Patients and Methods
A total of 100 Type 2 diabetes patients were enrolled. The presence of diabetic retinopathy was established by fundus examination. Hyperuricemia was defined as serum uric acid greater than 6 mg/dl (360 µmol/l). The study population was divided into two groups: group 1 (G1) consists of 50 patients with non complicated diabetes; group2 (G2) consists of 50 patients with diabetic retinopathy in absence of any other microvascular complications. The severity of DR was classified as non–proliferative diabetic retinopathy (NPDR), and proliferative DR (PDR).
Results
Out of 50 patients without DR (G1), there were 23 males and 27 females. Out of 50 patients with DR (G2), there were 22 males and 28 females. The mean age of the patients presented with and without DR was 58.88 and 56.88 years respectively. BMI and HbA1c did not statistically differ among the two groups (30.49 kg/m^2 vs 30.6 kg/m^2, 11.3% vs 11.1% respectively). Diabetes duration was longer in G2 compared to G1 (15.5 vs 9.06 years, $P = 0.1$). Hyperuricemia (serum uric acid >360 µmol/l) was more prevalent in group2 (26%) compared to group1 patients (18%). Mean serum uric acid levels were higher among patients with DR (336.36 µmol/l) compared to patients without DR (313.34 µmol/l) which was statistically not significant ($P = 0.2$). However, the concentration of SUA was significantly higher in patients with proliferative DR (373 µmol/l) compared to patients without DR or with NPDR (308 µmol/l), $P = 0.01$.
Conclusion
Patients with DR did not have significant elevation in serum uric acid levels than those without DR. However, an increased SUA levels were significantly correlated with the severity of DR.

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Pituitary and Neuroendocrinology

PEP3.1

Genetic profiling of a cohort of Italian patients with ACTH-secreting pituitary tumors and characterization of a novel USP8 gene variant

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Cushing's Disease (CD) is a rare condition characterized by an overproduction of ACTH by an ACTH-secreting pituitary tumor resulting in excess of cortisol release by the adrenal glands. Somatic mutations in the deubiquitinases USP8 and USP48, and in BRAF genes, have been reported in a subset of patients affected by CD. Aim of this study was to characterize the genetic profile of a cohort of 66 patients with ACTH-secreting tumors, searching for somatic mutations in USP8, USP48 and BRAF hotspot regions. 7 patients were found to carry USP8 somatic mutations in the 14-3-3 protein binding motif ($n = 5$ P720R, $n = 1$ P720Q, $n = 1$ S718del); 2 patients were mutated in USP48 (M415I); no mutation was identified in BRAF. In addition, a novel USP8 variant, G664R, located in exon 14, upstream the 14-3-3 protein binding motif, was identified in 1 patient. Functional characterization of G664R USP8variant was performed in murine corticotroph tumor AtT-20 cells. Transient transfection with the G664R USP8 variant resulted in a significant increase of ACTH release (201.1 ± 63.7% vs empty vector transfected cells, $P < 0.05$) and of cell proliferation (141.8±30.5% vs empty vector transfected cells, $P < 0.05$). Notably, USP8 proteolytic cleavage was enhanced in AtT-20 cells transfected with G664R USP8 (1.86 ± 0.58–fold increase of N-terminal USP8 fragment, vs WT-USP8, $P < 0.05$). Surprisingly, *In situ* Proximity Ligation Assay (PLA) experiments showed a significant reduction of PLA positive spots, indicating USP8-14.3.3 proteins colocalization, in USP8 G664R transfected cells with respect to USP8 WT transfected cells (−47.9±6.6%, vs WT-USP8, $P < 0.001$), thus suggesting a possible conformational rearrangement due to amino acid 664 replacement affecting the binding of USP8 with partner proteins. No significant difference in terms of ACTH secretion, cell proliferation and USP8 proteolytic cleavage were observed between G664R USP8 and S718del USP8 transfected cells. Immunofluorescence experiments showed that, contrary to S718del USP8 but similarly to WT-USP8 and other USP8 mutants, G664R USP8 display an exclusive cytoplasmic localization. In conclusion, recurrent somatic mutations were found in USP8 (10.6% vs 36.5% incidence of all published mutations) and in USP48 (3% vs 13.3% incidence) hot spot regions. A novel USP8 variant was identified in a CD patient. *In vitro* functional studies in AtT-20 cells suggested that this somatic variant might be clinically relevant in ACTH-secreting tumor pathogenesis.

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PEP3.2

Safety results from MPOWERED, a phase 3 trial of oral octreotide capsules in adults with acromegaly

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Background
Injectable somatostatin receptor ligands (iSRLs) have been a mainstay in acromegaly treatment. Oral octreotide capsules (OOC; MYCAPSSA®) were recently approved in the USA. Results from the placebo-controlled CHIASMA OPTIMAL and open-label CH-ACM-01 studies showed an OOC safety profile consistent with that of iSRLs with no new or unexpected safety signals. Results of the MPOWERED trial have enabled a comparison of OOC safety and efficacy with iSRLs.
Methods
To enter MPOWERED, patients must have the following: acromegaly diagnosis, biochemical control of acromegaly (insulin-like growth factor I <1.3 × upper limit of normal; mean integrated growth hormone <2.5 ng/ml), and ≥6 months' iSRLs treatment (octreotide or lanreotide). Eligible patients entered a 26-week Run-in phase to determine the effective OOC dose; responders at week 24 then entered a 36-week randomized controlled treatment (RCT) phase receiving OOC or iSRLs. Safety was monitored as adverse events (AEs) in both arms throughout the trial, including the RCT.
Results
In the RCT, incidence of treatment-emergent adverse events (TEAEs) was similar between groups; 39 patients (70.9%) in the OOC group and 26 (70.3%) in the iSRL group had ≥1 TEAE. 19 patients (34.5%) in the OOC and 15 (40.5%) in the iSRL group had treatment-related TEAEs. Occurrence was similar for serious AEs (OOC, 5.5%; iSRL, 8.1%) as well as TEAEs classified as severe (OOC, 9.1%; iSRL, 10.8%). One patient in the OOC group discontinued due to a TEAE. The most common gastrointestinal TEAEs were flatulence (OOC, 25.5%; iSRL, 21.6%), nausea (OOC, 20.0%; iSRL, 8.1%), diarrhea (OOC, 10.9%; iSRL, 13.5%), abdominal pain (OOC, 9.1%; iSRL, 8.1%), and constipation (OOC, 5.5%; iSRL, 13.5%). AEs of interest were infrequent, including cholelithiasis (OOC, $n = 0$; iSRL, $n = 1$ [2.7%]) and secondary hypothyroidism (OOC, $n = 1$ [1.8%]; iSRL, $n = 0$). In the iSRL group, 32.4% of patients reported injection site reactions (ISRs) during the RCT, and 47% of patients reported ISRs as part of the Acromegaly Treatment Satisfaction Questionnaire, a newly validated patient-reported outcome tool.[1]

Conclusion
Safety results from MPOWERED align with prior trials, showing that the OOC safety profile is consistent with that of iSRLs as well as the acromegaly disease burden. No new or unexpected safety signals were identified during the trial. Safety results were mostly similar between OOC and iSRLs, although patients in the OOC group did not experience any ISRs.
[1]Fleseriu M, *et al*. *Pituitary*. 2020 Aug;23(4):347–358.
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PEP3.3

Insulinoma-associated protein 1 (INSM1) may serve as a sensitive and specific immunohistochemical and molecular biomarker of neuroendocrine differentiation in pancreatic neuroendocrine tumors (PNETs)

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Introduction
Insulinoma-associated-1 (INSM1), encoded by the *INSM1* gene is key factor in pancreatic endocrine, sympatho-adrenal and pan-neurogenic development. It has also been identified in multiple tumors of neuroendocrine origin but not thoroughly investigated as a potential neoplastic biomarker. The aim of the study was to evaluated INSM1 as a semiquantitative immunohistochemical biomarker as well as quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) biomarker for pancreatic neuroendocrine tumors (PNETs).
Material and Methods
Metastatic PNETs (liver metastases) specimens (n = 24) matched control (normal) tissue were surgically collected and INSM1 expression for tumor and control tissue was analysed by immunohistochemistry. Additionally, mRNA expression was determined by qRT-PCR.
Results
INSM1 expression was significantly increased in neoplastic vs nonneoplastic tissue. Using immunohistrochemistry, we found that INSM1 was not detected in any control, nonneoplastic, non-neuroendocrine tissue. In PNETs tissue, INSM1 was detectable by immunohistochemistry and qRT-PCR in 22 of total 24 specimens (91.66%). Compared to normal tissue specimens, the INSM1 showed significant overexpression in metastatic PNETs.
Conclusion
Our findings highlight that INSM1 may serve as a promissing, novel, neuroendocrine, immunohistochemical and molecular biomarker in patient diagnosed with PNETs.

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PEP3.4

Benefits and harms of pituitary surgery for prolactinomas. A systematic review and meta-analysis

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Objective
The objective of this systematic review was to assess the proportion of patients with prolactinomas that obtain remission or experience adverse effects after transsphenoidal surgery.
Design
A systematic review. Registered at PROSPERO, registration number CRD42020213002
Methods
A bibliographical search of PubMed and Embase was performed and last updated on September 30, 2020. Eligible studies were studies that included patients who had undergone transsphenoidal surgery for prolactinomas. A random effects analysis was used to calculate the weighted proportions.
Results
Sixty-five observational studies assessing the effect of transsphenoidal surgery for prolactinomas in 4472 patients, were included. The overall proportion of patients obtaining remission after surgery was 61% (95% CI 56 to 65; I^2 = 84%), while the proportion of patients with microprolactinomas and macroprolactinomas obtaining remission was 79.8% (95% CI. 74 to 85) and 52.7% (95% CI. 44 to 61), respectively. Patient mortality was reported as 0% in 14 studies with 1413 participants. Meningitis was observed in 2.7% and postoperative CSF leakage in 4.4%.
Conclusion
This systematic review found an overall remission rate across a range of studies to be 61% (95% CI 56 to 65), and a remission rate for microprolactinomas of 79.8% (95% CI 74 to 85) after transsphenoidal surgery. There are few reported side effects and giving the improving results of transsphenoidal surgery it could be considered first line treatment in selected cases.

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PEP3.5

Endocrine function after tanssphenoidal surgery in patients with non-functioning pituitary adenomas: A systematic review and meta-analysis

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Background
Surgical resection is indicated in patients with non-functioning pituitary adenomas (NFPA) causing visual defects or tumor growth in proximity to the optic chiasm. The aim of this study was to systematically assess the benefits and harms of pituitary endocrine function after transsphenoidal surgery in patients with NFPAs.
Methods
This study was conducted a systematic review that searched for potentially eligible studies in Pubmed and EMBASE from database inception to Oct 11, 2020. Inclusion criteria were studies reporting on pituitary function before and after transsphenoidal surgery in patients with NFPAs with a minimum follow-up of one month. The pre-specified primary outcomes were the proportion of participants with improved or deteriorated pituitary function after surgery, and Secondary outcomes was assessment of the effect of pituitary surgery on individual axis. This study was registered with PROSPERO (registration number: CRD42020210853).
Findings
Of the 6228 identified record, 17 studies enrolling 2623 participants were included. The proportion of participants with overall improved pituitary function was 45·0 percent (95% CI. 34·1 to 56·4; I^2 = 91%) while the proportion of participants with overall deterioration of pituitary function was 10·8 percent (95% CI. 6·6 to 17·2; I^2 = 92%) after surgery. Subgroup analysis suggested a positive association between year of publication and risk of pituitary failure. The most likely hormonal axis to recover after surgery was the adrenal axis.
Interpretation
The mean proportion of patients with pituitary recovery after transsphenoidal surgery was between 34 and 56% across studies, while the proportion of patients with new pituitary failure after surgery was between 7 and 17% across studies. These estimates were associated with large heterogeneity, which was not explained by subgroup analysis. However, the effect estimates did include important clinical effects and pituitary surgery for recovery of endocrine function may be considered in selected cases**.**
Funding
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PEP3.6

Comparative study of growth hormone stimulation levels in growth hormone deficient children vs children with idiopathic short stature

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Introduction
Short stature (SS) assessment includes the documentation of growth hormone (GH) secretion via GH stimulation tests.

Objectives
To study retrospectively GH stimulation test results among Greek children with SS and investigate differences among GH deficient (GHD) children vs idiopathic short stature (ISS).
Methods
Data were collected retrospectively from 190 children who visited the pediatric endocrine clinic for the evaluation of SS. Age, gender, weight *z*-score, height *z*-score, BMI *z*-score, Tanner stages, bone age, annual growth rate, target height, insulin-like growth factor 1 (IGF-1) levels and GH stimulation test results were collected from the electronic medical records. GHD is defined as a serum peak GH concentration <10 ng/ml in a combination of two separate tests with glucagon (peak GH-G) and clonidine (peak GH-C). Both IGF-1 and GH were measured by a chemiluminescence sandwich type immunoassay on the analyzer Liaison XL, Diasorin.
Results
Eighty-four children (44%) were diagnosed with GHD, 56 (29%) with ISS, 38 with chronic disease (20%) and 12 with SGA (small for gestational age) (6%). All data concerning GHD and ISS children are summarized in table 1. IGF-1 levels did not differ significantly among ISS and GHD children. Pubertal children in both groups had significantly higher (*P*: <0.001) IGF-1 levels as compared to prepubertal: 283 ng/ml vs 156 ng/ml in ISS group and 258 ng/ml vs 138 ng/ml in GHD group. IGF-1 levels were not sex dimorphic in any group. Peak GH-G and peak GH-C were significantly higher in ISS versus GHD children but did not differ significantly in respect to sex/puberty.
Conclusion
GH stimulation test is of greater interest than IGF-1 levels alone in differentiating GHD from ISS children irrespective of puberty or sex.

Table 1. Values are presented as mean (s.d.). CA: chronological age, BA: bone age, SDS: standard deviation score, MPH: mid-parental height, BMI: body mass index.

	All (190)	ISS (56)	GHD (84)	*P* value
Chronological age (yr)	9.5(3)	10.2(2.6)	9.3(3.2)	0.34
Sex (M/F)	103/87	30/26	46/38	
Gestational age (wk)	37.9(2.0)	38.5(1.5)	37.7(2.5)	0.11
Birth length (cm)	48.6(4.9)	49.6(2.2)	48.7(3.4)	0.73
Height SDS	−1.99(0.7)	−1.92(0.9)	−1.95(0.7)	0.99
BA-CA (yr)	−1.84(1.2)	−2.1(1.1)	−1.75(1.3)	0.69
BMI SDS	0.1(1.8)	−0.06(0.9)	0.35(1.1)	0.61
Tanner stage				
	1	137	36	64
	>2	53	20	20
MPH SDS	−0.67(0.8)	−0.54(0.7)	−0.72(0.8)	0.55
IGF-1 (ng/ml)	176.6(94.8)	201.8(104.2)	166.1(88.3)	0.16
Peak GH-G (ng/ml)	8.6(6.7)	12.2 (6.8)	5.8(3.4)	<0.001
Peak GH-C (ng/ml)	8.1(5.1)	11.7(5.4)	5.7(2.7)	<0.001

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PEP3.7

Transcriptome alteration landscape of pituitary neuroendocrine tumour tissue

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Pituitary neuroendocrine tumors (PitNETs) are non-metastatic neoplasms of the pituitary that may overproduce hormones leading to systemic disorders or tumor mass effects causing headache, vertigo, or visual impairment. The overall estimated clinical prevalence of PitNETs is 1 in 400 to 1 in 1000 people. Although the pathogenesis of PitNETs has been extensively studied the molecular factors underlying tumorigenesis, remission, and therapy response of PitNETs are still unclear. The studies of PitNET transcriptome profiles could give insight into pathogenesis mechanisms that promote tumorigenesis properties like growth, invasiveness, response to treatment. First-line medical treatment of somatotroph PitNETs is somatostatin analogues (SSA) and dopamine agonists (DA) that decrease tumour mass and induce antiproliferative effects on PitNET cells. This study aimed to determine differences in transcriptome signatures that are induced by SSA/DA therapy in PitNET tissue. In this study we selected tumour tissue of twelve patients with somatotroph PitNETs, half of the patients had SSA/DA treatment before surgery and the other half was treatment-naive. The transcriptome sequencing was carried out, differentially expressed genes (DEGs) were identified and protein–protein interactions and pathway analysis was performed. We discovered 34 upregulated and 6 downregulated DEGs in patients with SSA/DA treatment. Three tumour development promoting factors *MUC16*, *MACC1* and *GRHL2* were significantly downregulated in therapy administered PitNET tissue. Protein–protein interactions and pathway analysis revealed extracellular matrix Here, we demonstrate that somatotroph PitNETs can be distinguished based on their transcriptional profiles following SSA/DA therapy, therefore, SSA/DA treatment can cause changes in gene expression. The SSA/DA significantly downregulated several tumourigenesis contributing factors, including *MUC16*, *MACC1* and *GRHL2*. Genes that were upregulated did not have a direct influence on the antiproliferative functions in the PitNET cells. This suggests that SSA acts in a tumour suppressive manner. Collagen related interactions and pathways were enriched in our data implicating extracellular matrix involvement in antitumoural effects of drug treatment.

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PEP3.8

Temporary oral NaCl tablets safely increase serum sodium in hospitalised elderly patients with hyponatraemia secondary to refractory idiopathic syndrome of inappropriate diuresis (SIAD)

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Introduction
Hyponatraemia is the most common electrolyte abnormality encountered within the inpatient setting and is associated with increased morbidity, mortality and length of hospital stay. It compromises a spectrum of symptoms, from being asymptomatic to varying degrees of neurological disturbances including gait abnormalities with increased risk of falls, confusion and rarely seizures. This is of particular relevance in the midst of an aging population worldwide and in the context of the current COVID pandemic, where measures are required to avoid lengthy hospitalisation. Syndrome of inappropriate diuresis (SIAD) remains the most common underlying cause. In addition to treating the aetiology, non-pharmacological treatment of SIAD include fluid restriction which is poorly effective. Medical treatment with demeclocycline and vaptans (vasopressin receptor antagonists) may offer reliable alternatives. However, these agents are not without risk, particularly where significant shifts in sodium levels are observed over a short time period. We propose the temporary use of sodium chloride (NaCl) tablets together with fluid restriction as an effective and safe way to treat refractory SIAD in hospitalised elderly patients, facilitating prompt discharge and reducing further risk of hospital-acquired morbidity.
Illustrative cases
We present two cases: 74-year-old and 82-year-old female patients who were admitted to the Cambridge University Hospitals NHS Foundation Trust between September and December 2020 and were found to be symptomatic with acute on chronic hyponatraemia. Clinical and biochemical assessment was consistent with SIAD, with chest and brain imaging excluding additional pathology. First line management involved commencement of an observed fluid restriction with a slow and limited improvement in the degree of hyponatraemia. Modified release NaCl tablets at a dose of 2.4 g twice daily were subsequently introduced whilst both patients remained on fluid restriction. Within 72 h of commencement of NaCl tablets, both patients improved clinically, with serum sodium correction to a level that was deemed safe for discharge (≥130 mmol/l). Their serum sodium did not increase more than 10 mmol/l in a 24-h period. A short course of oral NaCl tablets was recommended following discharge with follow up in the outpatient Endocrinology clinic.

Conclusion
The temporary use of oral NaCl tablets, in addition to fluid restriction, is a well-tolerated, safe and effective way to treat refractory SIAD in hospitalised elderly patients, thus facilitating early discharge and reducing the morbidity and mortality associated with prolonged hospital admissions.

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Reproductive and Developmental Endocrinology

PEP4.1

Effect of oral contraceptives containing estradiol valerate vs. ethinyl estradiol combined with dienogest on biomarkers of coagulation – a randomized clinical trial

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Objective
To compare the effects of combined oral contraceptives (COCs) containing estradiol valerate (EV) and dienogest (DNG) with ethinyl estradiol (EE) and DNG on biomarkers of coagulation: thrombin generation (TG), prothrombin fragments F1+2 (F1+2) and D-dimer (D-Di). A DNG-only preparation was included as a control.
Background
COC use increases the risk of venous thromboembolism (VTE) 2-6-fold compared with non-use. Traditional COCs contain synthetic EE. However, COCs containing natural estrogens, estradiol (E2) or EV have recently been introduced, with the expectation of a reduced impact on coagulation and potentially a lower VTE risk.
Study design
We performed a randomized clinical trial and report here the secondary outcomes. Fifty-nine 18-35-year-old, healthy, normal-weight, non-smoking voluntary women were randomized to either EV+DNG (2 mg+2–3 mg, $n = 20$), EE+DNG (0.03 mg+2 mg, $n = 20$), or DNG-only (2 mg, $n = 19$) for nine weeks. Three women discontinued, two women with FV Leiden mutation were excluded and two samples could not be analyzed (EV+DNG $n = 18$, EE+DNG $n = 18$, DNG $n = 16$). We assessed TG (with Calibrated Automated Thombogram, TG-CAT), F1+F2 and D-Di at baseline and nine weeks of treatment. From the TG-CAT, we analyzed endogenous thrombin potential (ETP, total amount of thrombin), thrombin peak (highest concentration), lag time (time from initiation to thrombin burst), and time to thrombin peak (time from initiation to peak).
Results
Mean ETP increased +23% in the EV+DNG-group vs. +61% in the EE+DNG-group ($P < 0.01$), and peak thrombin increased +40 vs. +127% ($P < 0.01$). Mean lag time and time- to- peak thrombin decreased: −7% vs. −26% ($P < 0.01$) and −8% vs. −21% ($P < 0.01$). In the EE+DNG-group the within-group differences for all TG-CAT variables were significant ($P < 0.01$). In contrast, in the EV+DNG-group only the change from baseline in ETP and peak thrombin were significant ($P < 0.01$). Mean F1+2 and D-Di decreased in the EV+DNG and increased in the EE+DNG -group compared with baseline (EV+DNG F1+2 -9% vs. EE+DNG +16%, $P = 0.04$ and D-Di -0.4% vs. +10%, $P = 0.06$), In the DNG-only group, we did not observe any significant changes.
Conclusions
Our results indicate that the estrogen component accounts for most alterations in coagulation activity induced by COC use. We suggest that COCs containing E2/EV have less impact on thrombin generation and thereby likely decreased VTE risk compared with preparations containing EE. The actual VTE risk for E2-based COCs will be revealed in future epidemiological studies.

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PEP4.2

Immunological and inflammatory biomarkers in non-obese patients affected by PCOS, correlation between hormonal and metabolic parameters: preliminary data

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Objective
Policystic ovary syndrome (PCOS) is a multifactorial disease characterized by reproductive and metabolic impairments. PCOS patients could present anovulation, hirsutism and infertility as well as higher prevalence of metabolic syndrome, glucose intolerance and diabetes. Insulin-resistance (IR) together with hyperandrogenism represent the main players, with reciprocal influences in a vicious circle: insulin promotes androgen secretion in thecal cells and hyperandrogenism has been related to adipose tissue dysfunction that lead to IR and hyperinsulinemia. Both factors contribute to create in PCOS patients a state of chronic low-grade inflammation (LGI), which may have an important role in the physiopathology of the disease; however, it is predominantly evaluated in obese PCOS. Therefore, we performed an observational case–control study to investigate inflammatory and immunological parameters, such as IgG subclasses and free light chains (FLCs) and hemolytic complement activity (CH50) in non-obese PCOS, evaluating their relations with metabolic and hormonal parameters.
Methods
36 subjects were studied: 16 PCOS patients (mean ± S.E.M. 27.13 ± 1.82 age; BMI 24.1±0.9 kg/m^2); 20 controls (aged 26.05 ± 0.73). Blood sample was collected for metabolic and hormonal parameters, IgG subclasses, k and λ FLCs, CH50. Hormones were measured by immunochemiluminometric assays; Metabolic parameters by enzymatic assays; subclasses of IgG, FLCs and CH50 were evaluated by turbidimetric method.
Results
PCOS patients showed significant lower IgG1, IgG2, IgG3 compared with controls (mean ± S.E.M. 3.76 ± 0.29 g/l, 2.63 ± 0.20, 0.62 ± 0.06, 0.34 ± 0.08 vs 6.49 ± 0.35, 4.28 ± 0.25, 0.84 ± 0.07, 0.33 ± 0.04, respectively) and higher levels of FLCs (k 12.22 ± 0.71 vs 6.03 ± 0.30, λ 10.10 ± 0.79 vs 8.04 ± 0.48 g/l) and CH50 (48.64 ± 2.65 vs 36.51 ± 1.38 U/ml); we found correlation between IgG2 and free-testosterone ($r = 0.72$, $P = 0.005$) and CH50 and vitamin D ($r = 0.54$, $P = 0.04$); an inverse correlation was found between IgG1 and, respectively, ACTH ($r = -0.57$, $P = 0.02$) and cortisol ($r = 0.78$, $P = 0.001$) in PCOS.
Conclusions
In the complex scenario of low-grade inflammation in non-obese PCOS, we showed lower levels of main subclasses of IgG and higher CH50 levels, suggesting involvement of other mechanisms other than "classical" pathway of complement activation; FLCs could be attractive to monitor inflammation degree, disease activity and influence on hormonal status.

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PEP4.3

Effects of a very low-calorie ketogenic diet on androgen levels in overweight/obese men: a single-arm uncontrolled study

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Low levels of testosterone and SHBG levels are often present in subjects with overweight and obesity; functional hypogonadism further alters the metabolic balance and may drag subjects in a sort of vicious cycle, reducing exercise and energy expenditure. The very low-calorie ketogenic diet (VLCKD) has been reported to rapidly reduce body weight, glycaemia and insulinemia, but its effects on total testosterone (TT) and SHBG levels are less clear. We thus aimed to evaluate the response of TT and SHBG circulating levels to a VLCKD in a cohort of overweight or obese nondiabetic male subjects. All subjects underwent a VLCKD for 4 weeks. Anthropometric parameters, oral glucose tolerance test (OGTT), bioelectrical impedance analysis, and blood testing for the measurement of glycaemia, insulin, TT, SHBG, LH, were performed before and after 1 and 4 weeks of VLCKD. Seventeen patients [mean age 41.3 (12.2) years, mean BMI 36.4 (5.2) kg/m^2, mean TT 2.5 (1.0) ng/ml, mean SHBG (24.2) nmol/l] were enrolled. After VLCKD treatment, body weight (−9.3 kg (1.8)), fat mass [−6.5 kg (2.1)] and BMI [−3.1 (0.7)]

significantly decreased, and a mean 14.9 ± 3.9% loss of the initial body weight was achieved. A significant increase of 0.49 (0.59) ng/ml and of 0.89 (0.91) ng/ml in serum TT levels was achieved after 1 and 4 weeks after VLCKD, respectively; similarly, a mean increase of 3.47 (4.73) and of 10.94 (12.87) in serum SHBG levels was achieved after 1 and 4 weeks, respectively. A stratification was further performed in high vs low responders in regard to TT variations after 1 week of VLCKD (>+0.44 vs <+0.44 ng/ml). While showing comparable variation of all variables analyzed, high responders differed only by the level of insulin sensitivity. Indeed, low responders, despite a comparable level of glycemia during OGTT, displayed a significantly higher level of insulinemia [area under curve: 25858 (11821) vs 13924 (11592)], indicating that they were more insulin-resistant vs high responders. This is the first study that evaluated the early response of androgen levels to institution of a VLCKD. VLCKD promotes a rapid effect on TT levels, especially in insulin-sensitive subjects with overweight or obesity. This highlights the tight relation between insulin action, energy balance, and testicular function. Further, VLCKD could be safely used to improve hypoandrogenemia, and possibly rescue obese patients from functional hypogonadism.

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PEP4.4

Insulin production by human spermatozoa in response to glucose stimuli

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Introduction
Metabolic homeostasis in the testis is essential for a healthy spermatogenesis. Insulin is regarded as one of the most important intervenients in the metabolic regulation of spermatogenesis, where it acts directly on the differentiation of spermatogonia into primary spermatocytes or indirectly through the metabolic modulation of Sertoli cells. Additionally, insulin is hypothesized to play a major role on human spermatozoa capacitation, although the mechanisms that regulate its production and secretion remain to be disclosed.
Aim of the study
The main objective of this study was to estimate the capacity of insulin production by human spermatozoa and if they express PC1/3 and PC2, which are enzymes responsible for the cleavage of proinsulin. In addition, we hypothesized that insulin production could respond to glucose stimuli.
Materials and Methods
Seminal samples of normozoospermic men (n = 15) were collected and submitted to a density gradient centrifugation. Two fractions of spermatozoa were then collected according to their motility condition (high vs low motility). The expression of insulin, PC1/3 and PC2 mRNA was evaluated in both spermatozoa fractions by RT-qPCR. The protein expression of insulin, PC1/3 and PC2 in spermatozoa was evaluated by immunofluorescence. The fraction of highly motile spermatozoa was then incubated in a medium conferring capacitating conditions and supplemented with increasing glucose concentrations (in mM: 0, 5.5, 11 and 22). After 6 h, the concentration of insulin in the medium was quantified by ELISA.
Results
Insulin, PC1/3 and PC2 mRNA, as well as the respective proteins, are expressed in human spermatozoa. The mRNA expression was found to be higher in the highly motile spermatozoa. Additionally, human spermatozoa release insulin to the medium in a glucose concentration-dependent manner.
Conclusion
This study shows that human spermatozoa are able to produce and release insulin in a glucose concentration-dependent manner. Future studies are required to further evaluate the role of insulin on human spermatozoa capacitation and fertilization capacity, opening an exciting new line of investigation.

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PEP4.5

Effects of metformin withdrawal after long and short term treatment in PCOS: observational longitudinal study

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Background
Metformin plays a consolidated role in the management of polycystic ovary syndrome (PCOS). However, there is no clear answer on how long we should treat and on how long its beneficial impact sustain after we stop treatment. We compared the effects of metformin withdrawal after long-term (LT) and short term (ST) treatment in PCOS women that had previously well responded to metformin.
Methods
We conducted observational longitudinal study including 44 PCOS women (31 (28–36) years and BMI 32.5 (27.7.-34-9) kg/m^2) that were followed for 6 months after metformin withdrawal. Prior inclusion, ST group had been treated with metformin on average for 1.03 ± 0.13 year, LT group for 5.07 ± 2.52 years. We followed anthropometric, metabolic, reproductive parameters and eating behavior as assessed by TFEQ-R18.
Results
After metformin withdrawal, ST group gained significant amount of weight (from 92 (75.5.–107.3) kg to 96 (76–116) kg; P = 0.019). Weight tended to increase also in LT users (from 87 (75–103) to 87 (73–105) kg; P = 0.058). More women in LT group maintained stable weight (27% in LT group vs 15% in ST group). Eating behavior deteriorated in both groups. Withdrawal of metformin resulted in a decrease of menstrual frequency (6 (6–6) to 6 (4–6) menstrual bleeds per 6 months; P = 0.027) and in borderline increase of androstenedione (6.4 (4.6–7.6) to 7.8 (4.8–9.6) nmol/l; P = 0.053) in LT group. Waist circumference, HOMA and glucose homeostasis remained stable in both groups. There were no differences between groups at 6-month follow up.
Conclusion
Collectively, present study implies some metabolic and endocrine treatment legacy in both groups as well as some group-specific deteriorations in clinical parameters 6 months after metformin withdrawal.

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PEP4.6

The effect of decamethylcyclopentasiloxane exposure to maternal mice in offspring behavior

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Decamethylcyclopentasiloxane(D5) is one of the most common chemical ingredient for cosmetic products, cleansing agents, hairdye, dry cleaning solvent and personal hygiene supplies. D5 is also known as estrogenic chemical. It can be absorbed through skin, airosol, and even oraly. People are exposed to D5 in daily environment. However, the risk of prenatal exposure to D5 has not yet been fully understood. Recent research shows that imbalance of dam's estrogen induces brain development disorder, in this study the effect of prenatal exposure of D5 on brain development were assessed by behavioral test of their pup. According to previous study, the estimated amount of daily exposure of D5 to human is around 0.6 mg/kg. Also, the systematical absorption ratio of D5 by oral is 10% in mice. Thus, we treated 3, 6, 12, 60 mg/kg of D5 with corn oil per a day to pregnant female mice from E10 through E19. All behavioral tests were performed after pups became 6 weeks old. In high dose treated D5 group showed decreased social behavior and cognitive ability in three chamber test. The impairment of memory and exploring ability were found on high dose D5 group pups in novel object test. These results show that maternal exposure to D5 impairs social ablilty and memory of pups. As pups were only exposed to D5 in prenatal period, these symptoms were caused by abnormal brain development while they were embryos. This study shows that maternal exposure to D5 cause the offspring's brain development disorders. Also, the results support the previous study that imbalance of estrogen disrupts brain development.

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PEP4.7

Functional ovarian reserve in women with infertility and euthyroidism: what is the role of thyroid autoimmunity?

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Introduction
Thyroid dysfunction is the most common endocrine disorder in women of childbearing age, and is associated with menstrual irregularities, anovulation and infertility. Whether it is thyroid function and/or thyroid autoimmunity (AI) that affects functional ovarian reserve remains to be clarified.
Aim
To evaluate the association between functional ovarian reserve and thyroid AI in women with infertility in euthyroidism.
Methods
Retrospective study of women with infertility, in euthyroidism, followed in a Human Reproduction Department, between May 2016 and January 2020. TSH, anti-thyroid peroxidase (TPO) antibodies, anti-thyroglobulin (TG) antibodies were measured. Functional ovarian reserve was assessed by anti-Müllerian hormone (AMH) levels with antral follicle count (AFC) performed by endovaginal ultrasound. Women with at least 1 of the following criteria were excluded: prior thyroidectomy, radioactive iodine treatment, cervical surgery/radiotherapy, oophorectomy, malignant/autoimmune pathology, chronic kidney disease, liver disease, polycystic ovary syndrome, current pregnancy and current medication with levothyroxine, methimazole or propylthiouracil. Results with P <0.05 were considered statistically significant.
Results
730 women were evaluated, with mean age of 34.9±3.9 years, with positive AI (≥ 1 positive antibody) present in 14.8% of cases. Anti-TPO antibodies were positive in 11.0% of patients and anti-TG antibodies in 7.0%. Mean TSH levels were 1.6±0.7 uUI/ml (NR: 0.4–4.0). Median body mass index (BMI) was 22.8 kg/m2 (IQR 5.1). Median AMH was 1.7 ng/ml (IQR 2.1), and mean AFC was 10.2±6.3. Patients with positive and negative AI did not differ significantly in age (P = 0.133), BMI (P = 0.784], AFC (P = 0.508) and AMH (P = 0.825). TSH levels were significantly higher in the positive AI group (2.0±0.8 vs 1.5±0.7 uUI/ml; P <0.001). In the univariate and multivariate analysis, only patient's age and AFC were predictive of AMH levels (P <0.001; P <0.001, respectively). TSH levels, BMI and thyroid AI were not predictive of AMH levels. In regard to AFC, in the univariate analysis, only age was predictive (P <0.001). TSH levels, BMI and thyroid AI were not predictive of AFC.
Conclusions
In this study we found that thyroid autoimmunity and TSH levels in the normal range, in women with infertility, apparently, do not have a predictive role for functional ovarian reserve.

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PEP4.8

Current clinical practice of prenatal dexamethasone treatment in at risk pregnancies for classic 21-hydroxylase deficiency in Europe

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Background
Prenatal dexamethasone treatment (Pdex) has been used since the 1980s to prevent virilization in female offspring suspected to have congenital adrenal hyperplasia (CAH). However, due to lack of strong evidence for its best practice as well as limited data regarding longterm adverse effects, use of dex is highly controversial. This study reveals the current medical practice regarding Pdex in female fetuses at risk of CAH due to 21hydroxylase deficiency (21OHD) in Europe.
Methods
A questionnaire was designed and distributed using Microsoft Forms, including 17 questions collecting quantitative and qualitative data. Thirty-six medical centres from 14 European countries responded and 28 out of 36 centres were reference centres of the European Reference Network on Rare Endocrine Conditions, EndoERN.

Results
36% (13/36) of the surveyed centres are currently providing Pdex. The treatment is initiated by different specialties i.e. pediatricians, obstetricians/gynecologists or geneticists. Regarding the starting point of Pdex, 15% of centres stated to initiate therapy as early as pregnancy is confirmed, 23% at 4 to 5 wpc, 31% at 6 wpc, and the rest at 7 wpc at the latest. A dose of 20 µg/kg/d is used and dose distribution among the centres varies between once to thrice daily. Prenatal diagnostics are conducted at 72% (26/36) of centres, which however mainly includes chorionic villous sampling ± genotyping of the sexdetermining region Y from maternal blood (SRYtyping) or amniocentesis and CYP21A2 genotyping. Noninvasive genetic testing from maternal blood is currently offered by one centre. The total number of pregnant women who received Pdex during the first trimester of pregnancy varied from 3 to 44 per centre (median = 10, total number of treated cases n = 197), while 0 to 13 cases (median = 5, total number of treated cases n = 70) were treated for the entire gestational period. A mean of 1.6 cases are treated at each centre per year. Registries for longterm followup are only available at 46% of the centres that are using Pdex. National registries are only available in 2 of the 14 corresponding countries.
Conclusion
This study reveals a high international variability and discrepancy on the use of Pdex across Europe. It highlights the importance of a European cooperation initiative for a joint international prospective trial to establish evidencebased guidelines on prenatal diagnostics, treatment and followup of pregnancies at risk for CAH. Evaluation of outcome and longterm health of already treated cases across Europe is highly recommended.

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Thyroid

PEP5.1

A rare case of resistance to thyroid hormone with recurrent papillary thyroid carcinoma

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Background
Resistance to thyroid hormone (RTH) involves an altered tissue response to thyroid hormones. RTH is characterized by increased serum thyroid hormone (TH) levels with nonsuppressed serum thyroid-stimulating hormone (TSH) levels. Herein, we report a rare case of RTH with recurrent papillary thyroid carcinoma (PTC).
Patient findings
A 38-year-old female patient was admited to outpatient clinic for the evaluation of neck swelling. She had no thyrotoxic symptoms and there was no family history of thyroid cancer. Physical examination revealed a 1 cm thyroid nodule and mildly enlarged thyroid gland. The initial laboratory examination revealed a normal level of TSH [(3.28 uIU/ml (0.35–5.5)] despite elevated levels of TH [(free T4: 2.11 ng/ml (0.74–1.52), free T3: 6.25 pg/ml (2.3–4.2)]. Thyroid autoantibodies were not detected against thyroglobulin, thyroperoxidase and TSH receptor. Normal pituitary gland was found in the MRI performed to exclude TSHoma. Thyroid ultrasonography (USG) showed multiple hypoechogenic nodules, the largest of which was 13x9x7 mm in diameter, in both lobes. Fine-needle aspiration was performed for the largest nodule with suspicious features of malignancy in the left lobe and the cytologic diagnosis was 'susupicious of malignancy' (*Bethesda Category* 5). She underwent total thyroidectomy with central lymph node dissection (LND). The histopathological results revealed classic PTC (tumor-node-metastasis staging; T1bN1bM0) in the left thyroid lobe with metastatic central lymph nodes. Tumor size was 1.3×0.7 cm. For to ensure the TSH suppression after surgery, levothyroxine therapy was initiated 150 mg/day. After six months of levothyroxine therapy her TSH level was still elevated (TSH 176.3 µIU/ml). Therefore the dose was gradually increased up to 300 mg/day. Recurrence of PTC with regional lymph node metastasis were revealed 12 months after surgery. She underwent re-surgery for complementary LND. Then she received radioiodine ablation therapy (150 mCi). In her last follow-up visit 18 months later, serum TSH level decreased to 33.2 uIU/ml. Serum free T4 and T3 levels were normal and thyroglobulin level was <0.20 ng/ml. She had no symptoms and signs of hypothyroidism. Also, her neck USG examination showed no pathological lymph node.
Conclusion
Only a few cases have been reported in the literature showing the coexistence of RTH and thyroid carcinoma. TSH suppression may not be obtained despite increasing doses of levothyroxine in patients with RTH and PTC, as was the case we report. Further studies are needed to reach a consensus on the management of thyroid carcinoma in patients with THR.

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PEP5.2

Low-risk papillary thyroid carcinoma: outcome predictive factors in a cohort of patients not treated with radioiodine therapy after total thyroidectomy

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Background
Papillary thyroid carcinoma (PTC) is the most frequent thyroid malignant neoplasm. American Thyroid Association (ATA) guidelines don't specify how to follow-up low-risk PTC patients not receiving radioiodine therapy (RAI) after total thyroidectomy (TT). Indeed, there is no consensus among authors regarding the interpretation of thyroglobulin (TG) levels and ultrasound neck (US) findings during follow-up in these settings.
Aim
To evaluate outcome predictive factors in low-risk PTC patients treated with TT but not with RAI.
Patients and methods
This retrospective study was conducted on 61 patients who were followed-up for at least 12 months after TT. Assessment of TG, TG-antibodies (ATG) and US was performed after TT and then every 18-24 months. ATA Guidelines Classification system of response to therapy (excellent, biochemical and structural incomplete, indeterminate) was applied even if RAI was not administered. We define as "suspected disease progression/relapse" (sPR) the appearance/growth of thyroid remnants (TR) by US and/or the detection of increased serum TG and/or ATG levels.
Results
The median follow-up was of 41.6±17 months; 5% of patients showed sPR. A slightly higher risk of sRP was observed in patients ≥ 55 years. All patients with sPR had been diagnosed with a microPTC and presented an indeterminate response during follow-up. No differences concerning sex, age, TNM, histology, thyroiditis history were observed as compared to indeterminate patients without sPR. In patients with indeterminate response, TG and ATG levels were found slightly increasing during follow-up even if TSH target levels were achieved with L-thyroxine therapy. In the whole cohort, during follow-up ATG absence was not associated with increased TG levels; in patients with excellent response, a slight variation in TG levels was likely due to TSH levels fluctuation without sPR development. Most ATG positive patients become negative at the end of follow-up and none of them showed sRP. 63% of patients showed TR disappearance after 15±8 months.
Conclusion
Low-risk PTCs have a favorable outcome and the presence of TR is not a risk factor for relapse. However, microPTC could lead to sPR and careful follow-up is advised especially in older patients. Slight variations in TG levels in ATG/US negative patients could be due to TSH fluctuations rather than sRP development.

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PEP5.3

Is the thyroid nodule location associated with the risk of malignancy?

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Introduction
Recent published studies suggest that the anatomical location of the thyroid nodule may be associated with different risks of malignancy. However, the results are still sparce and little consensual.

Aim
To evaluate the frequency of nodules on different locations of the thyroid gland and to determine whether their location correlates with different malignancy risks.
Methods
We present a retrospective study including all Fine-Needle Aspiration Biopsies (FNABs) performed in our department between January 2016 and December 2019. Demographic data, the number and location of nodules, their ultrasound characteristics and the respective EU-TIRADS classification, their cytological results according to Bethesda's classification and their histology were recorded. The nodule was considered benign in the presence of benign cytology or histology, and malignant when this diagnosis was confirmed histologically.
Results
From a total of 1497 FNABs included, performed in 1046 patients, 1004 had definitive diagnoses (934 [89.5%] benign; 70 [6.7%] malignant). The majority (86%) were done in female patients, with a median age of 56 years (P25–P75:47–66). The presence of a single thyroid nodule was associated with a higher rate of malignancy when compared to multinodular goiter (34.3% vs 22.1%, $P = 0.019$). The right lobe was the location with the highest description of nodules (452 [45.0%]), followed by the left lobe (425 [42.3%]) and the isthmus (127 [12.6%]). There were no differences regarding the risk of malignancy between these locations (7.7% vs6.4% vs 6.3% respectively; $P = 0.686$). In 686 patients, the longitudinal nodular position was documented (424 [61.8%] in the middle lobe; 206 [30.0%] in the lower lobe; and 56 [8.2%] in the upper lobe). Likewise, the rate of malignant lesions was not significantly more prevalent in any of these positions (8.0% vs 6.3% 10.7%, respectively; $P = 0.514$).
Conclusion
Although current literature has shown that thyroid nodule location can be an independent risk factor for a malignant lesion, our study could not confirm these data. In this large cohort of FNABs samples, we evidenced that there is no relationship between the anatomical location of the thyroid nodule and its risk of malignancy. Despite little consensus on this subject, some studies suggest that the isthmus and the lower lobe nodules have the highest risk, while others show this result in the middle lobe.

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PEP5.4

Pilot study with the luca device to optimize the diagnosis of thyroid cancer: preliminary results

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Introduction
Diffuse optic techniques exploit the capability of penetration of near infrared light to investigate the properties and physiology of tissues. Based on this property, the LUCA device (Laser and Ultrasound Co-Analyzer of Thyroid nodules), a multi-modal device that combines two different diffuse optical techniques – time resolved and diffuse correlation spectroscopies – with ultrasound in the same transducer, has been developed with the aim of optimizing the study of the thyroid nodules.
Materials and Methods
Pilot study that included 11 controls without thyroid pathology (normal thyroid function and ultrasound with negative antibodies) and 31 patients with thyroid nodules (13 with benign nodules, 10 with multinodular goiter and 8 with malignant nodules all confirmed by histology study). All of them were assessed with the LUCA device, using a pre-established protocol. Measurement of both lobes and sternocleidomastoid muscles (MECM) was performed, in addition to nodule determination in patients. In the preliminary analysis using mixed linear effect models, 4 variables were assessed: total Hemoglobin concentration (THB), Tissue oxygen saturation (StO2), dispersion coefficient at a wavelength of 785 nm (μs) and blood flow index (BFI).
Results
The study in controls (54.5% women, 35.3 ± 6.2 years) showed that LUCA can differentiate between thyroid tissue and MECM (P <0.05 for the 4 variables). The study in patients with nodular pathology (77.4% women, 52.2 ± 2 years) has shown a wide variability of the variables studied. The study using ROC curve in patients with single nodules suggests that the model that combines μs of the nodule together with the difference in THB between the nodule and the ipsilateral MECM offers an AUC of 0.92 with a Sensitivity = 100% and Specificity = 77% to differentiate between benign and malignant nodules.
Conclusions
Although this is a preliminary analysis, current results suggest that diffuse optics could help to optimize the diagnosis of malignant thyroid nodules. The study needs to be expanded with other diffuse optics variables along with ultrasound variables.
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PEP5.5

Association of microRNA expression with cervical lymph node metastases of thyroid carcinoma

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Background
Many microRNAs (miRNA) have been proposed as promising molecular markers of papillary thyroid carcinoma (PTC). However, there are limited data on the correlation between miRNA expression, and neck lymph node metastasis. Analysis of miRNAs expression data may improve perioperative decision making for patients with PTC, specifically in identifying patients harboring neck lymph node metastases (LNM).
Aim of the study
To determine and compare miRNA expression profiles of PTC with LNM and PTC without LNM and to determine the diagnostic utility of the detection of specific miRNAs in the preoperative assessment of thyroid nodules.
Methods
Sixty-two thyroid fine needle aspiration (FNA) samples with suspected thyroid carcinoma were collected in the prospective molecular study at Vilnius University hospital Santaros klinikos. Next generation sequencing was performed to characterize miRNA and gene expression profiles in these FNA samples. All 62 patients underwent thyroidectomy: 34 PTC without LNM, 14 PTC with LNM and 12 benign thyroid nodules were diagnosed histologically.
Results
Nine miRNAs were significantly differentially expressed between PTC with MTS compared with PTC without MTS (adjusted P value < 0.05; log2 fold change ≤ -1.0 or ≥ 1.0).
Conclusions
Analysis of miRNAs expression levels and detection of FNA miRNAs can be used for the pre-operative diagnosis of thyroid cancer cervical lymph node metastasis. To translate these data into clinical application, large cohort studies are required to examine the prognostic and diagnostic value of miRNAs panels.

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PEP5.6

Is the igf-1ec isoform a novel biomarker for advanced differentiated thyroid cancer?

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Background
Recent knowledge implicates a differential expression of the insulin-like growth factor-1 (IGF-1) mRNA splice variants (i.e., IGF-1Ea, IGF-1Eb and IGF-1Ec) in cancerous tissues, implying possible specific roles of the encoded IGF-1 protein isoforms in cancer biology. In particular, there is growing evidence that IGF-1Ec isoform may plays a distinct biological role

in various types of cancer. The aim of the present study was to investigate whether IGF-1Ec isoform expression is associated with a particular type of thyroid cancer.
Materials and Methods
Formalin-fixed paraffin-embedded tissue specimens of different types of thyroid cancer from 92 patients were assessed for IGF-1Ec expression profile by immunohistochemistry. In addition, thyroid cancer biopsies of different TNM staging histological types were evaluated for mRNA expression of the IGF-1Ec transcript by real-time polymerase chain reaction (rt-PCR).
Results
From the total number of 92 samples, 2 were anaplastic, 10 medullary, 4 hyperplasia of C-cell, 11 follicular, 5 hurtle cell carcinoma, 2 poor differentiated, 5 nodular hyperplasia, 1 lymphoma and 52 were papillary thyroid carcinomas. The age of the patients at the time of diagnosis or the tumor size did not affect significantly the IGF-1Ec expression. Among all types of cancer, IGF-1Ec was expressed in papillary differentiated thyroid carcinoma. Its expression/localization was mainly cytoplasmic and significantly positively associated with TNM staging and the presence of muscular and capsule cancerous invasion (P <0.05), while no differences were found regarding vascular or regional lymph node infiltration. Similarly, a differential profile was revealed regarding the mRNA expression of the IGF-1Ec transcript, which exhibited a higher expression in advanced papillary thyroid carcinoma.
Conclusion
The present data demonstrate that the expression of IGF-1Ec isoform in thyroid cancer is positively associated with more advanced stages of papillary thyroid carcinoma.

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PEP5.7

Multifocality in papillary thyroid carcinoma. Is it always the same tumor?

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Introduction
Multifocality is a common finding in papillary thyroid carcinoma (PTC), but its biological significance is not well established. In some cases not all foci present the same histological pattern.
Objective
To study the different histological patterns and molecular profiles of multifocal PTC (mPTC).
Material and methods
All patients with a confirmed diagnosis of PTC after total thyroidectomy in the period 2015–2019 at Vall d'Hebron Hospital Campus were included. At first, pathological reports were reviewed, and all mPTC cases were selected. In mPTC, all foci were evaluated by an expert pathologist to identify the coexistence of different patterns. In those cases, paired samples representative of the two major different foci were analyzed with the Next-Generation Sequencing (NGS) panel "Oncomine ™ Solid Tumor".
Results
A total of 74 (41.1%) of the 180 included patients had mPTC. Mean (± S.D.) age was 49.4 ± 13.6 years old, and 73% of them were women. In 10 (13.5%) of the 74 cases, two different histological patterns coexisted. In these, the size (median, IQR) of the primary focus (PF) was 12 (9–45) mm and that of the secondary focus (SF) was 5 (1–10) mm. The most frequent patterns of PF were: follicular (4) and conventional (2), while those of SF were: conventional (6) and follicular (4). In two of the 8 cases analyzed by NGS (25%), the panel showed a different molecular profile between the two paired samples. In the first case, the PF carried a BRAF (V660E) mutation and the SF had a KRAS (codon 61 – c.182A>G) mutation; and in the second case, both the primary as the secondary focus had the same PIK3CA mutation but the PF had a NRAS (codon 61 – c.182A>G) mutation, while the second case showed KRAS (codon 60 and 61 – c.180_181delTCinsAA) and EGFR mutations.
Conclusions
As it is already known, multifocality is a very common histological finding in PTC, but the fact that in some cases the different foci show different histological patterns and molecular profiles raises the possibility that they may actually be synchronous PTCs. This fact could have important diagnostic, therapeutic and prognostic implications.

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PEP5.8

Genetic profiles of aggressive variants of papillary thyroid carcinomas

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Background
Aggressive variants of papillary thyroid carcinoma (PTC) have been described with increasing frequency and are associated with unfavorable clinical outcomes. However, limited data exists on the comprehensive genetic profile of these variants.
Method
We performed targeted next generation sequencing in 36 patients with aggressive variants of PTC and compared it to PTC from The Cancer Genome Atlas project and poorly differentiated thyroid cancers (PDTCs)/anaplastic thyroid cancers (ATCs) from the Memorial Sloan Kettering Cancer Center.
Result
BRAF mutation was the most prevalent (89%) in aggressive variants of PTC compared to that in other thyroid cancers. NRAS mutation was identified in one patient (3%), which was less frequent than in others TERT promoter mutation (17%) ranged between that of PTCs (9%) and PDTCs (40%). Tumor suppressor genes, ZFHX3, TP53, and CHEK2 were mutated in 14%, 3%, and 6% of aggressive variants of PTCs, respectively. The total accumulation rate of tumor suppressor gene mutations was 23%, which was significantly higher than that of PTCs (4%), and lower than that of ATCs (76%). Mutations in three functional groups, histone methyl transferases, SWI/SNF chromatin remodeling complex, and the PI3K/AKT/mTOR pathway were present in 11%, 14%, and 11% of samples, respectively.
Conclusion
Aggressive variants of PTC had higher BRAF and lower NRAS mutation prevalence than other thyroid cancers. The prevalence of mutations in the TERT promoter, tumor suppressor gene, and genes encoding three functional groups ranged between that of PTCs and PDTCs/ATCs. These genetic profiles might be associated with clinical outcomes of aggressive variants of PTC.

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Calcium and Bone

PEP6.1

Comparative evaluation of bone turnover markers in diabetic rats treated with sitagliptin, canagliflozin, empagliflozin

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Background and aims
Although bone fracture risk increases in DM, bone mineral density does not completely reflect bone fragility. It is important to explore other methods of osteoporotic fracture risk evaluation. Nowadays bone turnover markers (BTM) investigation is not widely used in clinical practice. On the other hand, the action of some glucose-lowering drugs on bone remodeling is not completely explored. The aim of this study was to investigate and to compare BTM in diabetic rats during treatment with sitagliptin (SITA), canagliflozin (CANA), and empagliflozin (EMPA).
Materials and methods
Type 2 DM was modelled in male Wistar rats by high-fat diet and streptozotocin+nicotinamide. 4 weeks after rats were divided into 4 groups: "DM" (n = 4), "SITA" (n = 4) (treatment with SITA 50 mg/kg 8 weeks) "CANA" (n = 4) (CANA 25 mg/kg for 8 weeks), "EMPA" (n = 4) (EMPA 2 mg/kg 8 weeks). Also, there was a control group "CRL" (n = 4) treated with vehicle. Blood glucose level (BGL) was studied every 3rd day during the experiment. Blood samples for BTM (osteocalcin, OCL, osteoprotegerin, OPG, RANKL) evaluation were obtained prior to euthanasia.

Results
Treatment with both SITA and EMPA led to moderate increase in OCL level compared with DM (19.57[17.85;24.44], 16.0[15.72;17.0] and 10.69[8.87;11.03] ng/ml respectively) though OCL level did not achieve CRL value (49.1[47.98;54.57]). OCL in "CANA" (9.06[6.21;16.87]) and "EMPA" (16.0[15.72;17.0]) groups was significantly lower than in "SITA" (19.57[17.85;24.44]) and "DM" (19.57[17.85;24.44]) groups. All antihyperglycemic drugs caused decrease in OPG: (6.28[3.06;9.99], 1.26[1.04;1.88] and 1.85[1.19;1.9] pmol/l for SITA, EMPA, CANA, respectively) compared with "CRL" (12.53[11.1;13.7]) and "DM" (14.58[6.12;15.65]). Both SGLT-2 inhibitors led to more prominent decrease in OPG level than SITA (P <0.01). RANKL level in SITA (248.38[220.81;300.96] pmol/l) and EMPA (254.1[231.62;284.0] pmol/l) groups did not significantly differ from CRL one (247.81[205.36;289.67]). At the same time, the use of CANA led to significant increase in RANKL (342.86[280.0;355.29]) in comparison with other glucose-lowering agents. However, the OPG/RANKL ratio did not differ between the CRL (0.53[0.38;0.66]) and DM (0.53[0.19;0.58]) groups and was higher compared with treatment groups (0.24[0.01;0.45] for SITA, 0.005[0.003;0.007] for EMPA and 0.005[0.003;0.007] for CANA). The lowest OPG/RANKL ratio was in the EMPA and CANA groups, with no differences between them.
Conclusions
Both EMPA and CANA decrease osteogenesis and increase bone resorption, while effect of CANA might be more pronounced which manifests in higher RANKL level.

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PEP6.2

Yes associated protein 1 (YAP1) expression and modulation by calcium sensing receptor activation in human parathyroid tumors

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The Hippo pathway is involved in human tumorigenesis and regeneration. Here, we investigated the Hippo co-activator YAP1 and the kinase LATS1/2 in tumors of the parathyroid glands, which are almost invariably associated with primary hyperparathyroidism. Compared with normal parathyroid glands (n = 3), where YAP1 was detectable in the cytoplasm and in the nucleus, parathyroid adenomas (PAds; n = 10) had YAP1 accumulation mainly at the nuclear level, while in parathyroid carcinomas it was reduced at both nuclear and cytoplasmic levels (n = 6; 4 samples harboring *CDC73* inactivating mutations and 2 samples harboring *MEN1* inactivating samples). The kinase LATS1/2, which phosphorylates YAP1 promoting its cytoplasmic degradation and preventing its nuclear accumulation and transcriptional activity, was variably reduced in PAds. *YAP1* and *MEN1* map on chromosome 11, which is frequently interested by loss-of-heterozygosity in PAds; of note, *YAP1* silencing appeared to reduce the expression levels of *MEN1*, while *MEN1* silencing increased *YAP1* expression in PAds-derived cell cultures and in HEK293A cells. Besides, YAP1 nuclear accumulation was induced by the calcium sensing receptor (CASR) agonist R568-mediated activation of the CASR in both PAds-derived cells and HEK293A cells transfected with CASR, and this effect was abolished upon the incubation with RhoA/Rho-associated coiled-coil-containing protein kinase (ROCK) inhibitors Y27632 and H1152. Lastly, CASR activation increased the expression of the YAP1 gene targets *CYR61*, *CTGF*, and *WNT5A*, and the effect was blunted by *YAP1* silencing, suggesting that CASR-induced YAP1 nuclear accumulation is transcriptionally active in PAds-derived cells. Besides, YAP1 silencing did not affect *PTH*, *CASR*, *TBX1*, and *VDR* expression in PAds-derived cells, while YAP1 signaling may be partially involved in R568-stimulated *GCM2* expression levels. Concluding, we provided evidence of the involvement of the Hippo pathway in human tumor parathyroid cells, suggesting a role as tumor suppressor for YAP1 and LATS1/2, and identifying the activation of a CASR-ROCK-YAP1 axis, where CASR activation induces YAP1 transcriptional action, and resistance to $[Ca^{2+}]_o$ may reduce YAP1 nuclear accumulation.

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PEP6.3

Characterization of sarcopenia via different DXA derived indices and associations with uc-dpMGP

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Sarcopenia is a degenerative loss of skeletal muscle mass, quality, and strength. It increases the risk of falls and fractures, is associated with cardiac and respiratory disease and cognitive impairment and leads to mobility disorders. It decreases quality of life, leads to loss of independence, placement in long-term care and finally death. A variety of indices and parameters can be used to define sarcopenia. According to literature, matrix-GLA-protein (MGP) is associated with bone parameters and cardiovascular risk. We therefore investigated whether uncarboxylated, dephosphorylated MGP (uc-dpMGP) is associated with muscle/fat mass parameters and with sarcopenia defined by dual-energy X-ray absorptiometry (DXA) derived indices and/or hand grip strength (HGS). We analysed data from the BioPersMed cohort (n = 966, 531 females, 435 males, mean age 58 ± 9 years), a prospective elderly cohort of asymptomatic subjects at cardiovascular risk. Uc-dpMGP was measured with IDS-iSYS Ina*K*tif MGP Kit (Immunodiagnostic Systems Holdings PLC, UK). Muscle and fat mass parameters were determined by Lunar iDXA (GE Healthcare GmbH, Austria): ALM: Appendicular lean mass [kg]; LMI: Lean mass index [kg/m^2]; FMI: fat mass index [kg/m^2]; LESM: lower extremity skeletal muscle mass [kg]; TSM: total skeletal mass [kg]; TSMI: total skeletal mass index [kg/m^2]; ALMI^{BMI}: ALM/BMI. HGS was measured via JAMAR@Hand Dynamometer (Patterson Medical, Ltd, UK). Sarcopenia was defined via HGS, SMI (skeletal muscle mass index), LESMI (lower extremity skeletal muscle mass index), AMMI (appendicular skeletal muscle mass index), ASM (appendicular skeletal muscle mass), ALMI (appendicular lean mass index) and with all parameters. Cut off values: HGS [kg]: males: <27; females: <16 (at the weaker hand); SMI [%]: males: <29.9, females: <23.5; LESMI [kg/m^2]: males: 5.1, females: 3.7; ASM [kg]: males: 20, females: 15; AMMI [kg/m^2]: males: 7, females: 5.5; ALMI [kg/m^2]: males: ≤ 65 years: 7.59, > 65 years: 7.64, females: ≤ 65 years: 5.47, > 65 years: 5.78. ALM (P = 0.004), LMI (P = 0.004), FMI (P <0.001), LESM (P = 0.004), TSM (P = 0.014) and TSMI (P = 0.004) correlated positively and ALMI^{BMI} (P <0.001) negatively with uc-dpMGP serum levels. Uc-dpMGP serum levels were significantly higher in persons with sarcopenia according to SMI (P = <0.001), HGS (P = 0.008), AMMI (P = 0.011), ASM (P = 0.001) and all parameters (P <0.001). The number of persons with sarcopenia varied between 29 to 224 according to parameters used for characterization. Uc-dpMGP serum levels might be useful as a biomarker in the characterization of sarcopenia. Dependent on the indices used for its definition.

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PEP6.4

A rare cause of persistent hyperparathyroidism

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Ectopic parathyroid tissue remains a significant hurdle in the surgical management of hyperparathyroidism. In diagnostically challenging cases of persistent hyperparathyroidism, unusual ectopic locations of parathyroid adenomas must be considered in order to avoid numerous re-operative explorations and the associated risks to the patient. We present a 30-year-old female was referred to the endocrinology department for symptomatic hypercalcemia. Routine laboratory investigations showed a severe hypercalcemia (corrected serum calcium: 3.4 mmol/l), with an intact parathyroid hormone serum concentration of 269 ng/l. The serum phosphate was low (0.63 mmol/l) and urinary calcium was 5.1 mmol/24 hours (*N*). A ^{99m}Tc sestamibi scintigraphy showed a focus of radioactivity compatible with a hyperfunctioning lower right parathyroid. Thus, the lower right parathyroid gland was excised, with intra-operative testing for parathyroid hormone. Because the PTH value remained high the surgeon decided to remove 2.5 of the 3 remaining parathyroid glands, but the PTH value did not decrease. Pathology revealed 2 hyperplastic, 1 normal parathyroid gland and thymus gland instead of left lower parathyroid. A technetium (^{99m}Tc) sestamibi scan was performed, but the result was not conclusive. The patient underwent a Choline PET/CT, which showed a left retro-pharyngeal active nodule corresponding to a possible ectopic parathyroid tissue. The patient had a successful transoral removal of the lesion with normalization of serum calcium and iPTH after surgery. Pathology confirmed the presence of a parathyroid adenoma (3.2 × 1.7 × 1.2 cm, weighting 3.9 g). The genetic tests showed no mutations in the CDKN1B, MEN and RET genes. In conclusion, we reported a case with persistent hyperparathyroidism after cervical surgery, due to an ectopic retro-pharyngeal parathyroid adenoma for which different imaging techniques and particularly 18F-fluorocholine PET/CT were essential in guiding the surgical approach and enabling the surgeon to successfully locate and remove the ectopic parathyroid.

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PEP6.5

The effect of intra-operative autofluorescence monitoring on unintentional parathyroid gland excision rates and post-operative PTH concentrations – a single-blind randomized controlled trial

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Purpose
Intraoperative imaging of parathyroid glands (PGs) has been developed in order to reduce the risk of unintentional parathyroidectomy during total thyroidectomy. This novel modality is based on their intrinsic characteristic of autofluorescence (AF) after near-infrared light exposure. The aim of this study was to assess the effect of this method on the risk of unintentional PG excision (total or partial) during total thyroidectomy.
Methods
This was a single-blind, randomized, controlled trial including adult patients who underwent scheduled total thyroidectomy between December 2019 and March 2020. These patients were randomly allocated to two groups: one in which near-infrared autofluorescence imaging (NIRAF) was applied (NIR-group) and one without NIRAF (NONIR-group). Hormonal and biochemical assessment was performed pre- and 24 h post-operatively. AF findings and the number of PGs autotransplanted were recorded.
Results
One-hundred eighty patients were eligible. Unintentional (total or partial) PG excision rates during total thyroidectomy in the NONIR ($n = 90$) and NIR ($n = 90$) groups were 28.9% [95% confidence interval (CI) 19.8%–39.4%] and 14.4% (95% CI 7.7%–22.1%), respectively ($P = 0.02$). Furthermore, NIR reduced the risk of parathyroid tissue presence in the specimen sent for pathology (relative risk 0.51, 95% CI 0.28–0.92; $P = 0.02$). However, the number of PGs identified by NIR could not predict the risk of post-operative hypoparthyroidism.
Conclusion
NIRAF imaging during total thyroidectomy led to a significant reduction in PG excision rates. However, this modality did not result in the reduction of post-operative hypoparathyroidism or hypocalcemia risk.

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PEP6.6

Cardiovascular events in adult patients with chronic hypoparathyroidism treated with rhPTH(1–84) compared with a historical control cohort

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This study investigated risk of cardiovascular (CV) events over a period of up to 5 years in adult patients with chronic hypoparathyroidism treated with recombinant human parathyroid hormone (1–84), rhPTH(1–84), compared with a historical control cohort of patients who did not receive rhPTH(1—84). The rhPTH(1–84)-treated patient cohort was derived from the NCT00732615 (REPLACE), NCT01268098 (RELAY), and NCT01297309 (RACE) clinical trials. A control cohort of adult patients who did not receive rhPTH(1–84) or rhPTH(1–34) was selected from the US Explorys electronic medical record database (Jan 2007–Aug 2019) using selection criteria similar to the enrolment criteria used in the trials. Index date was the day after initiation of treatment for the rhPTH(1–84) cohort and the day after the first calcitriol prescription for the control cohort. The primary outcome was the risk of a composite CV event (defined as any event of cerebrovascular disease, coronary artery disease, heart failure, or peripheral vascular disease) in the rhPTH(1–84) cohort compared with the control cohort through 5 years post-index. Patients with a CV event at baseline were excluded from the analysis. Risk of a CV event was assessed in a Kaplan–Meier analysis and a Cox proportional hazards model adjusted for demographic characteristics, baseline clinical conditions, and baseline serum calcium levels. The analysis included 113 patients in the rhPTH(1–84) cohort and 618 patients in the control cohort. Patients in the rhPTH(1–84) cohort, compared with the control cohort, were younger (mean±s.d. age, 47.8±12.0 vs 51.0±16.8 years; $P < 0.05$) and fewer had acute manifestations of hypoparathyroidism before the index date (22.1% vs 69.6%; $P < 0.001$). In a Kaplan–Meier analysis, rhPTH(1–84)-treated patients had a significantly reduced risk of developing a CV event over the 5-year follow-up period compared with patients in the control cohort (3.5% vs 16.3%; $P < 0.01$). The adjusted hazard ratio for developing a CV event associated with rhPTH(1–84) treatment vs no rhPTH(1–84) treatment was 0.23 (95% CI, 0.07–0.74; $P < 0.05$). This analysis is limited by differences in patient management under predefined clinical trial protocols for the rhPTH(1–84) cohort vs real-world clinical practice for the control cohort. Over 5 years, patients with chronic hypoparathyroidism treated with rhPTH(1–84) in clinical trials had a significantly reduced risk of CV events compared with a control cohort of patients who did not receive rhPTH(1–84). Further research is needed to better understand the mechanism underlying the association between chronic hypoparathyroidism and risk of developing a CV event.
Encore abstract from ENDO 2021.

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PEP6.7

Change in estimated glomerular filtration rate in adult patients with chronic hypoparathyroidism treated with rhPTH(1–84) compared with a historical control cohort

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Changes in estimated glomerular filtration rate (eGFR) over 5 years were evaluated in adult patients with chronic hypoparathyroidism. A cohort of patients treated with recombinant human parathyroid hormone (1–84), rhPTH(1–84), was derived from NCT01297309 (RACE) and NCT01199614 (HEXT) clinical trials. A historical control patient cohort with hypoparathyroidism who did not receive rhPTH(1–84) or rhPTH(1–34) were from the large national US Explorys electronic medical record database (Jan 2007–Aug 2019) using criteria similar to trial enrolment criteria. Index date was the day after treatment initiation for the rhPTH(1–84) cohort and the day after first calcitriol prescription for the control. The analysis included patients with eGFR ≥60 ml/min/1.73 m^2 during the 6 months before index date, ≥2 eGFR measurements ≥3 months apart during the 5 years on/after the index date, and ≥1 eGFR measurement at 5±0.5 years. For patients from RACE, baseline and study visit data after rhPTH(1–84) initiation were collected from antecedent trials. Changes in eGFR were assessed in linear mixed and multivariable models (adjusted for age/sex/race, baseline eGFR, history of hypercalciuria/hypertension/type 2 diabetes [T2D]/acute hypoparathyroidism manifestations/cardiovascular condition). There were 72 patients in the rhPTH(1–84) cohort and 174 in the control cohort. Before the index date, patients in the rhPTH(1–84) cohort, compared with the control, were younger (mean±S.D., 47.5±11.0 vs 53.9±15.5 years; P <0.01), and a lower proportion had acute manifestations of hypoparathyroidism (22.2% vs 69.0%; P <0.001) and T2D (2.8% vs 17.8%; P <0.001). Over 5 years, the difference in rate of eGFR change between the 2 cohorts was 1.45 ml/min/1.73 m^2 per year and 1.33 ml/min/1.73 m^2 per year, in unadjusted and adjusted linear mixed models, respectively (both P <0.001). Over 5 years, eGFR was relatively stable in the rhPTH(1–84) cohort, but declined in the control at a rate of −1.58 ml/min/1.73 m^2 per year (unadjusted model, P <0.001), and −1.57 ml/min/1.73 m^2 per year (adjusted model, P <0.001). By year 5, patients in the rhPTH(1–84) and control cohort were predicted to have eGFR changes from baseline of +1.51 ml/min/1.73 m^2 and −10.48 ml/min/1.73 m^2, respectively. Data interpretation is limited by differing patient management (ie, predefined trial protocols and clinical practice for the control). In patients with chronic hypoparathyroidism, the annual rate of eGFR decline over 5 years was significantly lower in patients treated with rhPTH(1–84) compared with controls not treated with rhPTH(1–84). These results support a prior analysis of data from the same trials and a regional US health record database.[1]

Reference
[1]Chen *et al*. JCEM 2020;105(10):e3557–e3565.

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PEP6.8

Risk of chronic kidney disease in adult patients with chronic hypoparathyroidism treated with rhPTH(1–84) compared with a historical control cohort

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This study evaluated risk of chronic kidney disease (CKD) outcomes over a period of up to 5 years in adult patients with chronic hypoparathyroidism treated with recombinant human parathyroid hormone (1–84), rhPTH(1–84), compared with a historical control cohort of patients who did not receive rhPTH(1–84). The cohort of patients with chronic hypoparathyroidism treated with rhPTH(1–84) was derived from the NCT00732615 (REPLACE), NCT01268098 (RELAY), NCT01297309 (RACE) and NCT01199614 (HEXT) clinical trials. The control cohort of adult patients who did not receive rhPTH(1–84) or rhPTH(1–34) was selected from the US Explorys electronic medical record database (Jan 2007–Aug 2019), using criteria similar to the enrolment criteria used in the trials. Index date was the day after treatment initiation for the rhPTH(1–84) cohort, and the day after the first calcitriol prescription for the control cohort. Patients with CKD at baseline (defined as estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2 at the closest eGFR measurement before the index date) were excluded. All included patients had ≥1 eGFR measurement within 6 months before the index date and ≥2 eGFR measurements ≥3 months apart during the 5 years on or after the index date. The CKD outcome was defined as first occurrence of eGFR <60 ml/min/1.73 m^2 confirmed by a second measurement ≥3 months after. Risk of CKD was assessed in a Kaplan–Meier analysis and a Cox proportional hazards model adjusted for demographic characteristics, baseline clinical conditions, and baseline laboratory measurements. The analysis included 118 patients in the rhPTH(1–84) cohort and 478 patients in the control cohort. Patients in the rhPTH(1–84) cohort, compared with patients in the control cohort, were younger (mean±S.D. age, 45.3±11.4 vs 51.5±16.2 years; P <0.001) and a lower proportion had acute manifestations of hypoparathyroidism before the index date (15.3% vs 73.2%; P <0.001). In Kaplan–Meier analysis, rhPTH(1–84)-treated patients had a significantly reduced risk of developing CKD during follow-up compared with patients in the control cohort (11.0% vs 27.0%; P <0.01). The adjusted hazard ratio of developing CKD associated with rhPTH(1–84) treatment vs no rhPTH(1–84) treatment was 0.47 (95% CI, 0.25–0.88; P <0.05). Patients with chronic hypoparathyroidism treated with rhPTH(1–84) in long-term clinical trials had a significantly reduced risk of developing CKD compared with patients in a control cohort who did not receive rhPTH(1–84). These results should be viewed in light of possible treatment differences in the studied cohorts (ie, predefined trial protocols vs real-word practice for the control cohort).

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Diabetes, Obesity, Metabolism and Nutrition

PEP7.1

Effects of testosterone therapy on morphology and grade of NAFLD in obese men with functional hypogonadism and type 2 diabetes

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Aims
Non-alcoholic fatty liver disease (NAFLD) is emerging as a public health issue worldwide, is highly prevalent in patients with type 2 diabetes (T2D), and is linked to obesity, insulin resistance and atherogenic dyslipidemia. We aimed to evaluate effects of testosterone therapy (TTh) on morphology and grade of NAFLD in obese men with functional hypogonadism (FH) and T2D.
Research design and methods
55 obese males with FH and T2D participated in a two-year (first year double-blind, placebo-controlled study, second year follow-up) clinical trial. Total, calculated free and calculated bioavailable testosterone levels, fasting plasma glucose, glycated hemoglobin A_1c, lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), prostate specific antigen, routine blood tests (complete blood count, electrolytes, urea, creatinine, liver tests) were assessed at baseline, 12 and 24 months. Liver ultrasounds for NAFLD grade assessments were performed at the beginning and after two years. *T*-test and Wilcoxon's signed rank were used to detect changes from baseline. Normality of distribution of data was assessed with Shapiro–Wilk test.
Results
Participants were randomized into two groups. Group T (n = 28) received 1000 mg testosterone undecanoate (TU) both years of the study while group P (n = 27) received placebo first year and TU second year. Liver assessment showed improvement in NAFLD grades at statistically significant level (P <0.001) after two years of TRT. TTh normalized testosterone levels in both groups within first year and stayed in normal range after the second year of the study. No adverse events (prostate carcinoma, cardiovascular events) or side effects of TRT have been observed over the two-year course of this trial.
Conclusions
Two-year therapy with testosterone undecanoate normalized serum testosterone levels, reduced NAFLD grade, and quells the symptoms of hypogonadism in obese men with functional hypogonadism and T2D.

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PEP7.2

Resolution of severe anorexia nervosa by testosterone treatment in two male transsexual young patients

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Introduction
Anorexia nervosa is a severe and potentially lethal eating disorder. We report hereby the cases of two female-to-male transsexual patients whose anorexia nervosa was promptly resolved when they started gender-affirming hormone therapy.
Methods
Review of the patients' clinical records and of the relevant literature.
Case reports
A 15 year-old male transexual with Asperger syndrome and intense gender dysphoria did not start the recommended LHRH agonist treatment at the Tanner II puberty stage by age 11 because parental consent was not obtained. He developed a severe eating disorder diagnosed as anorexia nervosa which required interment in a specialized unit and forced nutrition. By his 14 birthday he weighed 34 kg with a height of 162 cm (BMI <13 kg/m^2). He had Tanner III axilarche and pubarche, Tanner II thelarche, and no menarche. At the age of 14 year 6 months parental consent for gender-affirming therapy was obtained and the patient began treatment with LHRH agonist and progressive transdermal testosterone treatment up to 60 mg/day. One year later his eating habits were normal, his BMI was 19.85 kg/m^2 (Height 177 cm, weight 62.2 kg), his FSH, LH and testosterone were in the normal male range and had no nutritional deficit except for low vitamin D. A 20 year-old male transsexual was interned due to extremely severe anorexia nervosa, with BMI < 11 kg/m^2, and inability to walk. He reported that he had gender dysphoria since childhood but had never expressed it. He had undergone female pubertal development with normal menses until the onset of anorexia nervosa, and had intense dysphoria centered in his breast development. When gender-affirming hormonal therapy and mastectomy were offered, he accepted nasogastric feeding and was discharged with parenteral testosterone treatment. 14 months later his eating habits are normal, his BMI is 20.4 kg/m^2, his FSH, LH and testosterone are in the normal male range and he has no nutritional deficit, but his mastectomy is still pending due to the COVID-19 pandemic.
Conclusion
In transsexual patients with severe gender dysphoria, a severe eating disorder (proposed name: dysphorexia), coherent with anorexia nervosa may be triggered by the desire to avoid the cisgender puberal transition. In these patients, gender-affirming hormone therapy can be extremely effective. We postulate that avoiding the cisgender puberal development with LHRH agonist treatment might be able to prevent the development of anorexia.

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PEP7.3

Dapagliflozin improves transaminitis in non alcoholic fatty liver disease among adults with type 2 diabetes

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Use of SGLT2 inhibitors are increasing worldwide due to its potential antihyperglycemic role. Additionally they have shown to be beneficial in reducing the cardiac and renal complications in diabetes. There are sporadic reports to show their effects on liver enzymes. We did a single centre, open label, prospective trial to evaluate the role of dapagliflozin on hepatic enzymes in diabetic patients with non alcoholic fatty liver disease (NAFLD). Abdominal sonography was used to diagnose NAFLD. Individuals who were on hepatotoxic drugs or other drugs that could alter the liver enzymes or those who were alcoholics or had a history of liver disease were excluded. None of the participants were prescribed SGLT2i before. Subjects were randomly assigned to receive either dapagliflozin or placebo. Fasting blood sample was collected for HbA1c, AST & ALT measurement at study enrollment and then after 12 weeks of intervention. Antidiabetic therapy was continued and no other change in the treatment regimen was made during the study period. Paired t test was adopted for the statistical comparison between the groups. A total of 232 patients (M/F 137/95) were recruited for the study, with 131 persons (M/F 73/58) in the dapagliflozin arm and 101 subjects (M/F 64/37) in the placebo arm. Mean values for duration of diabetes (10.9±7.0 and 11.0±6.1 years), HbA1c (8.6±1.8% and 8.8±1.2%), AST (43.6±10.1 mg/dl and 41.1±15.1 mg/dl) and ALT (47.5±12.2 mg/dl and 42.5±16.5 mg/dl) were comparable in both the groups at baseline. Post treatment, in contrast to the placebo arm, HbA1c in the dapagifozin arm declined significantly to reach 7.73±1.4% (P <0.001). Similarly, the aminotransferases showed substantial improvement in the dapagliflozin arm (P <0.05), whereas there was no change in those values in placebo arm (P 0.61). Dapagliflozin also helped to reduce body weight of the individuals significantly during the course of the therapy. In addition to reducing HbA1c and weight, Dapagliflozin also significantly improves transaminitis in diabetic adults with non alcoholic fatty liver disease.

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PEP7.4

Predictors of glucagon-like peptide-1 responses following oral glucose tolerance test in 3 ethnic groups of Malaysia

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Introduction
Glucagon-like peptide-1 (GLP-1) plays an important role in the pathophysiology of type 2 diabetes mellitus (T2DM). However, results from previous studies on the GLP-1 secretory responses in individuals with different glucose tolerance states remain controversial. This may be contributed by the heterogeneous characteristics of the patients recruited.
Aim
To examine whether GLP-1 secretion is affected by any of the demographic or metabolic parameters in 3 ethnic groups of Malaysian cohort.
Methods
In this cross sectional study, 171 subjects consisting of Malays, Chinese and Indians, were divided into normal glucose tolerance (NGT) (n = 57), prediabetes (n = 54) and T2DM (n = 60) after undergoing a 75 g oral glucose tolerance test (OGTT). Plasma total GLP-1 concentrations were measured at 0, 30 and 120 min during OGTT. As an index of GLP-1 secretory response, area under the curve (AUC) of GLP-1 (AUC_{GLP-1}) was calculated by trapezoidal rule. Relationships between parameters were examined by using stepwise multiple linear regression analyses.
Results
Using AUC_{GLP-1} as a depedent parameter, age, gender, ethnicity, systolic blood pressure (SBP), fasting total cholesterol and fasting triglyceride explained 27% (adjusted r^2) of the variation of GLP-1 response following OGTT. There was a strong positive association between increasing age and AUC_{GLP-1} (B = 44.81, P <0.001). Male had higher GLP-1 response to OGTT than female (B = −881.49, P = 0.043). Ethnicity was a significant determinant of AUC_{GLP-1} with the Indians exhibiting higher GLP-1 secretion than the Malays (B = 932.23, P = 0.005). AUC_{GLP-1} was negatively correlated with triglyceride (B = −676.38, P = 0.02). In contrast to our expectation, AUC_{GLP-1} was positively associated with increased SBP (B = 16.08, P = 0.039) and total cholesterol (B = 571.57, P = 0.031). No association was detected between AUC_{GLP-1} and body mass index, waist circumference, HbA1c, fasting insulin and fasting glucose.
Conclusions
In Malaysian cohort, older age, male and Indians had higher GLP-1 responses following OGTT. These demographic factors need to be taken into account when studying GLP-1 secretory responses between T2DM patients and healthy controls. Subjects with increased fasting triglyceride level had lower GLP-1 responses. The positive relationship between GLP-1 response and risk factors which increase insulin resistance such as high total cholesterol and increased SBP might involve an adaptive response and require further study.

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PEP7.5

Impact of SARS-CoV-2 lockdown and seasonal variations on diabetes compensation: a retrospective study in a tertiary setting in Switzerland

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Introduction
Metabolic compensation of patients with diabetes mellitus (DM) depends on psychosocial well-being and healthy lifestyle, both of which were influenced by the national lockdown in spring 2020 due to the SARS-CoV-2 pandemic. The goal of our study was to analyze the impact of Swiss national lockdown (17.3.2020–24.4.2020) on compensation of DM as expressed by the level of HbA1c.
Methods
We performed a retrospective observational study using electronic health records of the University Hospital Basel. Patients with DM with at least one HbA1c measurement before and one after the begin of the lockdown were included. The observation period was 16.12.2018–27.07.2020. Time periods three months before (winter) and four months after the begin of the lockdown (spring) were defined and compared to corresponding time periods one year before. Patient determinants affecting HbA1c values were identified using a mixed-model regression multivariable analysis.
Results
We included 1078 patients in our analyses (925 type 2 DM, 145 type 1 DM, 8 other). Metabolic compensation was susceptible to seasonal changes with HbA1c highest in January with mean (standard deviation, s.d.) 7.60% (1.68), and lowest in July with mean (s.d.) 7.29% (1.67). In patients with type 2 DM, HbA1c decreased more in spring 2020 as compared to 2019 (difference of means 2020 = −0.22%, 95% confidence interval (CI): −0.058, −0.39, $P = 0.008$; vs. difference of means 2019 = −0.15%, 95% CI: −0.33, 0.03, $P = 0.1$), respectively. The differences in type 1 DM were not significant. Subgroup analysis of 241 patients with HbA1c in all analyzed periods yielded no significant change in HbA1c after the lockdown. Inappropriate alcohol intake was identified as a risk factor for increased HbA1c after lockdown (OR 1.69, 95% CI: 1.03, 2.75). Number of hospitalizations per patient decreased significantly after the lockdown (winter 2019/2020 mean (s.d.) 1.42 (0.83) vs. spring 2020, 1.24 (0.55) $P = 0.028$). The lockdown led to no significant change in weight (mean difference = 1.72 kg, 95% CI: −5.07, 1.63, $P = 0.314$).
Conclusion
Metabolic compensation of patients with DM undergoes marked seasonal variations, with highest HbA1c in winter and lowest in summer. Contrary to expectations, HbA1c in patients with type 2 DM did not increase in four months after the begin of national lockdown but decreased to the same values as the year before.

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PEP7.6

Effect of Yogic technique Shavasana in T2DM patients on BP, blood sugar fluctuations and Sleep Quality

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Background
Diabetes is a multi-systemic disorder and psychosocial stress is a contributor for glycaemic derangement and resulting complications. Covid-19 has bought psychological stress and restriction of activity for many. Psychological risk factors such as anxiety and depression have been associated insomnia and fluctuations in BP and blood sugar values. Shavasana and other relaxation techniques have long been shown to reduce the stress. This relaxation can be utilized for reducing stress and resultant effects on health.
Aim
To see the effect of Shavasana a yoga-based stress reduction technique on blood sugar fluctuations, blood pressure rise and insomnia in diabetic patient during stressful situations during covid-19 Lockdown.
Method
120 patients, (35–65 years) with HTN and controlled T2DM in the past 2 years were randomly allocated to two groups of 60 persons each. Intervention was carried out at home base setting via web Parallel group – Shavasana group; and treatment-as-usual group (TAU). Therapeutic intervention comprised Shavasana practice 15 min daily at bedtime with walk for 15 min daily. The other 60 patients were only doing walk 15 min daily along with their usual treatment. (TAU Group). The participants were surveyed for blood sugar fluctuations, insomnia, ESS (Epworth Sleepiness Score), rise in BP more than 30 mmHg systolic from baseline measured daily.
Results
All patients completed intervention in the Shavasana practicing group. 2 patients left TAU group as they suffered other problems. Shavasana group had less incidence of blood sugar fluctuations 12% and 35% in TAU group. Insomnia was less in Shavasana group 13% as compare to TAU group 42 %. incidence of rise in systolic BP were 16% in Shavasana group as compared to 38% in TAU group. The Shavasana group had a lower ESS Score as compared to the TAU group.
Discussion
Shavasana based stress reduction techniques are beneficial in reducing stress and resulting in better sleep and less fluctuations in blood sugar and blood pressure values. There is a need to focus on these sorts of stress relaxation techniques as they could prove a handy tool in reducing the day-to-day stress and resulting adverse effects. Also, improvement in sleep quality and sleep patterns can promote health and reduce the adverse metabolic outcome due to insomnia. More studies should be conducted with various stress reduction techniques to see as to what helps most. These techniques can act as an additive treatment and reduce the pill burden and adverse outcomes.

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PEP7.7

The impact of dipper profile on diabetes complications. A study of 197 diabetic patients

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Background
Non-dipping of nocturnal blood pressure is common among people with type 2 diabetes (T2D) and hypertension. Although the mechanism underlying *the* blunted nighttime response is unclear, insulin resistance is thought to play a role.
Aims
This study aims to identify the pattern of nocturnal dipping of blood pressure in patients with T2D from a Portuguese population and its association with micro and macrovascular complications.
Methods
Data was collected from 197 patients with T2D and hypertension who had undergone 24 h ambulatory blood pressure (BP) monitoring. We assessed the correlations of different dipper profiles with the presence of diabetic complications. All statistical analyses were conducted using SPSS. Chi-square test was performed to evaluate the association between the variables. A P value ≤ 0.05 was considered to be significant.
Results
There were a total of 197 subjects (mean age 70) including 155 men and 42 women. The *mean time since diagnosis* of *diabetes* mellitus was 13.5 years. The prevalence of coronary artery disease (CAD), cerebrovascular disease, retinopathy and nephropathy was 20%, 13%, 9% and 29%, respectively. Normal dipping was observed in 33%, non-dipping in 39%, extreme dipping in 22% and 6% were risers. Regarding micro and macrovascular disease, 42% of dippers and extreme dippers presented at least one complication, versus 58% of non-dippers ($P < 0.05$). Non dippers and risers were significantly older ($P < 0.01$) with a higher prevalence of CAD ($P = 0.03$) and retinopathy ($P = 0.05$). No difference was found in other diabetes complications.
Discussion
Extreme dipping was found in more than a fifth of patients, reporting a higher prevalence than most studies. It has been proposed that extreme-dipping may have a significantly higher risk of silent myocardial ischemia. However, we found no increased risk of complications in this cluster. On the contrary, the prevalence of CAD in extreme dippers was 7% vs. 20% in dippers. Hypertension and nephropathy often coexist in patients with diabetes. Nonetheless, we did not observe any association between dipping status and nephropathy in this population. Our results indicate loss of nocturnal BP dipping as a risk factor for CAD and retinopathy in patients with T2D. This

highlights the importance of ambulatory BP monitoring, particularly in the elderly population. Therefore, targeted antihypertensive therapy should be implemented in order to restore normal circadian BP in patients with T2D.

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PEP7.8

Cholesterol-free ketogenic diet administration ameliorates experimental metabolic syndrome

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Background and aims
Metabolic syndrome (MetS) is a pathologic condition characterized by abdominal obesity, insulin resistance, hypertension, and dyslipidemia. The prevalence of MetS parallels the rise of obesity rate reaching pandemic proportions due to the increased consumption of high-calories-high-fat-high-carbohydrates low-fibers diet associated with a sedentary lifestyle. MetS is associated with a plethora of comorbidities as non-alcoholic fatty liver disease (NAFLD). Noteworthy, NAFLD is considered the hepatic manifestation of MetS, and it can further progress to non-alcoholic steatohepatitis (NASH) that, in its turn, can evolve to cirrhosis and hepatocellular carcinoma (HCC). Despite the clinical relevance of NAFLD/NASH, however, effective therapy is still lacking. Lifestyle changes, including diet and physical activity, are so far the most effective interventions in NAFLD. Referring to nutritional approaches, however, there is not a definitive agreement concerning the dietary regimen to introduce into clinical practice. In this study, we investigated the capacity of a cholesterol-free ketogenic diet (KD) to improve pathological parameters associated with experimental MetS.
Methods
MetS was induced in C57BL/6 mice by feeding with a cholesterol-enriched western diet (WD) up to 16 weeks followed by the switching to KD for further 8 weeks. WD and KD were chemical characterized through GC and SD-PAGE analysis.
Results
KD administration in MetS mice significantly improved the liver pathological manifestations by lowering the gene expression of pro-inflammatory/fibrogenetic markers such as CCl2, IL-12, CD11b, OPN, Gal-3, TGF-β and α1-procollagen. Furthermore, KD feeding decreased the hepatic content of triglycerides and the hepatocellular damage, as testified by the reduction in ALT release. These observations were further supported by the histological analyses that revealed a significant amelioration in the extent of steatosis, necro-inflammation, and collagen fibers deposition, as confirmed by the Sirius-red staining in KD-fed mice. Interestingly, KD reduced the splenomegaly observed in WD-fed mice suggesting a reduction in chronic systemic inflammation. Finally, KD feeding ameliorated WD-induced muscle atrophy as confirmed by the recovery of the gastrocnemius mass. Microbiota analyses are ongoing.
Conclusion
Altogether these results suggest that cholesterol-free ketogenic diet administration might represent a potential therapeutic strategy for MetS.

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Pituitary and Neuroendocrinology

PEP8.1

Oral octreotide capsules lowered incidence and improved severity of acromegaly symptoms compared to injectable somatostatin receptor ligands—results from the MPOWERED trial

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Background
Patients with acromegaly may have high symptom burden. The phase 3 MPOWERED trial assessed control of acromegaly by oral octreotide capsules (OOC; MYCAPSSA®) in comparison to injectable somatostatin receptor ligands (iSRLs) in patients responding to both OOC and iSRLs. iSRLs have been first-line medical treatment for patients with acromegaly for decades. OOC are newly approved in the US for patients previously controlled on iSRLs.
Methods
Eligibility criteria for MPOWERED included acromegaly diagnosis, biochemical control of acromegaly (insulin-like growth factor I <1.3 × upper limit of normal; mean integrated growth hormone, <2.5 ng/ml) and ≥6 months' iSRL (octreotide, lanreotide) treatment. Eligible patients entered a 26-week Run-in phase to determine the effective OOC dose; responders at week 24 then entered a 36-week randomized controlled treatment (RCT) phase receiving OOC or iSRLs. Acromegaly symptom number and severity (mild to severe, 1–3) were collected. Total score was calculated by summating all severity scores (Acromegaly Index of Severity [AIS]). Symptom results were assessed using total AIS score and proportion of patients experiencing individual symptoms.
Results
At beginning of Run-in, average AIS score of 92 randomized patients was 4.52, representative of symptoms experienced while previously receiving iSRLs. After 26 weeks' OOC treatment at end of Run-in, average AIS score was significantly reduced to 3.46 (P <0.001). More than 80% of patients on OOC improved or maintained AIS score during Run-in compared to baseline. Over this 26-week period, there was a significant reduction in extremity swelling (P = 0.01) and fatigue (P = 0.03). During the RCT, of patients randomized to OOC (n = 55), 73% maintained or improved AIS score, and 75% maintained or reduced overall number of active symptoms. In comparison, 68% of those randomized to iSRLs (n = 37) maintained or improved AIS score, and 70% maintained or reduced overall number of active symptoms.
Conclusion
Results from MPOWERED show that patients receiving OOC had significant improvement in number and severity of acromegaly symptoms after switching from iSRLs. These findings validate previous results from a phase 3 study of OOC in acromegaly in which patients switching to OOC from iSRLs showed significant reduction in joint pain, extremity swelling, and fatigue.[1]
Reference
[1]Melmed S, *et al*. *JCEM*. 2015;100(4):1699–1708.

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PEP8.2

Antioxidant response to DNA oxidative damage in adult growth hormone deficiency: a pilot study

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Adult growth hormone deficiency (GHD), a condition characterized by increased oxidative stress (OS), is related to augmented cardiovascular, metabolic and oncological risk. Thymidine-glycol (ThyG) (5,6-dihydro-5,6-dihydroxy-2'-deoxythymidine) is a marker of DNA oxidation produced when thymidine is damaged by hydroxyl radicals. It is considered a specific marker since it is not incorporated in RNA; while 8-OH-deoxyguanosine, a well-known marker of oxidative damage, is rapidly excised from DNA and excreted in the urine, ThyG remains in tissues, thus representing an appropriate marker for oxidative tissue

DNA damage. A case–control observational study has been performed to evaluate DNA oxidative damage analysing the production of ThyG in lymphocytes and its correlation with plasma antioxidant levels, evaluated as Total Antioxidant Capacity (TAC). GHD was diagnosed using GHRH 50 μg iv + arginine 0.5 g/kg test, with peak GH response <9 μg/l when BMI was <30 kg/m^2 or <4 μg/l when BMI was >30 kg/m^2. 16 patients, 9 males and 7 females, were classified as total GHD group; 11 patients, 5 males and 6 females, with GH peak between 9 and 16 ng/ml were considered as partial GHD group. Finally, 12 subjects, 7 males and 5 females, with GH peak > 16 ng/ml were included as control group. Age in total GHD group ranged from 37 to 70 years, in partial GHD group from 24 to 70 years and from 23 to 70 years in control group. Median ± interquartile BMI were 27.14 ± 2.85 kg/m^2, 26.23 ± 8.36 kg/m^2 and 22.51 ± 1.26 kg/m^2 in total GHD, partial GHD and control respectively. ThyG, TAC and IGF-1 have been determined respectively in lymphocytes, plasma and serum samples. ThyG levels were examined and interpreted with an optical microscope by three readers independently, who gave, respectively, a score from 1 to 5; the mean of the three evaluations was considered for each sample. When considering ThyG, we found a significant difference between total vs partial GHD and controls (mean ± S.E.M. 2.25 ± 0.4; 3.21 ± 0.47; 3.64 ± 0.49, respectively). Unexpectedly ThyG was lower in total GHD. The last datum was accompanied with a significant increase in plasmatic TAC, which was higher in total GHD vs the other two groups (70.00 ± 3.14; 47.14 ±ට.65, 43.75 ± 1.83 s, respectively). Our results showed that in adult GHD, the production of antioxidant species, in response to increased oxidative stress, could exert a protective effect on ThyG formation, and consequently on DNA intracellular damages.

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PEP8.3

Addition of cabergoline to oral octreotide capsules may improve biochemical control in patients with acromegaly who are inadequately controlled with monotherapy

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Background
Oral octreotide capsules (OOC; MYCAPSSA®) are approved in the US for individuals with acromegaly who responded to and tolerated treatment with injectable somatostatin receptor ligands (iSRLs). Add-on cabergoline therapy has shown effectiveness in patients previously inadequately controlled with iSRLS.[1] The phase 3 MPOWERED trial assessed maintenance of response with OOC compared to iSRLs. Patients receiving OOC and ineligible for randomized controlled treatment (RCT) phase were eligible for a sub-study evaluating combination therapy with cabergoline, a dopamine agonist.
Methods
Patients who fail to respond to 80 mg/d OOC for ≥2 weeks during the 26-week Run-in phase, or ineligible to enter the RCT on 80 mg/d OOC, due to inadequate biochemical control (insulin-like growth factor I [IGF-I] ≥1.3 × upper limit of normal [ULN] to <2 × ULN or IGF-I <1.3 × ULN and mean integrated growth hormone [GH] ≥2.5 ng/ml) were eligible for sub-study combination OOC 80 mg/d and cabergoline ≤3.5 mg/week (fixed algorithm) for 36 weeks. End points included categorical changes in IGF-I and mean GH levels at sub-study end and adverse event (AE) incidence and severity. Echocardiogram was performed at sub-study start and every 12 weeks after.
Results
Of 146 patients enrolled in MPOWERED, 14 entered the combination sub-study, 9 having IGF-I ≥1.3 × ULN at sub-study start. Final cabergoline doses were 1 (n = 5), 2 (n = 3), 3 (n = 1), and 3.5 mg (n = 5) with 25.4-week (S.D., 14.1) mean treatment duration. Week 36 IGF-I improved in most patients (n = 12; 85.7%). Of 9 patients with IGF-I ≥1.3 × ULN at sub-study start, 5 (55.6%; 95% CI, 21.2%–86.3%) exhibited IGF-I decreased to predefined responder range (<1.3 × ULN) by week 36. AE incidence and nature with combined treatment were similar to known octreotide safety profile and acromegaly disease burden. There were no serious AEs or AEs leading to discontinuation of either sub-study drug.
Conclusion
We have shown for the first time the benefit of an all-oral combination treatment for acromegaly and avoidance of injection-related burdens. Addition of cabergoline to OOC yielded biochemical control improvement (IGF-I reduction) in patients inadequately controlled with OOC monotherapy. As both combination and OOC monotherapy safety profiles were similar, adjunctive cabergoline may be helpful in patients with acromegaly who do not achieve adequate biochemical control on OOC alone.
Giustina A, *et al*. *Nat Rev Endocrinol*. 2014;10(4):243–248.

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PEP8.4

Whole exome sequencing (WES) reveals oligogenic aetiology in a case of combined pituitary hormone deficiency (CPHD)

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Background
CPHD is characterized by GH and at least one other pituitary hormone deficiency. Mutations in genes expressed in the developing head, hypothalamus, and/or pituitary cause CPHD. To date around 30 genes have been identified to be related to CPHD, however 85% of the cases remain with unknown molecular aetiology.
Patient and methods
A newborn boy (46,XY) delivered by CS due to IUGR with a birthweight of 2200 g, presented with refractory hypoglycemia and mild hypotonia. On physical examination he had micropenis with bilaterally palpable small testes. Endocrinological work up revealed secondary hypothyroidism, secondary adrenal insufficiency and hypogonadotropic hypogonadism (HH). MRI scan of the hypothalamic–pituitary region depicted hypoplastic anterior pituitary and ectopic posterior pituitary lobe with absence of pituitary stalk. WES was carried out on an Ion Torrent S5 platform, aligned to hg19 and annotated by Varaft. An *in silico* panel of 120 genes related to CPHD was employed to select variants (MAF values <1%). The pathogenic variants selected were verified by Sanger sequencing.
Results
Four heterozygous variants were found to be related to the patient's phenotype in four genes. Two of them were maternally inherited: *BMP4;* p.A42P and *NR4A*1; p.P148L and 2 paternally inherited: *GNRH;* p.Arg73X and *SRA1;* p.Q32E.
Conclusions
We speculate that a synergistic action of these gene variants may underlie our patient's phenotype. *BMP4* plays significant role in early organogenesis, pituitary development and function. *BMP4;* p.A42P has been described in a patient with tooth agenesis, however the *BMP4*; p.R300P has been reported in a CPHD and hypoplastic pituitary gland patient. *GNRH1*; p.Arg73X, has been described in a patient with HH. The *SRA1*; p.Q32E has been identified in a patient with HH and could probably explain the secondary adrenal insufficiency of our patient, since SRA1 regulates SF1 target gene expression by functioning as a coactivator in association with DAX1. *NR4A1* gene encodes for a protein, member of the steroid–thyroid hormone-retinoid receptor superfamily, which acts as a nuclear transcription factor and is highly expressed in the adrenals.

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PEP8.5

Osilodrostat provides sustained control of urinary free cortisol in patients with Cushing's disease: final results from a prospective, open-label study (LINC 2)

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Introduction
The oral 11β-hydroxylase inhibitor, osilodrostat, normalized mean urinary free cortisol (mUFC) in 79% (15/19) of patients with Cushing's disease at the end of the 22-week core LINC 2 study. Long-term efficacy and safety data following an optional extension phase are reported here.
Methods
Patients with clinical benefit at week 22 could continue receiving osilodrostat during the extension; dose adjustments were permitted based on efficacy/safety. Response status was assessed over time: controlled mUFC (≤ULN) or partially controlled mUFC (>ULN but ≥50% decrease from baseline). Efficacy and safety were assessed for all patients from core baseline to study end.
Results
Of 19 patients enrolled in the core study (female : male 14:5; mean [s.d.] age 36.8 years [8.4]), 16 entered the extension and 8 continued treatment until study end. Median (range) osilodrostat exposure was 282 weeks (2–351). mUFC decreased from 9.9xULN at baseline to ≤ULN by week 4, remaining stable thereafter. At each extension-phase assessment up to month 70, 50–88% of patients had controlled mUFC, and up to 18% were partially controlled. Mean (s.d.) percentage change in clinical signs from baseline to last assessment were: fasting plasma glucose, –10.8% (22.1) (baseline: 105.6 mg/dl [49.2]); HbA_{1c}, –2.1% (9.0) (baseline: 5.7% [0.7]); systolic BP, –3.3% (12.6) (baseline: 132.6 mmHg [11.6]); diastolic BP, –2.0% (10.4) (baseline: 85.0 mmHg [6.5]); BMI, –5.9% (8.8) (baseline: 30.7 kg/m^2 [7.0]). Nine patients discontinued treatment, mostly because of AEs or no longer requiring treatment (n = 3 each). The most common AEs during the overall treatment period were nausea (n = 10), adrenal insufficiency, and headache (n = 9 each). AEs related to hypocortisolism and adrenal hormone precursor accumulation occurred in 11 (mostly adrenal insufficiency, n = 9) and 12 patients (mostly hypertension, n = 4), respectively; most were grade 1/2 and managed with dose adjustment/interruption and/or additional therapy. Mean (s.d.) plasma ACTH increased from 1.8xULN (0.9) at baseline to 7.1xULN (12.3) at week 22 and 6.9xULN (12.6) at last assessment. Mean (s.d.) 11-deoxycortisol increased from 1.2xULN (1.3) at baseline to 13.6xULN (12.2) at week 22 and 3.6xULN (4.2) at last assessment. In females, mean (s.d.) testosterone increased from 0.8xULN (0.4) at baseline to 2.4xULN (2.1) at week 22 and 1.0xULN (0.9) at last assessment. AEs of hirsutism were reported in two female patients.
Conclusions
Osilodrostat provided rapid and sustained reductions in mUFC for up to 6 years of treatment, with improvements in clinical signs of hypercortisolism. Osilodrostat was well tolerated, with no new safety signals during long-term treatment.

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PEP8.6

Can the follow-up imaging interval for non-functioning pituitary microadenomas be extended?

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Background
Data on clinical characteristics and natural history of patients with non-functioning pituitary microadenomas (NFPmA) is limited to small-scale studies.
Methods
A retrospective evaluation of initial clinical presentation and natural history of patients with NFPmA (conservatively managed, years; 2004–2020) was undertaken. Initial symptoms, tumor size, and pituitary function were assessed. Exclusion criteria; surgery, radiation, dopamine agonists, pregnancy, radiologic findings of Rathke's cleft cyst. Patients on thyroid, glucocorticoid, sex hormone replacement, chronic opioids, or with traumatic brain injury were excluded from pituitary function analysis. Tumor size change ≥2 mm on pituitary MRI in any dimension was considered significant. SPSS was used for descriptive statistics, and STATA for incidence.
Results
A cohort of 262 patients with NFPmA (age 41.6±15.2 years; 64.9% female) was studied. Fatigue (77.1%) and headache (69.5%) were the most common presenting symptoms. Mean largest tumor dimension was 4.6±1.9 mm; 53% were <5 mm and 47% were 5–9 mm. Patients were taking thyroid (for primary hypothyroidism; 21.0%), 5.3% glucocorticoid, 2.7% growth hormone replacement, 0.4% desmopressin; 38.5% of females estrogen/progesterone and 22.1% of males testosterone. In patients with fully evaluable pituitary function, 94.5% had no deficiencies, 4.0% deficiency in 1-axis, and 1.5% in 2-axes (most commonly hypogonadism; 4.7% and growth hormone deficiency; 1.9%), 9.2% had drug-related and 1.5% transient hyperprolactinemia. During median MRI follow-up of 19 months, 8.7% of tumors grew, 38.5% shrunk, and 52.8% were stable. Growth incidence was 2.3/100 person-years (PYs) with a mean time-to-growth of 41.6±38.9 months. Tumors <5 mm and 5–9 mm showed no difference in growth. Tumor growth did not vary by sex. Mean time-to-growth was lower in patients ≥65 vs <65 years (14.5±7.9 vs 49.9±41.0 months, P = 0.01).
Discussion
Previous reported pituitary deficiency in patients with NFPmA ranges from 0 to 42%; our findings are on the lower end of this estimate. Interestingly, incidence of linear growth in our study was lower than volumetric growth in a previous study (2.3 vs 5.0/100 PYs), but percentage of enlarging microadenomas (8.7%) was similar to previously reported values (7.4–12.5%).
Conclusions
This is the largest single-center study of NFPmA with uniform clinical assessment and follow-up. Patients frequently reported fatigue and headache, without significant pituitary dysfunction. Enlarging tumors were rare and not associated with visual deficits or new hypopituitarism. Since time-to-growth was longer in younger patients, extending follow-up MRI timeline for microadenomas from current recommendations to up to 3-years in patients <65 years of age should be considered.

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PEP8.7

Russian hypothalamic and pituitary tumor registry (OGGO): current results

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Background
Pituitary disease registries are major instruments of epidemiological and clinical data collection used worldwide.
Objective
To assess the data of pituitary tumor registry in Russia.
Material and methods
Patient records, retrieved from online platform of the Registry.
Results
Currently there are 9858 patients registered in Russian Hypothalamic and Pituitary Tumor Registry (OGGO): 4792 (49%) with acromegaly (AM), 2449 (25%) with prolactinoma (PRL), 870 (9%) with Cushing's disease (CD), 1155 (12%) with non-functioning adenomas (NFPA), 420 (4%) with other tumors of pituitary region and 172 (2%) with rare pituitary adenomas. Mean age of disease onset is 43.3 years for AM, 34.4 for PRL, 34.0 for CD, 43.5 for NFPA. Estimated diagnostic delays in patients with AM was 2.1 years, 3.3 years for CD, 1.5 years for PRL, 1.2 years for NFPA. Median age for AM is 64.0 years [53;71] (72% female), 49.0 [39;61] for CD (84% female), 47.0 [38.0;60.0] for PRL (80% female), 58.0 [44.0;68.0] for NFPA (72% female). Adenoma size was available in 2031 acromegaly patient records (1567 macroadenomas), 266 patients with CD (106 macroadenomas), 830 patients with PRL (442 macroadenomas), 468 patients with NFPA (253 macroadenomas). Neurosurgical treatment was performed in 2082 patients

with AM (54.0%), 292 patients with PRL (12.0%), 593 patients with CD (68.6%) and 289 patients with NFPA (25.4%). Radiotherapy was used in 714 cases of AM (15.4%), 47 PRL (1.9%), 188 CD (21.5%), 28 NFPA (2.4%). 106 patients with CD (12.3%) underwent bilateral adrenalectomy. Concerning medical treatment of patients with acromegaly (1705 patient records), somatostatin analogues were used in 1557 cases (91.3%), dopamine agonists – in 414 cases (24.3%), GH receptor antagonists – in 7 cases (0.2%). Patients with prolactinomas (870 patient records) were treated with dopamine agonists in 865 cases (99.5%). 7 patients were additionally treated with octreotide. Patients with CD received ketoconazole in 60 cases (66.7%), in 39 patients (43.3%) – dopamine agonists, 6 patients (6.7%) – somatostatin analogues. Medical therapy was used in 83 cases of NFPA: dopamine agonists were used in 77 patients (92.8%), somatostatin analogues – in 6 patients (7.2%).

Conclusions

Russian Hypothalamic and Pituitary Tumor Registry is an important tool for assessment of epidemiological data and has promising capabilities for the analysis of clinical characteristics. However, there is a lack of sufficient up-to-date information on medication treatment in patient records, which suggests that better monitoring is needed to achieve data continuity and integrity.

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PEP8.8

Diagnosis and treatment of patients with neuroendocrine tumours: evidence from specialist Polish centres

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Background

Optimal management of patients with neuroendocrine tumours (NETs) is essential to ensure the best treatment results. This survey aimed to obtain a comprehensive picture of NET management in Poland by examining the pathway of patients with NETs throughout their diagnosis and treatment.

Methods

Physicians treating patients with NET in 17 Polish clinical centres/hospital wards, covering approximately 80% of patients with NET, were invited to complete an online questionnaire between August 20 and November 3 2020. The survey gathered information about the previous year (2019).

Results

In total, 138 NET specialists from 17 centres (6 oncological; 11 endocrinological), treated 4288 patients with NET in 2019 (27% of whom were newly diagnosed). Four centres managed more than 500 patients, and four managed fewer than 30. Patients were usually referred to NET treatment centres by surgeons, endocrinologists, or oncologists. About half (46%) of all patients with NET in 2019 were diagnosed accidentally. The average time from the first symptoms to diagnosis was 13 months. 54% of newly diagnosed patients with NET were previously misdiagnosed, usually with irritable bowel syndrome, inflammatory bowel disease, or psychosomatic disorders. Only 20% of all managed NETs were functional tumours. The most frequent initial symptoms were pain, diarrhoea, and flushing. The newly diagnosed NETs originated most frequently from the pancreas and midgut, with almost half of the patients presenting with metastases mainly to the liver and/or lymph nodes. After NET diagnosis, 27% of patients were referred to other wards, indicating the need for an interdisciplinary approach to treatment. A delayed treatment strategy (watch & wait) was used in 7% of patients; 36% underwent surgery to remove the primary tumours. 59% of all patients with NET received somatostatin analogues (SSA) as the first-line therapy; 84% who received peptide receptor radionuclide therapy (PRRT) had combined therapy with SSA. The Polish Network of Neuroendocrine Tumours guidelines, followed by the European Neuroendocrine Tumour Society (ENETS) guidelines, were regarded as the most helpful for therapy determination.

Conclusions

Our study provides important insights into the daily management of patient with NET in Poland, and may thereby contribute to the improvement of routine clinical practice and optimization of treatment outcomes.

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Endocrine-Related Cancer

PEP9.1

Long-term prognosis in patients with insulinoma

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Introduction

Insulinomas are the most common functional neuroendocrine tumours of the pancreas. Because previous data on the long-term prognosis of insulinoma patients are scarce, we wanted to study the morbidity and mortality in Finnish patients previously treated for an insulinoma.

Patients and methods

The Finnish insulinoma register consists of all adult patients diagnosed with an insulinoma in Finland during 1980–2010, including two patients with a MEN1 syndrome ($n = 79$). For each patient, 4 controls were chosen from the Finnish Population Register Centre, matched for age, gender and the place of residence, and alive at the diagnosis of the corresponding patient ($n = 316$). Morbidity due to endocrine, cardiovascular, gastrointestinal and mental disorders, and cancers was compared between the patients and controls by analysing the incidence rate ratios (RR) with the 95% Confidence Intervals (95% CI) using the Mantel–Haenszel method. Kaplan–Meier and Cox regression analyses were used to compare the overall survival (OS) of the patients and controls.

Results

Seventy (89%) of the insulinomas were non-metastatic and 9 (11%) were metastatic. The median length of follow-up after the insulinoma diagnosis was 11 (0.2–33) years for the patients and 12 (1.2–35) years for the controls. Morbidity due to thyroid disorders [RR 2.76 (95% CI 1.00–7.60], parathyroid disorders (RR not applicable), atrial fibrillation [RR 2.02 (95% CI 1.00–4.09)], intestinal obstruction [RR 18.65 (95% CI 2.09–166.86)], non-insulinoma pancreatic diseases [RR 13.04 (95% CI 2.12–20.36)], abdominal hernias [in patients with a non-metastatic insulinoma, RR 2.33 (95% CI 1.00–5.43)], breast cancer [RR 4.46 (95% CI 1.29–15.39] and kidney cancer (RR not applicable) was increased among insulinoma patients compared to controls, $P < 0.05$ for all comparisons. Postoperative disease progression or recurrence occurred in 6 (8%) of the 71 patients who underwent curative-intent surgery, the 5- and 10-year disease-free survival being 96% and 94%. The OS of patients with a non-metastatic insulinoma did not significantly differ from that of controls, but for patients with a metastatic insulinoma, the OS was significantly impaired, with a median survival of 3.4 years. In multivariate analyses, older age and distant metastases were associated with a decreased OS.

Conclusions

The long-term prognosis of patients with non-metastatic insulinomas is similar to the general population, except for an increased incidence of thyroid and parathyroid disorders, atrial fibrillation, intestinal obstruction,

non-insulinoma pancreatic diseases, abdominal hernias, and breast and kidney cancers. Metastatic insulinomas are rare, but entail a markedly decreased survival.

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Possible role of common RET polymorphisms in pheochromocytoma

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Background
In about 2/3 of pheochromocytoma patients, no pathogenic germline variant can be identified that might be responsible for the onset of the disease. However, in many patients, we observe the repeated appearance of one or more common polymorphisms in the gene *RET*. Each of them has been shown to be of no significance for pheochromocytoma and multiple endocrine neoplasm type 2 development, when analysed individually. We decided to test whether the co-appearance of more than one polymorphisms might have any impact on pheochromocytoma.
Materials and methods
51 pheochromocytoma patients with excluded pathogenic variants in the genes *RET, VHL, SDHB* and *SDHD* and with no clinical symptoms that would be indicative of neurofibromatosis type 1 were included in the study. The control group consisted of 51 healthy volunteers with no clinical symptoms that would indicate adrenal diseases and with negative family history for familial syndromes caused by pheochromocytoma-predisposing genes. The status of the following polymorphisms in the gene *RET* was evaluated by Sanger sequencing: rs1799939 (exon 11), rs1800861 (exon 13), rs1800862 (exon 14), rs2472737 (intron 14), rs1800863 (exon 15). Statistical analyses were performed with Statistica v13, with $\alpha = 0.05$ as statistical significance cutoff value.
Results
As expected, none of the polymorphisms differed between the patient and the control group when analysed independently. The groups did also not differ in the total number of the rarer variants identified nor the number of different polymorphisms present in the patient. Also, no disease-predisposing minimal haplotype has been identified by stepwise regression analysis. The pheochromocytoma group was then divided into three subgroups by unsupervised k-means clustering, based on the five analysed polymorphisms. Those three groups did not differ in means of age of disease onset, sex, localisation of the tumour, or PASS. However, significant differences were found for Ki-67 ($P = 0.0294$) and the hormonal status ($P = 0.0306$).
Conclusions
Although it is well established that common variants in *RET* are not responsible for the development of pheochromocytoma, their analysis might turn out useful in the prediction of a patient's clinical appearance. In order to draw final conclusions on the possible meaning of *RET* polymorphisms in the course of pheochromocytoma, a bigger number of patients needs to be analysed. However, our study indicates that this direction of research might be of clinical interest.

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PEP9.3

Pneumocystis pneumonia following surgical resection of pulmonary carcinoid causing ectopic ACTH syndrome: a case report

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Background
Cushing's syndrome due to ectopic ACTH secretion only accounts for 10% of all cases of Cushing's syndrome and is most often associated with pulmonary neuro-endocrine tumors. Treatment of ectopic ACTH syndrome is predominantly surgical with resection of the tumor. Following resolution of hypercortisolism, previously subclinical Pneumocystis jiroveci infection can become overt due to restored immune response.
Clinical Case
A 37 year old male was referred to the endocrinology outpatient clinic by his general physician with suspicion of secondary hypertension. Initial clinical evaluation revealed a Cushingoid appearance. Laboratory test results, including 24 h urine analysis, showed hypokalemia, elevated urinary free cortisol and elevated serum ACTH. MRI of the pituitary gland revealed absence of pituitary adenoma. Inferior petrosal sinus sampling suggested ectopic ACTH production. CT of the thorax and abdomen, followed by 68Ga-DOTANOC scan, was revealed a tumor in the right lower pulmonary lobe as the probable source of the ectopic ACTH production. Patient underwent surgical resection of the tumor with anatomopathological confirmation of typical carcinoid tumor with low proliferative index. Five days after surgery, patient presented to the emergency department with fever, dyspnea and a dry cough. Arterial blood gas analysis showed type I respiratory failure. Extensive bilateral peribronchial ground-glass opacities were seen on CT thorax. Laboratory test results showed important inflammation with elevated leucocyte count with neutrophilia and an elevated CRP. Patient was initially empirically started on intravenous amoxicillin/clavulanic acid antibiotic therapy and supportive treatment consisting of oxygen therapy and low molecular weight heparin. SARS-CoV-2 PCR on nasopharyngeal swab was negative. Bronchoscopy with broncho-alveolar lavage was performed with a positive PCR for Pneumocystis jiroveci. The diagnosis of bilateral Pneumocystis pneumonia (PCP), following resolution of an ectopic ACTH syndrome, was made. Amoxicillin/clavulanic acid was replaced by trimethoprim/sulfamethoxazole with favorable clinical evolution. A few months later patient is doing well and is almost fully recovered.
Clinical Lesson
Following resolution of hypercortisolism in Cushing's syndrome, subclinical Pneumocystis jiroveci infection can evolve into fulminant PCP due to immune reconstitution. During prolonged immune suppression, fungal lung burden of Pneumocystis jiroveci may accumulate, with development of extensive inflammatory reaction after abrupt decrease of cortisol levels. Especially in patients with ectopic Cushing syndrome the risk of developing PCP following surgical resection is considerable. Therefore timely chemoprophylaxis with trimethoprim/sulfamethoxazole must be considered in each patient treated for Cushing syndrome.

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Parathyroid carcinoma presenting as ventricular bigeminy in pregnancy

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Introduction
Parathyroid carcinoma is a very rare phenomenon with an estimated prevalence of 0.005% of all cancers. There have been fewer than ten cases of parathyroid carcinoma in pregnancy previously reported in literature. Clinical features are similar to primary hyperparathyroidism and the diagnosis is usually made on surgery or histology. We present a unique case of parathyroid carcinoma in pregnancy where ventricular bigeminy was the presenting feature.
Case report
A 38-year-old multiparous woman presented to the emergency department with severe palpitations in the second trimester of her fifth pregnancy. She also had headaches, dizziness and polydipsia. Admission laboratory results revealed severe hypercalcaemia (3.07 mmol/l), raised PTH (87 ng/l) and a mild hypophosphatemia (0.79 mmol/l). 12-lead ECG showed ventricular bigeminy. Initial management comprised of intravenous rehydration and beta-blockers. Further investigations included a 24-h ECG recording which showed ventricular bigeminy and high frequency premature ventricular contractions amounting to a burden of 26%. Echocardiography demonstrated a mildly dilated right atrium with good biventricular function. Neck ultrasound revealed a lesion in the posterior aspect of the right lobe of the thyroid. Despite drinking copious amount of fluids at home, she continued to have severe hypercalcaemia needing multiple hospital attendances for intravenous rehydration. Her case was reviewed in the endocrine multidisciplinary meeting where surgical management during pregnancy was deemed most appropriate given her recurrent hospital admissions and potential risks to foetal wellbeing. Consequently, she underwent a right

unilateral neck exploration at 23 weeks gestation. Intraoperative concerns of cancer led to an en-bloc resection of the right parathyroid and thyroid lobe. Histology results confirmed parathyroid carcinoma. Post-operatively, the patient recovered well and was biochemically hypothyroid thus treated with Levothyroxine. Gene testing did not reveal any known genetic causes of parathyroid carcinoma. She had regular growth scans, calcium and TSH monitoring for the remainder of the pregnancy and underwent an uncomplicated caesarean section (patient preference) at 39 weeks.
Conclusions
The vague nature of symptoms, entwined with overlapping features of pregnancy makes recognition of parathyroid carcinoma in pregnancy challenging. To our knowledge, this is the first case of parathyroid carcinoma presenting as ventricular bigeminy and highlights several key points. Firstly, the importance of early recognition and timely surgical management in reducing maternal and foetal complications. In addition, it illustrates the value of interprofessional collaboration between different specialities to provide good quality care and ensure optimal outcomes in potentially challenging and rare diseases.

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PEP9.5

Endothelial and vascular function, biomarkers and clinical presentation in patients with small intestine NETs

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Background
20–30% of patients with metastatic small intestine neuroendocrine tumours (SI-NETs) suffer from carcinoid syndrome (CS), i.e. diarrhea, flushing, and bronchospasm. Of these, 25–50% develop carcinoid heart disease (CHD) characterized by valve fibrosis and right heart failure. There are no early predictive markers of CHD, which typically is diagnosed in the advanced stage.
Aims of the study
To 1) detect possible early predictive alterations in endothelial and vascular function in carcinoid syndrome; 2) compare endothelial and vascular function in patients with and without increased S-5-HIAA; 3) study possible relationships between other biomarkers and clinical features with S-5-HIAA.
Subjects and methods
Sixty-six patients (50% men, mean age 64.2–8.8 years, duration of disease 75.7–57.6 months) with SI-NET treated at HUH. Biochemical and clinical features were assessed from electronic patient records and symptom questionnaire. Vascular and endothelial function was measured with pulse wave analysis (PWA), pulse wave velocity (PWV), and peripheral arterial tonometry (PAT). An expert abdominal radiologist assessed hepatic tumour load with a cutoff point of 10% for categorical statistical analysis. Patients were divided into two groups (high vs low) based on the upper limit of normal for the S-5-HIAA assay.
Results
fP-CgA (mean 164 vs. 3.0 nmol/l; P <0.001), weekly frequency of diarrhea (4.7 vs. 2.5 days; P = 0.011), use of somatostatin analogue (SSA; 97% vs. 81%; P = 0.034) and hepatic tumour load (P <0.001) differed significantly between the high vs low S-5-HIAA group. We found no differences in age, tumour Ki-67, S-proBNP (347 ng/l vs. 191 ng/l, P = 0.247), or prevalence of flush between the groups, neither in any vascular function measurements, including aortic systolic or diastolic pressure, systemic vascular resistance, aortic pulse wave velocity and rate controlled central augmentation index (C-AGPH HR75) between the groups. In the high S-5-HIAA group, S-5HIAA correlated inversely with C-AGPH HR75 (−0.363, P = 0.035). No such correlation was found in the low S-5-HIAA group (−0.303, P = 0.098).
Conclusions
Patients with increased S-5-HIAA concentrations are characterized by significantly higher fP-CgA, more frequent diarrhea and SSA use, and higher hepatic tumour load compared to those with normal S-5-HIAA. In patients with SI-NETs, S-5-HIAA did not predict endothelial dysfunction or increased arterial stiffness.

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PEP9.6

Characterization of signaling pathways and molecular mechanisms underlying kisspeptin response in pancreatic neuroendocrine tumor (panNETs) cells

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Pancreatic neuroendocrine tumors (panNETs) comprise several neoplasms in which a precise diagnosis and therapeutic treatment are hampered by their diversity and heterogeneity which in turn, hind the identification of common molecular signatures and the development of efficient therapeutic approaches. Subsequently, there are no clinical, biochemical, anatomopathological, immunohistochemical or molecular features capable to currently predict either tumor prognosis or post-surgical treatment for panNETs. In this sense, the KiSS/KiSS-R regulatory system has been documented to be expressed and play anti-tumoral actions in different endocrine-related tumors. In fact, we have previously showed the presence of KiSS/KiSS-R system in human panNET, and analyzed its relationship with several tumor distinctive clinical features associated to tumor prognosis. Specifically, we reported a higher KiSS- and a lower KiSS-R expression in panNET tumor tissues compared to their adjacent non-tumor tissues. Furthermore, KiSS expression appeared to be up-regulated in panNET samples from patients harboring metastatic disease, whereas KiSS-R expression was significantly lower when compared to samples from non-metastatic patients. On the other hand, we also reported the potential functional role of this regulatory system in BON-1 pancreatic cell line. Thus, we documented that proliferation and migration processes were regulated upon kisspeptin-10 (kp-10) treatment in naïve and KiSS1-R overexpressing cells. Ongoing analyses indicate that the anti-tumor actions of KiSS/KiSS-R system in BON-1 panNET cell line and in xenograft tumors derived from KiSS1-R overexpressing cells, involve the modulation of various oncogenic signaling pathways and different molecular mechanisms. Thus, proteomic analysis reveals a clear and general decline in the phosphorylation level of several components of MAPK and AKT oncogenic pathways after kp-10 treatment in both *in vitro* and *in vitro* experimental settings being this effect sensitized in several proteins by the KiSS-R overexpression. Furthermore, transcriptomic studies in BON-1 cells show the up-regulation and down-regulation of different genes after kp-10 administration. An ulterior enrichment analysis (KEGG/Reactome) reveal that these deregulated genes are associated to relevant pathways involved in pancreatic cancer, endocrine resistance and cell cycle among others. Altogether, our results provide original evidence for the presence and functional activity of the KiSS/KiSS-R system in panNETs, suggesting its potential role in the development and/or progression of this devastating pathology, and paving the way to explore its value as a novel biomarker and/or therapeutic target in panNETs.
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PEP9.7

Hypercalcaemia due to ovarian small cell carcinoma of the hypercalcaemic type (SCCOHT)

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Background
Hypercalcaemia is commonly encountered during clinical practice. SCCOHT is a rare ovarian malignancy typically found in young women. In two thirds of patients, it causes a paraneoplastic hypercalcaemia which is usually asymptomatic.
Case Report
A thirty-seven-year-old lady, presented to casualty with a one -week history of worsening nausea, vomiting, anorexia, abdominal pain, polydipsia, and polyuria. On examination all clinical parameters were within normal

range. Her abdomen was distended but soft. Blood investigations revealed a corrected calcium level of 3.9 mmol/l. She was started on intravenous normal saline at one litre every six hours as acute management for hypercalcaemia. Additional tests revealed a PTH of <5 (15–65 pg/ml), a PTHrP of 5.7 (<1.5 pmol/l), a 25-hydroxyvitamin D level of 17 (30–100 ng/ml) and normal renal function. The combination of a low PTH together with a high parathyroid hormone related protein (PTHrP) suggests humoral hypercalcaemia of malignancy. A computed tomography scan of the abdomen showed a large, hypodense, soft tissue pelvic mass arising from the left ovary. A magnetic resonance scan of the pelvis confirmed an 18×12×5 cm mass arising from left tubo-ovarian region with areas of internal cystic change, internal necrosis, prominent venous drainage, and a peripheral enhancement pattern A bone scan showed no evidence of abnormal foci of increased tracer uptake throughout the skeletal system. Despite three days of continuous fluid replacement her serum calcium remained high. She received one dose of the intravenous bisphosphonate Zoledronic acid 4 mg which reduced her calcium to 2.38 mmol/l after 48 h reaching a nadir of 1.94 mmol/l within five days. She underwent a bilateral salpingo-oopherectomy and total abdominal hysterectomy. Histology showed a left SCCOHT with sheets of small, uniform, hyperchromatic cells together with a single cystic pseudofollicle; very typical for SCCOHT. She is receiving Cisplatin/Etoposide combination chemotherapy to be followed by pelvic radiotherapy. A repeat CT scan after 3 cycles showed no distant metastases. Her calcium levels have since remained normal, repeat PTHrP and PTH levels have normalised.

Conclusion

SCCOHT was initially reported in 1979 by Scully. Fewer than 500 cases have been reported worldwide. Abdominal pain is the most frequent symptom at 68%. At surgery 50% of patients have extra ovarian spread. It has a high rate of recurrence and overall survival is less than 10%. A combination of surgery, chemotherapy ± stem cell transplant and radiotherapy produce the best results.

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PEP9.8

Outcomes of a multicenter surveillance protocol in asymptomatic Succinate Dehydrogenase (SDH) B and C mutation carriers

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Introduction

Based on the evidence available back then, in 2015 we developed a provincial multicenter protocol for screening and follow up of no-index patients with SDHB and SDHC mutations.

Objectives

1. To evaluate the performance of the protocol designed for the follow-up of asymptomatic SDHB and C carriers. 2. To describe the penetrance of manifestations associated with hereditary PGL-FEO syndromes type 3 and 4 in a provincial cohort of non-index carriers.

Methods

prospective observational study (January 2015–March 2019). Non-index SDH B and C mutations carriers were included. Once a year we determined catecholamines in a 24-h urine sample. Imaging and functional studies were established depending on type of mutation and catecholamines results. For SDHB+ we initially performed PET/CT with ^{18}F-DOPA and ^{18}F-FDG. For SDHC+ patients a head and neck MRI was requested if catecholamines were normal and ^{18}F-DOPA PET/CT if elevated. After the first negative screening, patients continued with imaging follow-up (MRI) every two years added to annual urine catecholamines. For quantitative variables, results are expressed as mean±s.d. for normally distributed data and as median [range] for nonparametric data.

Results

$n = 65$.

– SDHB ($n = 50$, 11 families). 54% men. Age at genetic diagnosis: 46.5 ± 17.7 years. Follow-up time 25.9 ± 16.7 months. Abnormal uptakes were detected in 14/40 cases with ^{18}F-DOPA and/or ^{18}F-FDG PET/CT (2 false positives for ^{18}F-FDG PET/CT and 12 true positives). Ten patients showed 11 lesions related to the syndrome: 5 abdominal PGL, 3 cervical PGL, 1 thoracic PGL, 1 pheochromocytoma and 1 medullary hyperplasia (60% functioning; age at diagnosis 35.2 [11–72] years; size 4.5 [1.1–10] cm). One metastatic case. Histological confirmation was obtained in 8/10 cases. Unrelated neoplasms were found in 2 patients (one lung squamous cell carcinoma and one large cell neuroendocrine carcinoma). The sensitivity and specificity of PET/CT with ^{18}F-FDG were 100% and 93.9% (87.5% and 100% with ^{18}F-DOPA). The penetrance was 22%.

– SDHC ($n = 15$, 2 families). 53% women. Age at diagnosis 49.9 ± 13.1 years. Follow-up time 26.9 ± 16.4 months. Only 2 patients showed lesions (one pituitary macroadenoma and one benign lymph node – false positive of MRI). The penetrance was 13.3%.

Conclusions

The proposed protocol detected PGL/FEO in 20% of non-index SDHB mutation carriers and only 60% had elevated catecholamines. In addition, it allowed us to detect other unsuspected neoplasms. The penetrance in SDHC mutation carriers is low, as expected.

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Thyroid

PEP10.1

A semi-automatic, non-radioactive 384-well high throughput screening DIO2 assay

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Thyroid hormone (TH) homeostasis depends on the coordination of several key events to maintain proper local TH signaling, including iodide uptake, hormone synthesis, metabolism, and elimination. The three isoenzymes, Deiodinases (DIO1-3), are essential components of hormone metabolism. They catalyze iodide release the outer and/or inner ring of TH structure to convert between their active and inactive forms. The activity of DIOs has been identified as an important endpoint regarding the screening of compounds for TH system disruption. The classical DIO assays rely on the liberation of radioactive iodide from a tracer substrate. Furthermore, substrate deiodination can also be followed by using mass spectrometry as readout. However, radioactively labeled substrate molecules are expensive, not always commercially available, legally restricted and limited in their half-life. Mass spectrometry involves costly and sensitive instrumentation and skilled personnel. To avoid these difficulties, we established a cost- and time-effective semi-automatic, non-radioactive 96-well DIO2 assay, based on the Sandell-Kolthoff (SK) reaction, and adapted it to the 384-well High Throughput Screening (HTS) plate format to identify inhibitors or activators of DIO2 activity from a small molecule compound library. A robust 384-well HTS platform for non-radioactive determination of DIO2-catalyzed iodide release by the SK method was developed. The SK reaction describes the reduction of yellow-colored cerium IV to non-colored cerium III by arsenic III. Reaction rate is increased in a concentration-dependent manner by presence of iodide and can be quantified photometrically. The development process included optimization of protein concentration using recombinantly expressed human DIO2 and incubation conditions (time, temperature, shaking, kinetics). Furthermore, assay performance parameters were examined such as linear measuring detection range and *Z*-factor. Several steps of the protocol were performed on and optimized for the Biomek Workstation (Beckman Coulter) platform. 50 µg total protein/reaction and 4 h incubation time at 37°C with an endpoint measurement at OD 20 min delivered the most robust parameters of the semi-automatic, non-radioactive 384-well HTS DIO2 assay with a *Z*-factor consistently above 0.5. The presented work demonstrated the successful setup of an HTS-screening platform, qualified to detect and initially characterize endocrine disruptors, affecting DIO activities. The respective HTS protocol provides the basis for further testing of large chemical libraries against DIO2, and can be adapted to other deiodinating enzymes, e.g. DIO1 and dehalogenases. Furthermore, its use to generate large data sets on libraries covering diverse chemical structures will enable the setup of predictive *in silico* tools by providing respective training sets.

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PEP10.2

Graves' disease and concurrent immune thrombocytopenia in a patient with albinism following alemtuzumab treatment for multiple sclerosis: a rare case report

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Introduction
Alemtuzumab is an anti-CD52 antibody, leading to lysis and transient depletion of T and B lymphocytes. Its therapeutic effect is mediated by the alteration in immune repertoire that accompanies subsequent lymphocyte reconstitution. It is mainly used for the treatment of relapsing–remitting multiple sclerosis (RRMS). Common side effects are autoimmune diseases, including thyroid disease (>40%), immune thrombocytopenia (ITP, 1–3%) and nephropathy (<1%). Concurrent Graves' disease with other alemtuzumab-related autoimmune disorders have not been described so far.
Case-report
A 27-year-old female with oculocutaneous albinism and RRMS diagnosed in 2009, received three cycles of alemtuzumab between 2016 and 2018. Twenty-one months later, she presented to the emergency department with petechiae, purpura and tachycardia. Laboratory tests revealed severe thrombocytopenia, autoimmune hemolytic anemia, leukopenia and mildly elevated liver enzymes. Immunological and virological tests were negative. Thyroid function tests revealed hyperthyroidism with positive anti-Tg, anti-TPO and TSHR antibodies. Increased uptake in thyroid scan confirmed the diagnosis of Graves' disease. Of note, her family history is significant for thyroid dysfunction and rheumatoid arthritis. She was treated with low dose thiamazole and propranolol, as well as methylprednisolone and gamma globulin. Interestingly, a fluctuating course with alternating phases of hypo- and hyperthyroidism followed and ITP relapse was observed following treatment initiation. Currently, she is on concomitant treatment with thiamazole and thyroxine, and remains euthyroid with normal hematological and biochemical laboratory tests. Methylprednisolone was discontinued 2 months ago.
Discussion
Hyperthyroidism associated with ITP is rare, and only 160 cases have been reported so far. To our knowledge our case with Graves' disease and concurrent ITP after alemtuzumab is the first described in the literature. The exact mechanism of autoimmunity in alemtuzumab-treated patients with RRMS is poorly understood. It has been proposed that the quick/complete recovery of B lymphocyte numbers (6–12 months), versus the slower/partial recovery of T lymphocytes, during the reconstitution phase, is responsible for the enhanced production of autoantibodies. In addition, lymphocytes escaped from cytolysis undergo homeostatic proliferation, potentially setting up an exaggerated and self-oriented response behind adverse autoimmune events. In our case the production of both platelet-associated IgG, and antithyroid antibodies, may be responsible for the coexistence of both diseases. Another contributory factor may be the increased reticuloendothelial phagocytic activity induced by hyperthyroidism, which may shorten the platelet survival. Genetic predisposition as well as smoking, family history of autoimmunity, female gender, younger age, and early brainstem involvement may also have played a role to this unusual case.

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PEP10.3

Levothyroxine replacement reduces BMI, HbA1c, insulin resistance, LDL-C and triglyceride in overt primary hypothyroidism in Asian Indians

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Background
Dyslipidemia is relevant association of hypothyroidism and consists of raised levels of total cholesterol, apolipoprotein B, triglycerides, low density lipoprotein (LDL) cholesterol, and reduced levels of high density lipoprotein (HDL) cholesterol.Thyroid hormones also have a role in modulating glucose metabolism and insulin resistance. The aim of study was to assess glycemic status, Homeostasis model assessment–estimated Insulin Resistance (HOMA–IR), and fasting lipid profile in individuals with newly detected overt primary hypothyroidism and to evaluate HOMA –IR, glycemic status and fasting lipid profile after achieving euthyroid status.
Methods
54 interested participants with Overt Primary hypothyroidism attending clinic from October 2017 to May 2019 were included. Individuals with diabetes, individuals on treatment for dyslipidemia or on treatment which can affect weight like steroids, anticonvulsants were excluded. Parameters were compared before and after achieving euthyroid state.
Results
Mean age of participants was 42.37±16.45 years. 79.6% were women. The mean duration to achieve euthyroid state was 8.626+0.782 weeks. The mean TSH before initiation of Levothyroxine was 27.55 µIU/l and after achieving euthyroid state was 2.63 µIU/l. The mean BMI before and after treatment was 23.83 ± 2.32 kg/m2 vs 22.87 ± 1.82 kg/m2 which was statistically significant.There was a statistically significant reduction in FPG,PPPG, HbA1c after treatment. The mean FBS before and after treatment were 123.50 ± 35.7 vs 95.31 ± 11.45 mg/dl,PPBS was 137.76 ± 42.98 vs 107.02 ± 18.55 mg/dl, and HbA1c 5.55 ± 0.90 ± 5.09 ± 0.53 %. There was a statistically significant difference found in TC,TG, LDL before and after achieving euthyroid state. The mean TC, TG LDL(mg/dl) before and after treatment were 173.09 ± 42.4 vs 144.83 ± 28.15, 156.20 ± 95.29 vs 103.76 ± 37.33, 110.02 ± 36.01 vs 85.84 ± 26.43 (P <0.001) respectively. The mean HDL before and after treatment was 41.74 ± 12.51 vs 44.00 ± 9.73 (P value 0.097). The mean HOMA – IR and fasting insulin before and after treatment were 3.60 ± 3.02 vs 1.84 ± 0.61, 10.42 ± 6.26 vs 7.91 ± 2.73 respectively and the difference was statically significant. FBS, PPBS, HbA1c, Total cholesterol, Triglycerides, LDL, HOMA IR, Fasting insulin all had positive correlation with TSH and were statistically significant.
Conclusion
Levothyroxine replacement is associated with significant improvement in insulin sensitivity and significant reduction in BMI, total cholesterol, triglycerides, low density lipoprotein, however HDL-C increase did not meet statistical significance.
Keywords
Hypothyroidism, HOMA-IR, Dyslipidemia.
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PEP10.4

Efficacy of a combined administration of myo-inositol and vitamin D in patients with autoimmune thyroiditis

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Background and aim
Autoimmune thyroiditis (AIT) is one of the most common autoimmune diseases, affecting more than 10% of females and 2% of males in the overall population. Clinical evidence suggests that oral supplementation with myo-inositol (MI) and vitamin D (VD) is useful in the treatment of AIT. MI is a carbocyclic polyol precursor of phosphoinositide synthesis. It is involved in cell signaling and, precisely, as a second messenger regulating the activities of Thyroid Stimulating Hormone (TSH). The aim of this study was to investigate the efficacy of a combined administration of MI and VD in patients with AIT.
Patients and methods
74 outpatients (mean age 42.39 ± 8.2 years) with AIT were enrolled in this prospective randomized controlled trial from May to September 2019. A total of 74 patients with AIT having TSH levels between 4.0 and 6.0 µIU/ml, elevated serum thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab), normal free thyroxine (fT_4) and free triiodothyronine (fT_3) levels were randomized into 2 groups: one receiving MI-VD and the other one VD alone. To provide additional information concerning thyroid tissue texture, high-resolution ultrasound scan of the thyroidal area was carried out.
Results
A significant decrease in serum TSH levels was noted in patients of group MI-VD compared prior and after treatment (P < 0.05), showing at baseline 5.18 ± 0.52 µIU/ml and 3.06 ± 0.48 µIU/ml over 6 months treatment. The decrement in control group before vs. post-treatment was not significant (4.93 ± 0.82 µIU/ml and 4.16 ± 0.81 µIU/ml). TSH, thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab) levels were significantly decreased in patients treated with combined MI-VD after six months of treatment. Also, a significant free serum thyroxine (fT_4) increase

was observed in MI-VD group. In both groups at baseline plasma VD levels were not different (19.4 ± 3.7 ng/ml group MI-VD; 18.9 ± 2.8 ng/ml group VD). After 6 months treatment, VD values were significantly augmented in each group compared to baseline.
Conclusions
The administration of MI-VD is significantly effective in decreasing TSH, TPO-Ab and Tg-Ab levels. Such treatment restored euthyroidism in patients diagnosed with AIT.
Keywords
Autoimmune thyroiditis, Myo-inositol, Vitamin D.
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PEP10.5

The prevalence of intestinal metaplasia in APCA positive patients with Graves' disease

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Introduction
A strong association between autoimmune atrophic gastritis and other autoimmune disorders has been well documented. The prevalence of gastric mucosa alterations in patients with thyroid autoimmunity is not well known. The aim of our study was to assess the prevalence of intestinal metaplasia in patients with Graves' disease (GD) and positive anti-parietal cell antibodies (APCA).
Methods
This is a single-center observational study in an outpatient clinic of autoimmune endocrinopathies at a Tertiary, General, University Hospital. Patients with GD and increased levels of thyroid-stimulating immunoglobulin (TSI >1.75 IU/l) were included in the study. Laboratory tests for TSH, T3, FT4, TSI, APCA, TgAbs, TPOAbs, blood count, liver enzymes and thyroid sonography were performed in all patients. All APCA positive patients underwent OGD.
Results
A total of 107 patients were analyzed, of whom females were 75.4% (81/107). The mean age and BMI of the patients were 46.5±14 years and 25.9±4.7 mg/kg^2 (18.7–36.8), respectively. TPOAbs were present in 65.5% (55/84), TgAbs in 47.6% (40/84) and APCA in 12.7% (9/71) of the patients. 14.6% (14/96) of the patients had undergone thyroidectomy. Personal history for other autoimmunities was present in 21.7% (18/83) and family history for thyroid autoimmunity in 49.5% (50/101) of the patients. 9/101 (8.9%) patients had PTC and 7/101 (6.9%) had other cancers. Histology in the 9 APCA positive patients revealed gastric atrophy in 55.6%, ECL hyperplasia in 33.3%, intestinal metaplasia in 44.4%, and *Helicobacter pylori* infection in 22.2% of the patients.
Conclusion
According to our study, intestinal metaplasia is a frequent finding in APCA positive patients with Graves' disease.
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PEP10.6

Influence of pro-inflammatory cytokines polymorphisms on the interrelationship between Graves' disease and diabetes

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Background
Graves' Disease (GD) is characterized by production of stimulating autoantibodies to thyrotropin receptor resulting in hyperthyroidism. Hyperthyroidism is associated with insulin resistance, hyperglycemia and ketosis. Our aim was to evaluate if single nucleotide polymorphism (SNP) in pro-inflammatory cytokines contributes to dysglycemia in GD.
Methods
We evaluated 98 patients with Graves' disease. Genetic variants in IL6-174 G/C, TNFA-308 G/A, IL1B-511 C/T, and IFNGR1-56 T/C were analyzed by real-time PCR. Patients were evaluated with oral glucose tolerance test with determination of glucose, insulin, C peptide and indexes of insulin resistance: HOMA-IR (homeostatic assessment insulin resistance index), HOMA-β (HOMA of β-cell function) and WBISI (whole-body insulin sensitivity index). Diabetes was defined according to ADA criteria. The associations of genetic variants with glycemic profile were evaluated with analysis unadjusted and adjusted for age and sex.
Results
The allele T in IL1B-511 C/T was significantly associated with a higher prevalence of diabetes (P = 0.029). The A allele in TNFA-308 G/A was associated with higher levels of fasting insulin in the adjusted analysis (P = 0.042) and higher levels of HOMA-β in both analyses (P = 0.027; P = 0.020). The T allele in IFNGR1-56 T/C polymorphism was associated with significantly higher mean values of fasting glucose (P = 0.047), as well as higher levels of C peptide (P = 0.026) in the unadjusted analysis.
Conclusions
SNP in pro-inflammatory cytokines may affect glycemic profile in patients with GD. These polymorphisms are associated with higher levels of fasting insulin and HOMA-β, increased fasting glucose and C peptide, and higher prevalence of diabetes.
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PEP10.7

Novel coronavirus disease and Hashimoto's thyroiditis in children (series of clinical cases)

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The impact of novel coronavirus (COVID-19) infection in adult patients with endocrine diseases is well established, with the evidence showing a link between endocrine pathology and disease severity (A. Badawi, S.G. Ryoo, 2016, J. Yang *et al*, 2020, S. Cianfarani, A. Brancatella, 2020). The thyroid gland and the virus infection with its associated inflammatory-immune responses are known to be engaged in complex interplay (L. Scappaticcio, *et al*, 2020). To date, no study has reported data on the interaction between novel coronavirus infection and endocrine diseases (for example, thyroiditis) in children (BTA/SFE, 2020).
Aim
To study impact of COVID-19 on the thyroid in children with Hashimoto's thyroiditis.
Patients and methods
We observed 7 clinical cases of the disease in children after COVID-19. We studied retrospectively seven cases (6 girls and 1 boy, aged 10–18 y.o.) of Hashimoto's thyroiditis in children enrolled in the pediatrics department. A clinical examination, hormonal analysis (free thyroxine, T4f, thyroid-stimulating hormone,TSH, thyroid peroxidase antibody, TPO and thyroglobulin antibodies, ATG) and thyroid ultrasound examination (USE) were conducted.
Results
COVID-19 had been mild in all children. Before the COVID-19 (6 months earlier) all children had a normal thyroid volume (WHO) and function both were normal, TPO level was was within 100–600 E/ml (ref: < 5.6 E/ml), ATG level was within 50–200 IE/ml (ref: < 18 IE/ml). In the treatment of COVID-19, human recombinant interferon alpha-2b preparations were used. After COVID-19 all cases showed an increase in thyroid volume by 20–30% at thyroid USE. At laboratory exams in all children were found to have elevated TPO (to 1000 E/l and more), in one patient was found to had elevated ATG (to 500 IE/ml and more), in one girl developed subclinical hypothyroidism and another patient presented with hypothyroidism.
Conclusions
A clinical case study showed that novel coronavirus infection aggravates the thyroid in children with Hashimoto's thyroiditis. There is required careful thyroid monitoring in patients with Hashimoto's thyroiditis during the pandemic of COVID-19.
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PEP10.8

Transient hyperthyrotropinemia in outpatient children treated due to acute infections of the respiratory system

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Introduction
Diagnostics of thyroid dysfunctions is frequently based on the measurements of TSH serum concentration only. Currently, due to a tendency to minimize stressful situations for a child (such as venipuncture to take a blood sample), some tests (i.e. TSH assessment) are performed at the Primary Healthcare Centre while other diagnostic tests (e.g. during an infection) are run. If TSH serum concentration is outside the reference range, it leads to the implementation of the diagnostic procedure used in patients with a thyroid disorders. Clinical observations indicate that in a considerable number of these patients, a thyroid disease is not confirmed, and the results of the tests performed so far are in fact falsely positive. The aim of the study was to assess the incidence of transient hyperthyrotropinemia during acute infections of the respiratory system in generally well-being children without previously diagnosed thyroid disease.
Material
The study group consisted of 94 children (49 boys and 45 girls), aged 2.2–17.3 years, who were consecutive admitted to a single Primary Healthcare Centre due to acute respiratory infection during one year. Obese and undernourished children were excluded from the study, similarly to patients treated for thyroid diseases and those who displayed typical signs and symptoms of thyroid disorders. In every case, a complete blood count (CBC) test was performed and C-reactive protein (CRP) as well as TSH in serum was measured. The tests were run on the next day after the visit (at the morning after an overnight fasting). Next, the parents were asked to bring the child for a check-up examination $\geq$ 2 weeks after recovery. At the next visit, the patient's condition was evaluated again and a blood sample was taken in order to assess the same parameters: CBC, CRP and TSH.
Results
Among these children manifesting both with or without fever, regardless of the elevated CRP concentration and of the type of infection (viral or bacterial), elevated TSH values are found in about 10% of patients, and they go back to normal values after resolution of symptoms. A prospective analysis showed a reduction of TSH values in approx. 65% of all examined children, and the TSH results at the control time point were significantly lower than during acute infection.
Conclusion
It seems that TSH levels should not be assessed during an acute infection. If thyroid dysfunction is suspected, the examination should be performed in the healthy state.

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Adrenal and Cardiovascular Endocrinology

PEP11.1

Fascin-1, a novel-circulating marker for the prognosis of the metastatic adrenocortical carcinoma

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Fascin-1(FSCN1) is an actin-bundling protein expressed in several solid carcinomas and often associated to an invasive and aggressive phenotype as it is involved in cytoskeleton rearrangement and filopodia formation. Adrenocortical carcinoma (ACC) is a rare endocrine malignancy characterized by a poor prognosis, particularly when metastatic at diagnosis. Complete surgical resection of the tumor mass is the main therapy for ACC patients in addition to the adjuvant administration of mitotane. Therefore, it is necessary to identify new markers indicative of tumor progression for a better management and monitoring of the patients. In our previous work, we found that FSCN1 detected in tumor samples could represent a new prognostic biomarker for invasive ACC. The main objective of the present study was to assess if FSCN1 was also detectable in the bloodstream of ACC patients and its prognostic value. We demonstrated that FSCN1 can be detected both in serum and plasma samples of a small local cohort of ACC patients (n = 27) compared to healthy controls (n = 4), through a specific ELISA assay for human FSCN1. FSCN1 circulating levels resulted significantly higher in ACC compared to controls, (FI: 9.66±1.22, P <0.01). In addition, we longitudinally evaluated FSCN1 concentrations both in pre-operative blood samples as well after the resection of the tumor mass. Consistently, patients with stage III/IV showed levels of serum FSCN1 significantly higher than those in stage I/II both in pre- and post-surgery blood samples, (FSCN1pre: 22.8±1.1 vs 15.8±1.8 ng/ml, P <0.01; FSCN1post: 21.4±1.5 vs 18.0±0.8 ng/ml, P <0.05). In order to evaluate the prognostic power of circulating FSCN1, we performed Kaplan–Meier analysis of patients stratified in 2 groups of high and low FSCN1 serum levels (cut off value: median of FSCN1 distribution): the pre-operative but not the post-surgical levels of circulating FSCN1 can significantly predict tumour recurrence (Log Rank = 0.013), but nor overall survival (Log Rang = 0.317). In conclusion, these findings – though preliminary – suggest that circulating FSCN1 may represent a new non-invasive prognostic marker in ACC, in particular when measured before surgery and histological diagnosis.
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PEP11.2

Establishment of novel multidimensional models for the adrenal gland and adrenal tumors

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The adrenal gland displays an important role in integrating neuronal, immune, vascular, metabolic and endocrine signals under a common organ capsule. The adrenal is the central organ of the stress response system, responsible for responses to acute and chronic stress stimuli and, thereby, playing a major role in numerous stress-related disorders. While for other diseases translational scientists developed programs to generate healthy cells to regenerate damaged tissues in patients, such approaches have been widely overlooked in other fields of endocrinology, except for type-I-diabetes. Moreover, tumor formation is very common in the adrenal gland and these tumors are furthermore highly heterogeneous. However, high throughput applications reflecting this heterogeneity and furthermore relevant 3D-structures in vitro are still widely lacking. Recently, we initiated the development of standardizable multidimensional models of adrenal organoids and tumor spheroids. For this purpose we utilized microwell plates providing stem cell quality clustering without adhesion, enormous scalability and medium change possibility. In a first step, we assessed for the human adrenocortical cell lines NCI-H295R and MUC-1 the impact of different cell numbers, incubation periods and methods of spheroid preparation. Based on these experiments we were able to successfully establish and dimensionally preserve stable tumor spheroids for both tumor models. Subsequent histological and immunohistochemical investigations revealed viable spheroids with characteristic cellular abundance and localizations for important tumor and steroidogenic marker such as Ki-67, SF-1 and 3betaHSD. Real time PCR analyses demonstrate no significant differences in SF-1 and Ki67 expression compared with monolayers. Our experiments indicate furthermore potential applicability for drug screenings. Treatment with 75 µM mitotane over 72 h revealed significantly decreased Ki67 Indices compared with untreated controls for both models (NCI-H295R: P <0.001; MUC-1; P <0.01) while adavosertib affected primarily MUC-1 spheroids (P <0.01). Moreover, we aimed at the development of bovine derived adrenal organoids and we are now also able to establish viable (H&E), as for organoids expected low/not proliferating (Ki67) and steroidogenic active (SF-1 and 3betaHSD) adrenal organoids. Preliminary data indicate furthermore mixed cell populations originating from both, adrenal cortex and medulla. Moreover, cell culture supernatants have been analyzed in a pilot experiment by LC–MS/MS and confirm specific secretion of hormones such as aldosterone, cortisol, and progesterone among others. In next steps, these models will be extended to human primary tumors of

adrenal origin and assessed regarding further applications and read outs. Thereby, we hope to provide new avenues for adrenal tissue replacement and mechanistic insights into adrenal (tumor) biology.

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PEP11.3

Identification of carbonic anhydrases III and IX in the adipose microenvironment of adrenocortical carcinoma

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The adipose tissue (AT) is an important endocrine organ. Upon energy imbalance, the adipose cells become dysfunctional, supporting the development of metabolic pathologies and tumours. The adipose cell is among the main actor of the tumor microenvironment, and is able to establish a crosstalk with the cancer cell resulting in a reciprocal reprogramming. Adrenocortical carcinoma (ACC) is a rare endocrine malignancy affecting the adrenal cortex. In the most aggressive forms, cancer cells infiltrate the visceral fat mass surrounding the adrenal, establishing a crosstalk between the tumour mass and the adipose microenvironment. Carbonic anhydrases (CAs) are a wide family of metalloenzymes with a relevant role in some pathologic conditions such as obesity and cancer. The objective of our study was to assess the distribution of the two CA isoforms, CAIII and CAIX, in AT (biotic samples of subcutaneous, SAT, and visceral,VAT, AT of obese and lean subjects) and in ACC tumor samples from a monocentric patient cohort by qRT-PCR, Western Blot and immunohistochemistry. We also evaluated their involvement in an in vitro coculture system between adipose stem cells, ASCs and adrenocortical cancer cells H295R, where coculture results in an increased aggressiveness and invasiveness, mimicking the interaction between adipose microenvironment and ACC in vivo. CAIII expression was higher in lean than in obese patients (SAT:FI = 26.9 ±Ð9.0,*P* = 0.01;VAT:FI = 5.2 ± 1.4,*P* = 0.01), while CAIX was mainly expressed in VAT than SAT of lean (FI = 480.5 ± 119.7, *P* = 0.01) and obese (FI = 361.4 ±Ð79.2,*P* = 0.000) subjects. CAIII expression in biopsies of ACCs stage I/II (*n* = 8) was significantly higher than in the aggressive ACC stage III/IV (*n* = 4)(FI = 4.0 ± 0.9,*P* = 0.001), while CAIX had an opposite behaviour (stage III/IV vs I/II FI = 5.7 ± 1.8,*P* = 0.03). CAIII and CAIX were also expressed in H295R. *In vitro* adipose differentiation of ASCs resulted in a significant increase of CAIII (adipo vs ASC FI = 54 ± 25,*P* = 0.04,*n* = 5) and CAIX (adipo vs ASC FI = 5 ± 1.5,*P* = 0.003,*n* = 5) expression. ASC-H295R cocultures resulted in an increased aggressiveness and invasiveness which was accompanied by a decrease in CAIII and an increase in CAIX expression in H295R cells in coculture vs monoculture, confirming the differences observed in ACC samples. In conclusion, our findings show an altered distribution of CAIII and CAIX expression in AT according to obesity condition, and in ACC, according to the tumor aggressiveness. Our data suggest a possible involvement of the two CAs in adipogenesis and tumor progression. We hypothesize an active role of CAIII and CAIX in the cross-talk between the adipose microenvironment and ACC, opening new prospective in the treatment of ACC with selective CA inhibitors.

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PEP11.4

Computerized tomography texture analysis in pheochromocytoma: correlation with clinical, biochemical, and histopathological data

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Computerized tomography (CT) texture analysis (TA) provides a valuable amount of quantitative data on single voxels and their relationship in a target lesions, giving additional value to the CT scan. CTTA has been applied to several oncologic diseases. We aimed to correlate the data derived from CTTA of pheochromocytoma to clinical, biochemical and histopathological data in 30 consecutive patients. Pheochromocytoma was confirmed at histology. The CTTA was performed on unenhanced, late arterial, venous, and delayed phases images. We analyzed first and second order features and performed correlation with blood pressure levels, urinary metanephrines and histopathological parameters: Pheochromocytoma of the Adrenal gland Scaled (PASS) and Grading of Adrenal Pheochromocytoma and Paraganglioma (GAPP) scores, Ki67 values, and *SDHB* expression at immunohistochemistry. We performed a multivariate regression model to assess the correlations and a cluster analysis to identify a "radiomic signature". Urinary metanephrines correlated with skewness (b = 0.905, P <0.001), kurtosis (b = 0.337, P = 0.015), and mean value of the distribution of Hounsfield Unit (HU) in arterial phase (b = −0.007, P = 0.030). Urinary normetanephrines correlated with the maximum HU value (b = 31.649, P <0.001) and the energy in arterial phase (b = 97030.7, P = 0.007). Ki-67 showed a significant correlation with the standard deviation of HU values distribution in portal phase (b = 0.155, P = 0.001) and the skewness of distribution in unenhanced phase (b = −1.118, P = 0.047). PASS score showed weak correlation (R^2 = 0.182) with the tumor volume (b = 5.33x10^{-5}, P = 0.037). GAPP score was correlated with energy (b = 112.27, P = 0.006) and maximum HU value (b = 0.002, P = 0.003) in arterial phase, kurtosis in HU distribution of portal phase (b = −0.829, P = 0.023), and tumor volume (b = 2.25x10^{-5}, P = 0.008). Tissue expression of *SDHB* correlated with kurtosis of HU distribution in portal phase (b = 0.453, P = 0.031), and shape compacity (b = 3.856, P = 0.001). Two clusters were identified, based on radiomic features. When compared to cluster 2 (n = 7), cluster 1 (n = 18) showed higher compacity (15.4 vs 8.9, P = 0.001), lower volume (10.2 ml vs 42.7 ml, P <0.001), lower maximum HU value in unenhanced (86.1 vs 94.7, P = 0.040) and arterial (197.4 vs 241.9, P = 0.021) phase, and higher minimum HU value in portal phase (−24.2 vs −53.3, P = 0.046). Patients in cluster 2 had higher systolic and diastolic blood pressure at diagnosis, and a higher GAPP score (4 vs 6, P = 0.050). All patients with metastatic disease were included in cluster 2 (0% vs 28.6%), even though the difference was not significant (P = 0.070). CTTA provided useful parameter that may be helpful for a thorough preoperative characterization of the pheochromocytoma.

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PEP11.5

Pre-operative hypercortisolism and post-operative adrenal insufficiency in pheochromocytomas: a single center retrospective analysis of 168 patients

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Introduction
Pheochromocytoma might be associated with hypercortisolism and post-operative adrenal insufficiency. The aim of this study is to determine the frequency of cortisol dysregulation before and after pheochromocytoma surgery.
Methods
Single center retrospective study of consecutive pheochromocytoma patients investigated in the Endocrinology department of Cochin Hospital before and after surgery from 2008 to 2020. Demographic characteristics, medical history, treatment, clinical examination, genetic analysis, hormone levels (dexamethasone suppression test, urinary free cortisol, plasma cortisol levels, preoperatively and ACTH-stimulation test postoperatively) as well as histology reports were reviewed.
Results
187 patients with pheochromocytoma underwent workup and surgery between 2008 and 2020. 168 patients were analyzed (19 cases excluded for insufficient data). Median age was 53 years old (18–89). 70 (42%) were men, 98 (58%) women. 8 patients (4%) had bilateral pheochromocytomas. Prior to admission, 50% of patients were on antihypertensive treatment and 25% had diabetes. The majority of pheochromocytomas were incidentalomas (87 cases, 52%), 37 patients (22%) presented with classic symptoms and 12 (7%) were diagnosed during a blood pressure workup. The other 12.5% (21 patients) presented with cardiovascular manifestations such as cardiac arrest and Takotsubo cardiomyopathy whereas 11 patients (6.5%) were found positive upon genetic disease monitoring (VHL, MEN2, NF1). Preoperative workup showed abnormal dexamethasone suppression

test (cortisol >50 nmol/l) in 30/168 (18%) and high urinary free cortisol in 18/168 (11%). 1 patient had adrenal insufficiency before surgery. 32 patients (19%) presented postoperative adrenal insufficiency: in 15 cases (9%), adrenal insufficiency was primary (due to bilateral adrenalectomy or previous unilateral adrenalectomy) and in 13 (7.7%) of central origin. 7/13 patients with post-operative corticotroph deficiency presented pre-operative biological hypercortisolism, while 6/13 had no abnormal preoperative investigations (4/6 having not received post-operative glucocorticoid before post-operative assessment). Histology showed coexistence of adrenocortical adenoma and pheochromocytoma in the same adrenal gland in 5 patients (3%), of whom 1 had signs of Cushing, elevated urinary free cortisol preoperatively, and adrenal insufficiency postoperatively. In 1 other case, pheochromocytoma cells stained with anti-ACTH antibody (this patient also presented signs of Cushing and elevated cortisol levels).

Conclusion

Possible cortisol excess is present in up to 18% of pheochromocytomas while demonstrated Cushing with histologic evidence for adrenal or ectopic Cushing and post-operative corticotroph deficiency is present in less than 5% of the cases. Post-operative glucocorticoid replacement therapy has to be discussed on an individual basis taking in account clinical and systematic hormonal pre-operative assessment.

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PEP11.6

Increased risk of cardiometabolic disease in patients with benign adrenal tumours with and without cortisol excess: a case–control study

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Background

Benign adrenocortical tumours are found in 3–5% of adults and can be non-functioning (NFAT) or associated with cortisol excess. The latter group divides into patients with clinically overt signs (adrenal Cushing's syndrome, CS) and patients lacking CS signs (mild autonomous cortisol excess, MACE). The 1 mg-overnight dexamethasone suppression test (DST) further differentiates MACE into MACE-1 (possible MACE; post-DST cortisol 50–138 nmol/l) and MACE-2 (definitive MACE; post-DST cortisol >138 nmol/l). A recent systematic review and meta-analysis reported a high prevalence of metabolic syndrome in patients with benign adrenocortical tumours; however, large-scale prospective data are lacking.

Methods

We included 1305 patients with confirmed benign adrenal tumours recruited to the prospective ENSAT EURINE-ACT study (2011–2016). The prevalence of hypertension, resistant hypertension (defined as treatment with ≥3 anti-hypertensives), type 2 diabetes (T2D), T2D with insulin use, and need for with lipid-lowering medications in the EURINE-ACT cohort was compared to 5268 population controls from the 2014 cohort of the Health Survey for England, which monitors health trends in the UK. Multinomial logistic regression was used to obtain BMI-, age, and sex-adjusted odds ratios (aOR).

Results

Cortisol excess was highly prevalent, affecting 50.3% of patients (MACE-1 34.6%, MACE-2 10.7%, CS 5%). Patients carried an increased risk of hypertension, which gradually increased with the degree of cortisol excess: NFAT aOR 3.66 (95%CI 3.02–4.43); MACE-1 aOR 5.03 (3.96–6.40); MACE-2 aOR 6.72 (4.37–10.32); CS aOR 11.86 (6.50–21.65) (all P <0.001). Similarly, all groups presented with an increased risk of resistant hypertension: NFAT aOR 6.40 (4.72–8.68); MACE-1 aOR 7.43 (5.43–10.16); MACE-2 aOR 10.04 (6.36–15.86); CS aOR 31.37 (16.00–61.50) (all P <0.001). Furthermore, patients showed an increased risk of T2D: NFAT aOR 2.62 (2.00–3.44); MACE-1 aOR 2.75 (2.05–3.69); MACE-2 aOR 4.06 (2.45–6.71); CS aOR 11.00 (5.31–22.77) (all P <0.001). Patients with cortisol excess and T2D more often required insulin treatment: MACE-1 aOR 2.70 (1.58–4.62); MACE-2 aOR 4.24 (1.98–9.09); CS aOR 11.08 (3.62–33.90) (all P <0.001). The use of lipid-lowering drugs was also higher in patients with NFAT (aOR 2.11 [1.71–2.59]), MACE-1 (aOR 2.20 [1.75–2.76]), and MACE-2 (aOR 2.65 [1.80–3.89]) (all P <0.001).

Conclusions

Patients with benign adrenocortical tumours have an increased prevalence of cardiometabolic disease and present with a more severe phenotype. The risk increases with the degree of cortisol excess and is highest in CS and MACE-2. However, even NFATs carry a considerably increased cardiometabolic burden, which may be due to underlying autonomous cortisol secretion that is not picked up by currently employed biochemical testing.

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PEP11.7

All-cause mortality in adrenal insufficiency patients with primary and secondary adrenal insufficiency

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Background

Increased mortality risk of patients with adrenal insufficiency has been inconsistently reported. This might have resulted from the disparity of time and place of clinical care between the study patients and reference population. Also, data of patients with secondary adrenal insufficiency was limited as majority focused on other types of pituitary disorders. Therefore, we compared all-cause mortality of patients with primary and secondary adrenal insufficiency with individually matched controls.

Subjects

In a UK general practitioner database (Clinical Practice Research Datalink; CPRD), 6821 patients with adrenal insufficiency of any type (2052 primary adrenal insufficiency, 3948 secondary) were compared with 67564 matched controls (20366 primary, 39134 secondary).

Methods

Each study patient was individually matched with up to 10 controls who had the same sex, GP practice (representing place of clinical care and degree of deprivation), 5-year strata of the year of birth, and 5-year strata of the start of follow-up. Follow-up began on the latest of the date at which patients were diagnosed, registered to GP, or the GP provided standard information. Follow-up finished on the earliest date of death, or de-registering from the GP. All-cause mortality rate and the hazard ratio of the study patients relative to controls was analysed in overall and separately according to type of adrenal insufficiency.

Results

In adrenal insufficiency of any type, the mortality rate of the patients was significantly higher than controls (35.2 [95%CI, 33.4–37.0] vs. 21.0 [20.6–21.5] per 1000 person-years, P <0.0001) with a follow-up period of 40799

and 406899 person-years, respectively. The hazard ratio of mortality in adrenal insufficiency of any type was increased (1.68 [95%CI, 1.58–1.77], P <0.0001). In patients with primary adrenal insufficiency, the hazard ratio was 1.83 (95%CI, 1.66–2.02, P <0.0001), which was higher than those with secondary adrenal insufficiency (HR, 1.52 [95%CI, 1.40–1.64], P <0.0001).
Conclusion
With taking account of sex, age, time and place of clinical care, all-cause mortality risk remained increased in both primary and secondary adrenal insufficiency patients but more predominant in primary adrenal insufficiency.

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PEP11.8

Urinary steroid profiling for adrenocortical carcinoma patients' surveillance

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Background
The aim of the study was to evaluate urine steroid metabolomics by gas chromatography–mass spectrometry (GC–MS) for the adrenocortical carcinoma (ACC) metastases` biomarkers detection in patients after the surgery.
Patients and methods
33 postoperative ACC patients were examined before and after the surgery. The median age was 47 years (41–60). The Weiss score was more than 3 points according to the histological analysis. 9 patients were disease-free in the early postoperative period (up to 12 months after surgery). Metastases were detected 1–5 years after the operation in 18 patients. The control group consisted of 25 patients with adrenocortical adenoma (ACA) without malignant features defined by the histological analysis. The median age was 52 (47–61) years. We studied urine steroid profile using gas chromatograph–mass spectrometer SHIMADZU GCMS – QP 2020. Statistical data was processed with software STATISTICA for WINDOWS (Version 10). Results comparison was made using Mann–Whitney test.
Results
The ACC`s main biomarkers urinary excretion (dehydroepiandrosterone (DHEA), 16α-DHEA, etiocholanolone (Et), pregnandiol (P2), pregnantriol (P3), pregnendiol (dP2), 16-hydroxypregnendiol (16-OH-dP2), pregnentriol (dP3), tetrahydro-11-deoxycortisol (THS) was determined using GC–MS. The abovementioned metabolites excretion rates were decreased in all disease-free postoperative patients as compared to the same patients` preoperative steroid profiles. Nevertheless, the 16α- DHEA, 16-OH-dP2, THS excretion was increased compared with control group. The 21-hydroxypregnendiol (21-OH-dP2), 20-on-3,11,17 and 21-pregnentetrol (20-on -dP4) were identified in the urine of all ACC recurrence patients. The increased 16-OH-dP2-3β excretion and decreased 16-OH-dP2-3α/16-OH-dP2-3β ratio (<2.0) were typical for ACC recurrence patients in comparison with disease-free patients. The 10 patients of the disease recurrence cohort had the THS, androgen (DHEA and its metabolites), progestogenes (P2, P3), 5-ene-pregnenes (dP2, dP3, 16-OH-dP2) increased excretion. While in the other 8 patients of the same cohort THS and 5-ene-pregnenes increase was observed.
Conclusion
ACC postoperative recurrence biomarkers were obtained using urinary steroid profiling. The study of androgen, progesterone, pregnenolone metabolites, THS, 3β,16,20-dP3, 21-OH-dP2, 21-OH-dP4 urinary excretion and 3α,16,20-dP3/3β,16,20-dP3 ratio is of particular importance for detecting the ACC metastases development in the early postoperative period.

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Diabetes, Obesity, Metabolism and Nutrition

PEP12.1

Cellularity and lipolytic function of human perirenal and subcutaneous adipose tissues in patients with pheochromocytoma

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Pheochromocytomas are catecholamine-producing tumours with diverse cardiovascular and metabolic outcomes including insulin resistance and weight loss. However, impacts on adjacent and distal fat depots are not fully defined and more particularly concerning induction of beige/brown adipose tissue (AT). The aim of the study is to characterize the cellular composition, the metabolic function and the expression of brown AT markers in matched perirenal (PRAT) and abdominal subcutaneous AT (SAT) in association or not with pheochromocytoma. Paired biopsies from PRAT and SAT are collected from patients undergoing adrenalectomy for pheochromocytoma, cortisol-producing adrenal adenoma or non-secreting and benign adrenal tumours. AT are enzymatically digested to isolate mature adipocytes and stroma-vascular fraction (SVF) cells. The adipocyte diameter repartition is determined by image analysis, lipolytic activity by glycerol and free fatty acid quantifications in the presence of lipolytic pharmacological agents (isoprenaline, epinephrine, atrial natriuretic peptide ANP), and finally adipocyte gene expression is analysed by RT-qPCR approaches. The cellular composition of the SVF (progenitor, endothelial and immune cells) is determined by flow cytometry analyses. Our results demonstrate that, whatever the clinical context, PRAT adipocytes are less hypertrophied than paired SAT adipocytes, and that pheochromocytoma patients tend to exhibit smaller adipocytes whatever the AT depot. Multilocular brown-like adipocytes are observed in PRAT only and in patients with pheochromocytoma. Their presence is associated with higher beige/brown gene expression marker (UCP1, uncoupling protein 1). PRAT and SAT adipocytes show distinct lipolytic responses to beta-adrenergic receptor agonist (isoprenaline, epinephrine) and ANP in pheochromocytoma patients compared to others. In agreement, the transcriptomic profiles of adrenergic receptors, lipolytic enzymes and lipid droplet associated proteins are different according to AT depot. Finally, the distribution of progenitor cell subsets, macrophages and lymphocytes, specific of PRAT and SAT, is modulated in pheochomocytoma patients. Our study shows that PRAT exhibits specific cellularity and metabolic lipolytic function compared to SAT and both AT depots are different in pheochromocytoma patients. Finally, presence of brown-like multilocular and UCP1 positive adipocytes is only observed in PRAT from such patients.

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PEP12.2

Growth factors and state of lipid peroxidation in hypertensive patients with type 2 diabetes mellitus

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The combination of hypertension and type 2 diabetes mellitus (T2DM) greatly increases the risk of adverse cardiovascular events. Identification of factors which accelerate the development of atherosclerosis, it is important to more fully understand the mechanisms of progression of these diseases.
The aim is to study the relationship between levels of transforming growth factor-β1 (TGF-β1), insulin-like growth factor-1 (IGF-1) and lipid peroxidation in patients with essential hypertension (EH) and T2DM.
Methods
The study involved 76 p atients with grade 2 EH (40 men and 36 women, aged 48 to 60 years): 42 patients with EH with T2DM and 34 hypertensive patients without T2DM. In all patients, the development of EH preceded the development of T2DM. The control group consisted of 24 healthy individuals. The blood levels of TGF-beta1, IΦP-1 and malonic dialdehyde (MDA) were measured in all subjects.
Results
TGF-β1 and MDA blood levels were significantly higher in EH patients with T2DM compared with hypertensive patients without diabetes (p1 = 0.032 and p2 = 0.043, respectively) and with the control group (p1 = 0.018 and

p2 = 0.027, respectively). The level of IGF-1 in the blood of patients with EH and T2DM was significant lower compared with patients with EH without diabetes (P = 0.034) and with healthy individuals (P = 0.042). The levels of IGF in patients with EH without diabetes and in healthy individuals didn't differ. At the same time, in hypertensive patients with T2DM, positive correlations of blood levels of TGF-β1 with MDA (P = 0.003), as well as blood levels of TGF-β1 and MDA with low-density lipoprotein cholesterol (LDL-C) (P = 0.038 and P = 0.026, respectively) were revealed.
Conclusion
The established increase in the levels of TGF-β1 and lipid peroxidation products in combination with a decrease in the level of IGF-β1 creates conditions for the accelerated progression of atherosclerotic damage in hypertensive patients with T2DM.

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PEP12.3

Association between triglyceride-glucose index (TyG) and serum urate concentrations in young adults

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Background
Serum urate (SU) has been positively and independently associated with type 2 diabetes in observational studies, but causal roles remain unclear.[1] Triglycerides and glucose (TyG) index can be a useful and easily performed indicator of insulin resistance for daily clinical practice.[2] The aim of this study was to evaluate the association between SU and TyG index in 22-year-old participants of a birth cohort.
Materials and methods
During 1993, all live born babies in the city of Pelotas (Brazil) were invited to take part in a prospective study and sub-samples of this cohort were followed-up since then. At the 22-year follow-up, interviews and clinical measurements were performed and non-fasting blood samples were drawn from the participants. SU, blood glucose and triglycerides were evaluated by enzymatic-colorimetric assay. Insulin was assessed by electrochemiluminescence immunoassay. The TyG index was calculated as *Ln* [fasting triglycerides (mg/dl) × fasting glucose (mg/dl)]/2. The co-variables used were fasting period, body mass index, alcohol use disorder and systolic and diastolic blood pressure. Variables are shown as mean (±S.D.) or median (25–75 IQR). Sex-stratified linear regressions have been performed using STATA 13 and P <0.05 was considered statistically significant.
Results
The sample was composed by 1657 (46.3%) men and 1921 (53.7%) women of 22 years old. Mean (±S.D.) SU (mg/dl) was higher in men than in women (5.2±1.2 vs. 3.9±1.1); the same was observed for blood glucose (mg/dl) (91.7±25.7 vs. 88.5±20.9). Median (25–75 IQR) insulin (μU/ml) was also higher in men [20.5 (10.9; 39.3) vs. 18.4 (10; 34.2)]. Median (25–75 IQR) triglycerides (mg/dl) was higher in women [87 (63; 117) vs. 85 (62; 120)]. The adjusted linear regression coefficient (95%CI) between SU and TyG index was 0.50 (0.39; 0.61) for men and 0.41 (0.32; 0.51) for women; both with P <0.001. SU was positively associated with TyG index in both sexes, although there was no statistically significant association in adjusted analyses between SU and insulin concentrations.
Conclusion
The increase of SU was associated with increasing TyG index in early adult age, even when adjusted for potential confounders. The association of SU with TyG index may occur earlier than with serum insulin.
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PEP12.4

Relationship between adiponectin, TNFα and SHBG in prepubertal children with obesity

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Sex hormone-binding globulin levels are low in adult subjects with obesity when compared to normal-weight individuals. Obesity is associated with higher tumor necrosis factor alpha (TNFα) plasma levels and lower adiponectin levels. Moreover, we have recently elucidated the molecular mechanisms by which TNFα and adiponectin regulate hepatic SHBG production. The main objective of this study was to assess if the adult associations between TNFα, Adiponectin and SHBG are present in prepubertal children. We determined several morphometric and biochemical parameters in normal-weight and obese prepubertal children, as well as quantified plasma SHBG, TNFα-R1, and adiponectin levels. Our results showed that prepubertal children with obesity had decreased plasma SHBG levels compared to normal-weight controls (67 nmol/l vs 172 nmol/l). Importantly, SHBG plasma levels correlated significantly (P < 0.05) with TNFα (negatively, **ßstd** = −0.31) and adiponectin (positively, ßstd = 0.58) suggesting an important role of these two cytokines in determining plasma SHBG levels in prepubertal children. Furthermore, the results showed that plasma adiponectin levels are may play a more important role than TNFα in influencing plasma SHBG levels in our prepubertal population with obesity.

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PEP12.5

Anthropometric and laboratory features of children with type 1 diabetes and coexisting autoimmune disorders

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Objective
To determine predictive factors of co-existing autoimmunity in children with type 1 diabetes mellitus (T1D).
Material and methods
64 children with combined autoimmune pathology (T1D and autoimmune thyroid diseases or celiac disease) - main group, age 12.14±3.54 years) and 81 patients with only T1D (comparison group, age 11.57±3.34 years) were recruited. Groups were comparable in age (P = 0.34) and T1D duration (P = 0.81). Assessment of anthropometric parameters; biochemical blood parameters; glycosylated hemoglobin (HbA1c), vitamin D, thyroid hormones, antibodies to thyroid peroxidase (anti-TPO), glutamate decarboxylase (GAD) and zinc transporter8 (ZnT8) levels was carried out. The assessment of height and body mass index (BMI) was carried out using the *z*-criterion (who, 2007). Results were processed using Excel 10.
Results
In the main group 44 children had combinations of T1DM with autoimmune thyroiditis (AIT), 15 – celiac disease (CD), 3 – Graves' disease, 1 – AIT and CD. Children with T1D and autoimmune thyroid diseases had significantly higher *z*-scores of BMI (+0.24 vs −0.19, P = 0.019) and the prevalence of overweight (26.5 vs 12.0%, P = 0.029) than the comparison group. Children with concomitant thyroid diseases demonstrated higher triglycerides (P = 0.032) and very low density lipoproteins (P = 0.038) compared to the comparison group. Among the risk factors for autoimmune thyroid damage, the association of thyroid pathology with severe vitamin D deficiency (level <10 ng/ml) ($\chi 2$ = 6.848, P = 0.009, odds ratio (OR) 3.57, 95% confidence interval (CI) 1.07–5.46), female gender (OR 3.08, CI 1.48–6.36), GAD antibodies (OR 5.13, CI 1.23–21.35) and ZnT8 antibodies (OR 5.13, CI 1.23–21.35) was detected. Children with concomitant thyroid diseases and severe vitamin D deficiency had higher risk of diabetes decompensation (HbA1c>9%) compared with the patients with vitamin D concentration > 10 ng/ml (χ^2 6.848; OR 7.00; CI 1.50–32.72, P = 0.011). Association of CD with early (less than 4 years old) T1D onset (χ^2= 8.250; OR 7.022; CI 2.22–22.20, P = 0.003) and severe vitamin in D deficiency was established (OR 9.82; CI 5.27–17.34, P = 0.001).
Conclusions
1. Higher levels of HbA1c were detected in children with polyglandular autoimmune pathology and severe vitamin D deficiency.
2. Higher risk of autoimmune thyroid disease was found in patients with severe vitamin D deficiency, high levels of GAD ant ZnT8 antibodies, female gender and late puberty. Among the risk factors of CD early onset of T1D and severe vitamin D deficiency was detected.

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PEP12.6

Serum leptin and urine cortisol to cortisone ratio are correlated in familiar partial lipodystrophy type I (Kobberling Syndrome)

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Background
In lipodystrophy (LD) adipose tissue function is impaired, leading to a severe metabolic syndrome. Familiar Partial LD (FPLD) type I (Kobberling Syndrome) overlaps with Cushing's syndrome phenotype. The latter and the metabolic impairment observed in FPLD1 may suggest a crosstalk between the HPA axis, assuming that leptin sensitivity is preserved in this context. We aimed to evaluate if leptin levels are associated with glucocorticoid activity in FPLD1.
Methods
12 adult patients (2 males, 10 females) with PLD were recruited. Physical parameters, plasma lipid profile, renal function, liver enzymes, glucose, HbA1c, and leptin levels were determined. 24-h urine cortisol (F) and cortisone (E) through LC–MS/MS analysis were also measured.
Results
Twelve adult subjects were classified as Köbberling syndrome after the genetic and immune exclusion of other LD forms. All of them presented increased waist circumferences, decreased hip circumference and peripheral skinfold thickness. All patients had type 2 diabetes under treatment (insulin with or without other antidiabetic drugs), with high HbA1c levels (8.2±0.3%). The patients were treated for high lipid levels (statin, ezetimibe, fibrates, omega 3, PCSK9 inhibitors alone or combined), with LDL in the target range in 33%, and triglycerides lower than 150 mg/dl in 26.6%. Leptin levels were in the lower range according to sex and BMI (29.5±5.5 µg/l). All subjects had correct serum cortisol suppression after an overnight 1-mg dexamethasone test. Leptin levels correlated in all the subjects and females alone with BMI (r: 0.623), HDL-cholesterol (r: 0.485), estimated glomerular filtration rate (eGFR, r: −0.687), and 24 h urine F/E ratio (r: 0.750), but not with urine F and E alone. F/E ratio was also correlated with eGFR (r: −0.457). Urine F/E ratio, in a stepwise model composed of significant variables, was positively predicted by leptin levels and BMI (R: 0.756, R2: 0.562, P <0.032).
Conclusion
In FPLD 1 (Kobberling), leptin levels are directly associated with the 24 h urine F/E ratio suggesting complex crosstalk among leptin, 11β-hydroxysteroid dehydrogenase 1 and 2 activity. Glucocorticoid sensitivity and renal impairment could contribute to the severity of the phenotype.

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PEP12.7

Systems biology approach identifies key genes and related-pathways for childhood obesity

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Introduction
Epidemiological studies have suggested that obesity during childhood increases the risk of developing metabolic comorbidities, such as type 2 diabetes, later in life. Childhood obesity is a complex disease whose molecular mechanisms are not completely elucidated. However, studies have demonstrated that approximately 65% of the variation associated with obesity is due to genetic factors. In this context, a system biology approach could contribute to the scientific knowledge regarding genetic factors related to childhood obesity onset.
Aim
To identify molecular mechanisms involved in childhood obesity by implementing a system biology approach.
Methods
Experimentally validated and computationally predicted genes related to Pediatric Obesity (C2362324) were downloaded from the DisGeNET v7.0 database. The protein–protein interaction (PPI) network was constructed using the STRING v11.0 database and analyzed using Cytoscape v3.8.2. The relevance of each node for the network structure and functionality was assessed using the degree and betweenness algorithms to define the hub-bottleneck genes. Functional and pathway enrichment analyses were performed based on Gene Ontology (GO) terms and KEGG Pathways.
Results
The search on the DisGeNET database retrieved 191 childhood obesity-related genes. After the PPI network analysis, 12 hub-bottleneck genes were identified: *INS, LEP, STAT3, POMC, ALB, TNF, BDNF, CAT, GCG, PPARG, VEGFA,* and *ADIPOQ*. These hub-bottleneck genes are involved in several biological processes, including regulation of gluconeogenesis, lipid export from cells, and response to vitamin E. Regarding KEGG pathways, these genes were enriched in adipocytokine signaling, insulin resistance, longevity regulation, thermogenesis, and cytokine signaling pathways.
Conclusion
Our approach identified 12 hub-bottleneck genes that are highly connected and probably have a key role in childhood obesity. Moreover, functional enrichment analyses demonstrated that they are enriched in several biological processes and pathways related to the underlying molecular mechanisms of obesity. These findings provide a more comprehensive information regarding genetic and molecular factors behind childhood obesity pathogenesis.

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PEP12.8

Medicsen smartpatch: a new approach to diabetes management

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Introduction
Diabetes, a metabolic disorder characterized by abnormal blood glucose levels, is a serious chronic disease that implies an important public health problem. Being Insulin the main hormone for modulating blood glucose levels, subcutaneous injections are the main way for its administration in the diabetes treatment. However, this way of administration can lead to poor patient compliance, apart from several side-effects. Although other ways of administration have been investigated, such as oral or inhaled insulin, these have enough drawbacks to not be consider as substitutes of subcutaneous injections. To face this problem, Medicsen is developing a Smartpatch that integrates a wide range of technologies, all of them tested in laboratory, with the purpose of ensuring the correct transport of insulin from the surface of the skin to the bloodstream using a non-invasive and painless way through a phenomenon induced by the sonophoresis.
Materials and methods
Several *in vitro* and *in vivo* tests have been performed in order to prove the efficacy and safety of the technology, allowing us to collect experimental evidence through different methodologies that demonstrate the therapeutic potential of the device. Among these methodologies there are permeability studies using Franz diffusion Cell and swine models (that prove efficacy of the technology) as well as safety studies, for both the insulin and the skin.
Results
All tests performed have been successfully accomplished with results indicating the lack of damage to either the insulin molecule, which maintains its biological function and stability, as seen in vivo, in HPLC studies or in the circular dichroism spectra of the samples, which shows no variability, reaching the characteristic minimum at 219 nm (s.d. ± 8.31) in all groups tested, or to the skin, which suffers none significant damage, as proven by electron microscopy evaluation of the skin or by ELISA and other biochemical assays in which changes in the expression and concentration of relevant skin cellular compounds such as TNF α and IL-2 were studied. Lastly, the technology proved to be effective in the delivery of insulin molecules through the skin in a non-invasive way, as observed in a Franz Diffusion Cell system and in the *in vivo* model of blood glucose reduction.
Conclusions
Results observed during *in vitro* and *in vivo* studies indicate that the technology developed by Medicsen is effective and safe for the patient. Following steps, including human trials, will be critical to fully demonstrate its potential in the treatment of diabetes.

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Pituitary and Neuroendocrinology

PEP13.1

Factors associated with Aryl hydrocarbon Interacting Protein (AIP) expression in gonadotroph pituitary neuroendocrine tumours (Pit-NETs)

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Introduction
AIP is a predisposing gene for GH/PRL-secreting PitNETs. Clinically non-functioning PitNETs (NFPT) occasionally occur in the setting of AIP germline mutations, sometimes arising from Pit-1 lineages. However, AIP overexpression has been observed in unselected NFPT and associations with the gonadotroph phenotype and/or tumour aggressiveness were suggested. We wished to evaluate the significance of AIP expression in gonadotroph tumours defined by the WHO 2017 classification.
Material and methods
Thirty-seven gonadotroph Pit-NETs (GnPT) were studied, displaying positive immunostaining for FSH/LH (n = 30) or SF1 only (n = 7). Male patients predominated (26M, 11F, median age 57 years (IQR 46-66)). Tumours were characterized for size, invasiveness and Ki-67 immunostaining. Gene expression of AIP, β−FSH, β−LH, SF1, Cyclins A2, B1 and D1 was evaluated in surgical samples and in 3 normal pituitaries (NP) by Real-Time qRT-PCR, based on a Taqman methodology using commercial probes and β−bactin as a housekeeping gene (Applied Biosystems). AIP immunostaining (AIP-IHC) was evaluated on paraffin-embedded sections by a semi-quantitative score (n = 31). Non-parametric tests (Wilcoxon and Spearman correlation) were used for statistical analysis.
Results
Gene overexpression of AIP was found in 18/37 GnPT (48.6%), tended to be more frequent in M (57.7 vs 27.3% in F, P = 0.09), and not significantly correlated with tumour size, invasiveness or Ki67. A single case of AIP downregulation was observed. AIP transcripts were significantly correlated with β-LH (ρ = 0.54, P = 0.0019) and cyclin A2 (= 0.35, P = 0.031), with a similar trend for β−FSH and SF1 (P = 0.06 each), but unrelated to Cyclin D1 or B1. AIP-IHC was significantly associated with AIP transcripts (ρ = 0.51, P = 0.010) and classified as high/moderate/low in 38.7%, 41.9%, 19.3% of the cases, with no male predominance and irrespective of tumour characteristics.
Discussion
Compared to NP, the proportion of AIP gene overexpression in GnPT (48.6%) is probably underestimated due to its normal mammo-somatotroph localization. Indeed, 80% of NFPT displayed clear AIP immunostaining (38.7% with a high score). Neither AIP gene or protein overexpression was significantly associated with tumour aggressiveness. A significant correlation was also found between AIP and Cyclin A2 transcripts. However, unlike cyclins D1 and B1, Cyclin A2 overexpression has not yet been associated with NFPT proliferation or invasion. Rather, AIP transcripts were associated with gonadotroph features, in particular β-LH.
Conclusion
AIP expression appears to be associated with the endocrine phenotype of GnPT rather than with their volume or invasiveness. The potential implications of these findings in the natural history of GnPT should be better defined.

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PEP13.2

Use of free triiodothyronine level in central hypothyroidism management

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Introduction
There is no consensus about biological targets in patients with central hypothyroidism (CH). The main objective of this work was to characterize our patients with CH.
Design
We conducted a retrospective study at the University Hospital of Amiens. In our center, patients with CH are considered "well substituted" if the free thyroxine (FT4) is in the upper half of the reference interval and the free triiodothyronine (FT3) within the normal range. We studied the FT4/FT3 ratio in all and "well-substituted" patients and the determinants of FT4/FT3 in patients with normal FT3.
Results
124 patients were included between 01/07/2016 and 31/07/2018. CH was due to pituitary adenoma in 100 patients. The average dose-weight of levothyroxine was 1.34 µg/kg/day. The average FT4/FT3 ratio was 4.04 with a a physiological ratio (3.10–3.30) in only10 patients. 36% of the patients were considered "well substituted". They had a significantly higher TeBG (P = 0.028) and lower triglycerides (P = 0.044) ; the ratio was physiological in only 2 patients and ratio was higher in women than men: 4.54 vs 3.94 (P = 0.034). 101 of all patients had FT3 within the normal range. FT3 was significantly lower in obese patients (P <0.01). Patients with FT3 higher than the calculated median had a FT4/FT3 ratio closer to the physiological ratio.
Conclusion
Treatment of CH remains a challenge for the endocrinologist. It seems relevant to target a FT3 close or higher than the median, without considering the FT4 to obtain aphysiological FT4/FT3 ratio but the obtention of a clinical improvement has to be evaluated.

Key-words
central hypothyroidism, levothyroxine, free thyroxine, free triiodothyronine, FT4/FT3 ratio

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PEP13.3

Natural history of nonfunctioning pituitary incidentalomas and adenomas. A systematic review and meta-analysis

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Objective
The objective of this systematic review was to assess the incidence of growth, new pituitary endocrinopathies, and the incidence of surgery and/or radiotherapy in conservatively treated non-functioning pituitary adenomas/incidentalomas (NFPAs/NFPIs).
Method
A bibliographical search of Embase and Pubmed was conducted in order to identify eligible studies.
Results
33 Cohort studies including 1554 patients with a mean follow-up time of 3.8 years were extracted. During follow-up 482/1554 (31.02%) tumors grow corresponding to a risk of 6.4/100 (95% CI. 4.8 to 8.1; I^2 = 90) person years (py). Surgery was necessary in 136/1151 (11.82%) cases corresponding to a risk of 2.8/100py (95% CI. 1.9 to 3.4; I^2 = 58%). New endocrinopathies were observed in 76/901 (8.44%) patients corresponding to a risk of 1.4/100py (95% CI 0.7 to 2.1; I^2 = 74%). However, subgroup analysis suggested that growth of microadenomas occurred at a rate of 0.9/100 py (95% CI. 0.4 to 1.3; I^2 = 47%).
Conclusion
Conservatively treated NFPAs/NFPIs are in significant risk of growth, however, new endocrinopathies and active treatment is quite rare. Especially, the risk of growth in microadenomas was rarely observed. This, new evidence, supports differentiated follow-up protocols of NFPAs/NFPIs based on baseline tumuor size. However, the evidence was based on studies with methodological issues that need to be addressed in order to improve future decision making.

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PEP13.4

Long term management in aggressive thyrotropinoma

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Introduction
Thyrotropinoma is a rare pituitary tumor (<2% of pituitary adenomas) arising from PIT1-lineage cells, which expresses and secrete TSH. In most cases, the etiology is unknown but rare cases have been described to arise in context of MEN 1 syndrome. Diagnosis is often delayed by confusion with primary hyperthyroidism, which determine the tumor to be already large and invasive at the time of diagnosis. GH and prolactin cosecretion is an increased factor of aggression. We present the case of a 17-year-old patient, female, diagnosed 10 years ago with a pituitary tumor with autonomous cosecretion of TSH and GH, in which the first symptoms were weight loss, sweating, fatigue and palpitations. Early imaging described a tumor size of 20/31/37 mm, with central necrosis and parasellar extension in the bilateral cavernous sinus, including the internal carotid artery, optic chiasm, with no limit to separate from the frontal gyrus. The patient underwent multiple operations (6 times) both transsphenoidal and transfrontal, in combination with gamma knife radiosurgery but without significant tumor control. The patology exam revealed pituitary adenoma positive for TSH and GH with a Ki67 proliferation index of 20%. The patient is negative for the AIP mutation. Under treatment with progressively increased doses of octreotide acetate and cabergoline, no tumor control was obtained. Thus, in 2017, the last transsphenoidal intervention was performed, followed by local pituitary radiotherapy, with secretory active tumor residue, for which lanreotide was administered in combination with cabergoline. The patient presents a stationary clinical and biological condition in the last 2 years, with a tumor remnant of 72/54/40 mm, with retro and left parasellar extension, with TSH values after dilution slightly decreasing (1020 IU/ml), with therapeutic efficacy of GH profile. The patient underwent total thyroidectomy for voluminous goiter in 2014, which revealed multifocal, encapsulated, papillary carcinoma, pT3b G1, radioiodotreated, currently cured. The patient has corticotroph insufficiency and diabetes insipidus in replacement therapy and a history of early puberty and hyperestrogenism TSH-induced.
Discussions
Thyrotropinoma, although a rare benign tumor, is a life-threatening disease, especially when associated with hormonal cosecretion and high rate of proliferation. The consequences determined by the mass effect (convulsions, headache, oculomotor paresis, blindness), post-surgical and post-radiotherapy complications (bacterial meningitis, corticotroph insufficiency, diabetes insipidus) as well as those after long administration of somatostatin analogues, represent a challenge in the evolution and the patient's long-term prognosis.

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PEP13.5

Cushing's syndrome and chronotype

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Patients with Cushing's syndrome have a poor quality of sleep. However, little is known about their timing of sleep as regulated by the circadian clock, the so called-chronotype. Considering that patients with Cushing's syndrome lose their rhythmic circadian cortisol secretion and that corticosteroids act as synchronizer of the circadian clock in cells, aim of the study was to determine whether patients with Cushing's syndrome alter the timing of their sleep compared to a control population and, if so, whether this persists after remission of the disease. To this aim, we administered the Munich Chronotype Questionnaire (MCTQ) and collected data from 12 patients with Cushing's syndrome (mean age 45 ± 14), 58 patients in remission (mean age 48 ± 12) and 26 controls with no history of hypercortisolism (mean age 45 ± 12). The MCTQ analysis revealed that patients with Cushing's syndrome have a significantly shorter weekly sleep duration vs. patients in remission (05:10 ± 01:56 vs. 06:43 ± 01:36 P = 0.019). The Cushing's patients woke earlier on both workdays and work-free days vs. controls (P = 0.001 and P = 0.005 respectively) and vs. patients in remission (P = 0.011 and P = 0.009 respectively). The mean wake time of Cushing's patients on workdays and work-free days was at 0443 ± 0117 h and 0535 ± 0145 h respectively, while for control and remission groups sleep ended at 0618 ± 0119 h and 0604 ± 0120 h respectively on workdays and at 0721 ± 0140 h and 0717 ± 0137 h respectively on work-free days. The mid-sleep-time on free days "MSF" was earlier in patients with Cushing vs controls (P = 0.051) and vs remission (P = 0.094). The mid-sleep-time on free days corrected for the "oversleep" due to the sleep deprivation that people accumulate during the workdays (Midsleep time on Free days sleep-corrected, MSFsc) was significantly earlier in patients with Cushing vs. controls (P = 0.035). These data suggest that patients with Cushing's syndrome have an early chronotype due to wake-up time and that this alteration could recover after remission. It is noteworthy that the mean sleep-offset of the controls is almost the same compared to that of patients in remission. The MCTQ could be a new instrument in the complex and challenging diagnostic approach to Cushing's syndrome, and in the detection of recurrence. Based on our findings, we suggest that information on sleep timing should be routinely collected on patients suffering from Cushing's syndrome. This data will contribute to understanding how the homeostat and the circadian clock interact to yield consolidated sleep at a particular phase according to the individual.

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PEP13.6

Improved acromegaly patient satisfaction with oral octreotide capsules compared with injectable somatostatin receptor ligands in the MPOWERED trial

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Background
Improved patient-reported outcomes (PROs) are increasingly becoming a key treatment objective in acromegaly. Validated PROs were used to assess disease and treatment burden in the MPOWERED phase 3 trial in acromegaly, which also assessed safety and efficacy of oral octreotide capsules (OOC; MYCAPSSA®) compared to injectable SRLs (iSRLs).
Methods
Eligible patients had acromegaly diagnosis, biochemical control of acromegaly (insulin-like growth factor I <1.3 × upper limit of normal; mean integrated growth hormone, <2.5 ng/ml) and ≥6 months' iSRL treatment (octreotide or lanreotide). Eligible patients entered a 26-week Run-in phase to determine the effective OOC dose; responders at week 24 then entered a 36-week randomized controlled treatment (RCT) phase receiving OOC or iSRLs in a 3:2 ratio. The Acromegaly Treatment Satisfaction Questionnaire (Acro-TSQ) is a recently validated tool that includes 27 items in 6 domain scores for PROs in acromegaly.[1] Acro-TSQ data were collected at baseline (reflecting outcomes on iSRLs), end of Run-in (reflecting outcomes on OOC), and end of RCT (OOC or iSRLs).
Results
Of 146 enrolled patients, 92 entered RCT (OOC, N = 55; iSRLs, N = 37). Acro-TSQ scores at the end of Run-in (26 weeks' OOC treatment) were compared to baseline (iSRLs). In the 92 patients randomized, 3 of 5 Acro-TSQ domains (emotional reaction, treatment convenience, and treatment satisfaction) showed significant improvement at end of Run-in compared to baseline. Injection site interference was not assessed as no injection site reactions were observed with OOC. Other domains showed a nonstatistically significant pattern of improvement at end of Run-in when compared to baseline. Patients randomized to iSRLs in the RCT after receiving OOC in the Run-in (N = 37) reported more anxiety (RCT end, 53%; Run-in end, 29%) and frustration (RCT end, 45%; Run-in end, 34%) with iSRLs compared to OOC. Overall treatment satisfaction was higher while receiving OOC (Run-in end, 92%; after receiving iSRLs in RCT, 75%). Breakthrough symptoms were reported more frequently with iSRLs (31%) than OOC (15%) at the end of RCT.

Conclusion
Higher patient satisfaction, convenience and emotional well-being, and improved symptom control based on the newly validated Acro-TSQ PRO reporting tool were observed with OOC compared to iSRLs in patients enrolled in the MPOWERED trial.
Reference
[1]Fleseriu M, *et al*. *Pituitary*. 2020 Aug;23(4):347–358.
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PEP13.7

Hepcidin is lower in patients with acromegaly compared to healthy control subjects
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Introduction
Hepcidin, main body iron regulator protein, decreases iron concentration available for erythropoiesis. Oppositely, excessive erythropoiesis in acromegaly patients (increased GH and IGF-1), may inhibit hepcidin production. GH stimulates bone marrow, whereas IGF-1 receptors are expressed in erythrocytes. Exogenous GH administration in healthy subjects reduced hepcidin level. The role of hepcidin in iron metabolism of acromegaly patients has not been established. This prospective, cross-sectional study evaluated for the first time the hepcidin level in relation to iron parameters in newly diagnosed acromegaly patients.
Materials&Methods
We included 25 patients (16 men and 9 women) of mean age 49 ± 17 years at the time of acromegaly diagnosis, expressed by elevated IGF-1 and GH level. Control group consisted of 25 healthy subjects matched by age and sex (CS). Applied exclusion criteria were pregnancy, breastfeeding, anaemia, haemolysis, haemorrhage, hemochromatosis, inflammation, neoplasms, kidney and liver diseases, autoimmune diseases, supplementation of iron, vitamin B12, folic acid and erythropoietin or hormonal treatment. Bioacvite form, Hepcidin-25, was measured in serum by high-sensitive ELISA (DRG Instruments GmbH, Germany). GH and IGF-1 serum concentrations were analysed by Hitachi Cobas e601 chemiluminescent analyser (Roche Diagnostics). To adjust IGF-1 to age and gender, percent over the upper limit of normal rage was used in some calculations (%IGF-1). Additionally, blood and iron parameters (complete blood count, haemoglobin, haematocrit, ferritin, iron) were evaluated.
Results
The median serum hepcidin concentration was significantly lower in acromegaly patients than in CS (9.8 vs 21.3 ng/ml, $P = 0.003$). Low hepcidin level in the acromegaly group was observed in both males (13 vs 23.9, $P = 0.03$) and females (7.6 vs 21.3, $P = 0.09$). Hepcidin correlated negatively with IGF-1 ($P < 0.05$, rho = −0.44) in acromegaly patients. The positive correlation was seen between iron concentration and%IGF-1 in acromegaly male subgroup ($P < 0.05$, rho = 0.532). Ferritin level was significantly lower ($P = 0.02$) in acromegaly males (94 ng/ml), than in healthy male subgroup (184 ng/ml). Red blood cell and iron parameters were within normal ranges in all subjects.
Conclusions
Acromegaly is characterized by diminished hepcidin serum concentration without concomitant iron and complete blood count abnormalities. Presumably, somatotropin axis disturbances in the course of acromegaly, may negatively impact hepcidin, which might be a mechanism aiming to increase iron availability for cells excessive replication resulting in tissue overgrowth, seen in acromegaly. This has to be proved in further studies.
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PEP13.8

Use of antisense oligonucleotides as a therapy for Cushing's disease
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Background
Cushing's disease (CD) is caused by high levels of blood cortisol resulting from excess secretion of adrenocorticotropic hormone (ACTH) from an anterior pituitary corticotroph adenoma. Clinical manifestations include diabetes, hypertension, osteoporosis, and depression. If untreated, CD has an increased mortality of five-fold owing to cardiovascular comorbidities, stroke or raised vulnerability to infection. Currently, transsphenoidal surgery is considered the first-line treatment but remission is achieved in only 65% of cases and the relapse rate is high. Furthermore, medical treatments are often accompanied by unpleasant side-effects. Antisense therapy is a technique for suppressing gene expression at the level of translation using antisense oligonucleotides (ASOs) against the mRNA of interest.
Aims
To investigate antisense therapy as a treatment for CD by targeting ASOs against ACTH-encoding POMC mRNA thereby reducing secretion of the hormone. To transfect mouse AtT20 cells (cells that secrete high levels of ACTH) with ASOs against POMC at varying doses to determine which is the most effective at reducing ACTH secretion.
Methods
An AtT20 cell line that secretes high levels of ACTH was used as the in vitro model system. ASOs were designed to specifically target exon 3 of the POMC gene. Transfection of AtT20 cells was carried out using Lipofectamine, and secreted ACTH levels were determined by immunoassay. Statistical analysis was done using ANOVA; P values < 0.05 considered significant.
Results
ASOs that targeted POMC exon 3 (ASO-2 and ASO-3) were transfected into AtT20 cells at 10 and 100 nM. Control ASOs were ASO-1 (matched to POMC sense strand) and ASO-4 (a scrambled version of ASO-3). Experiments included untreated AtT20 cells and AtT20 cells treated with transfection reagent or ASOs alone. The results of six experiments indicated that ACTH secretion from AtT20 cells was reduced after transfection with ASO-2 and ASO-3 at 100 nM (ANOVA, $P = < 0.05$) and 10 nM (ANOVA, $P < 0.05$) when compared with untreated AtT20 cells. ASO-1 and ASO-4 had no effect on ACTH secretion by AtT20 cells (ANOVA, $P > 0.05$).
Conclusions
ASOs against POMC can reduce ACTH secretion from AtT20 cells and may be useful as a novel therapy for CD.
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COVID-19

PEP14.1

Is initial hypocalcemia related to poorer outcomes in COVID-19 patients?
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Introduction
Although most patients with COVID-19 have mild symptoms, some develop severe manifestations of the disease, leading to hospitalization and death. Previous studies reported that calcium played a central role in viral infections and replicative mechanisms of SARS-CoV. Hypocalcemia is a common finding among these patients. The aim of this study was to investigate the prevalence of hypocalcemia in a population of COVID-19 patients and to evaluate its clinical implications.
Material and Methods
Was performed a retrospective study that included adult COVID-19 patients admitted to the emergency department (ED) from March 15 to September 15, 2020, with ionized calcium (IC) measured in blood gas analysis. Demographic and clinical data were collected. Hypocalcemia was defined as calcium level below 1.18 mmol/l. Patients with comorbidities and on therapies influencing calcium metabolism were excluded. Assessed outcomes included hospitalization, length of stay and death. Statistical analysis was conducted with SPSS 3.5.0; the effect of IC on the outcomes was determined using generalized linear models; significance level considered was $\alpha = 0.05$.
Results
We included 179 patients (50.3% male; median age = 69 years); 138 patients required hospitalization. Hypocalcemia was present in 78.8% (n = 141) of the patients admitted to ER, and in 71.7% (n = 99) of the hospitalized patients. Assessing the relation between the IC value at admission in the ED and hospitalization, it was found that there is a statistically significant association between hypocalcemia and requirement of hospitalization, especially for patients with less than 60 years of age ($P = 0.033$). Among the hospitalized patients, the IC value wasn't related with the length of stay ($P = 0.24$). Of the 138 hospitalized patients, 28.2% (n = 39) died. The IC value wasn't related with death ($P = 0.29$).

Conclusion
Hypocalcemia was present in a significant number of patients in this population. Hypocalcemia on admission is significantly related with hospitalization need. This finding may have relevance in clinical practice, as the presence of hypocalcemia in an arterial blood gas analysis at admission in the ED may alert to the need of hospitalization, especially among patients below 60 years-old.

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PEP14.2

Selenium, zinc, and vitamin D supplementation affect the clinical course of COVID-19 infection in Hashimoto's thyroiditis

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Introduction
Adequate supply of zinc, selenium, and vitamin D is essential for resistance to other viral infections, immune function, and reduced inflammation. Low levels of micronutrients are associated with adverse clinical outcomes during viral infections. Vitamin D improves the physical barrier against the virus and stimulates the production of antimicrobial peptides. It can prevent cytokine storms by reducing the production of inflammatory cytokines. Selenium enhances the function of cytotoxic effector cells. Furthermore, selenium is important for maintaining T cell maturation and function, as well as for producing T cell-dependent antibodies. Our goal was to determine the effects of selenium, zinc, and vitamin D supplementation on recovery from COVID-19 in patients with pre-existing Hashimoto's thyroiditis.
Methods
A cohort observational study was conducted. Adult patients with pre-existing Hashimoto's thyroiditis admitted to the "Dr. Al-Tawil" outpatient clinic with COVID-19 from March 15 to December 31, 2020 were included. Of the 356 Hashimoto's patients who had COVID-19 infection, 270 (75.8%) took supplements and 86 (24.2%) did not.
Results
Most Hashimoto's patients (93%) who had COVID-19 were euthyroid. The study showed that Hashimoto's patients (24.2%) who did not take selenium, zinc and vitamin D increased their risk of adverse outcomes from COVID-19 infection. In those who did not take supplements, 28% required hospitalization. There were no deaths. After adjusting for age, gender, BMI, smoking status, we found an association between the absence of supplements and the risk of hospitalization, and invasive mechanical ventilation. Patients with Hashimoto's thyroiditis who had COVID-19 infection and who had previously taken supplements such as selenium, zinc, and vitamin D had milder clinical outcomes, or no symptoms compared to those who did not receive supplements who had a moderate or severe outcome (P <0.05).
Conclusions
For the treatment of people with Hashimoto's thyroiditis who become infected with COVID-19, the addition of selenium, zinc, and vitamin D3 could be beneficial. Randomized controlled trials and large population studies should be performed to evaluate these recommendations.
Keywords
COVID-19, Hashimoto thyroiditis, micronutrients, selenium, zinc, vitamin D
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PEP14.3

Multi-omics approach to analyze the molecular pato-physiology of the low T3 syndrome, observed in COVID-19 patients

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We have previously shown that Low T3 syndrome is associated with serum markers, radiologic and clinical scores of COVID-19 severity and it can be considered as a novel biomarker of the severity of the disease (Endocrine Abstracts 2020, 70 AEP1091). With the aim to analyze the mechanisms that are at the basis of this condition as well as the pathways involved, we applied an integrative approach of multi-omics data. We performed: i) *multiplex cytokine assay*, using the Bio-Plex Pro Human Cytokine 27-Plex Immunoassay and a panel of cytokines and growth factors, ii) *immune phenotyping by CyTOF analysis*, using the Maxpar Direct Immune Profiling Assay, analyzed with the Maxpar Pathsetter automated package and visualized with the high-dimensional Cauchy Enhanced Nearest-neighbor Stochastic Embedding (Cen-seð map and iii) *transcriptome analysis by NanoString*, using the nCounter PanCancer human IO 360 panel. We analyzed data from 4 patients affected by COVID-19, 2 with low FT3 serum values (≤ 1.7 pg/ml) and 2 with normal FT3 serum values (> 1.7 pg/ml and < 3.71 pg/ml). Results were compared to those obtained in 2 healthy control subjects. The study was approved by our Institutional Ethical Committee (RIF. CE 5773_2020). Cytokine assay indicated that some cytokines, namely IL-1b, IL-1ra, IL-6, IL-8, IL-10, IP-10, MCP-1 and MIP-1a, were increased in COVID-19 patients with low FT3 syndrome, some, namely IL-4, IL-7, IL-12, IL-13, Eotaxin, PDGF-bb and RANTES, were reduced and some others, namely IL-2, IL-9, IL-17A, FGF-basic, MIP-1b and TNF-a, were unchanged. CyTOF analysis indicated that Low T3 Syndrome in COVID-19 patients was associated with a reduction in CD45+, CD3+ T lymphocytes and CD19+ B lymphocytes, while there was an increase in CD3-/CD56+ NK cells as well as in CD14+ Monocytes. Finally, NanoString analysis showed a different expression pattern, with divergent allocation on the Principal Component Analysis plot and identified four genes, namely NLRP3, IFIT3, CD38 and CD79B, that were clearly deregulated in COVID-19 patients with Low T3 syndrome. NLRP3 was clearly downregulated while the IFT3, CD38 and CD79B were upregulated. In conclusion, we were able to identify, in our COVID-19 patients, specific immune and gene expression signatures associated with the occurrence of the Low T3 syndrome. Our approach allowed us to obtain insights on the mechanisms and on the pathways involved in the thyroid hormone regulation of immune response to SARS-CoV-2 infection and to identify new molecules of potential clinical utility in the management of severe COVID-19.

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PEP14.4

SARS-CoV-2: potential trigger for a cerebral venous thrombosis associated to subacute de Quervain's thyroiditis?

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Context
Thyroiditis is defined as an inflammation of the thyroid gland. There are several kinds of thyroiditis, and they can be associated with either increased, decreased, or normal thyroid function (triphasic-course). Subacute granulomatous thyroiditis, also known as subacute thyroiditis (SAT), giant-cell thyroiditis, or de Quervain thyroiditis, is a self-limited thyroiditis characterized by neck pain and thyroid dysfunction. Generally, it is preceded by an upper respiratory tract infection, which supports the viral or postviral origin (parotitis, Coxsackie, Influenza, adenovirus and echovirus). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that began in Wuhan, China, has spread rapidly worldwide and is triggering more cases of thyroid disease. Routine assessment of thyroid function during hospitalization for COVID-19 is not recommended by the clinical management guidelines. However, worsening of pre-existing thyroid dysfunction (i.e. differentiated thyroid cancer [DTC], Hashimoto thyroiditis [HT]) or *de novo* (SAT), possibly caused by infection itself, should not be missed, to avoid misleading work-up, unnecessary medicalization, and its potential negative prognostic impact.
Objectives
The aim of this case is to report a SAT related to the triggering factor for SARS-CoV-2 infection and associated with a cerebral venous thrombosis (CVT).

Methods
A 49-year-old woman who, in the context of a SARS-CoV-2 pandemic, was referred to the Emergency-Department for fever, neck pain radiated to the jaw, palpitations and sinus tachycardia (110 bpm) without structural heart disease, intense headache, predominantly occipital and right temporal, associated with nausea, vomiting and visual disturbances, occurring 7 days after a SARS-CoV-2-positive oropharyngeal swab.
Results
A CT-scan was performed, which revealed a hyperdense image of the superior longitudinal sinus which, after intravenous administration of contrast, presented a filling defect in its interior, suspecting CVT. MRI and MRA confirmed the absence of flow in the right transverse and longitudinal sinus. A congenital thrombophilia study was conducted. The *G20210A* mutation of the prothrombin gene was evidenced in heterozygosity (A/G). Thyroid-function-tests: TSH <0.005 µIU/dl, FT4 8.7 ng/dl, TPOAb 0.84 IU/ml and TSHrAb <1 IU/l. CRP 33 mg/l and ESR 52 mm. Hemogram: lymphocytic leukocytosis. Thyroid-ultrasound: hypertrophic, heterogeneous gland (multiple diffuse hypoechoic areas), without significant vascularization. The patient had no history of thyroid disease.
Conclusions
We reported a case with a clinical suspicion of SAT associated CVT potentially related to SARS-CoV-2 infection as a triggering factor (underlying hypercoagulability-state) in presence with other acquired or hereditary prothrombotic factors. Physicians should be aware of possible connections between SARS-CoV-2 with thyroid and neurologic disfunctions or additional clinical manifestations, which should be investigated by prospective studies.

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PEP14.5

Macro-TSH as a cause of refractory hypothyroidism in a covid-19 patient: description of the first case

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Context
The effects of COVID-19 on the thyroid axis remain uncertain. Recent evidence has been conflicting, with Euthyroid-Sick-Syndrome-ESS, thyrotoxicosis or suppression of thyroid-function-tests (TFTs) reported which can lead to inadequate diagnoses and treatments.
Objective
The aim of this case report is to describe, for the first time, a possible interference of macro-TSH in a patient with SARS-CoV2 and thyroid carcinoma.
Case report
56-year-old male evaluated in the Emergency-Department for fever, fatigue and cough. Chest-X-rays: lung parenchyma with multiple bilateral ground-glass areas suggestive of viral pneumonia in the context of the COVID-19 pandemic. Positive RT-PCR nasopharyngeal swab.
Patient's medical-history
Parathyroidectomy (hyperparathyroidism secondary to parathyroid adenoma) and total thyroidectomy (multinodular goiter). Fine Needle Aspiration (FNA) of dominant nodule in left-*thyroid-lobe*: negative for malignancy. Multifocal papillary microcarcinoma (right-*thyroid-lobe* [3.3 mm] and left-*thyroid-lobe* [4.0 mm]) as an incidental finding; without ablative treatment with I131. Replacement therapy: Levothyroxine 137 µg/day. During admission, TFTs were developed, and we observed that TSH levels increased compared to previous studies. The Levothyroxine was readjusted (150 µg/day). Malabsorption (parenteral nutrition) and/or incorrect dose are ruled out. TFTs can seem discordant/incongruent with the clinical picture, so we decided to develop a study of possible interference.

Results*	Sample-1	Sample-2
TSH (0.5–4.0 µU/ml)	0.33	40.03
FT4 (0.8–2.0 ng/dl)	0.66	0.83
FT3 (1.7–4.0 pg/ml)	1.43	1.81

Conclusion and discussion
We identified a possible interference of non-functional macro-TSH complexes (mostly TSH-IgG) in the determination of thyrotropin in patients with underlying thyroid pathology and infection by SARS-CoV2 performed on immunoassay platforms. *Interference-detection* and mitigation methods: serial dilutions and precipitation with polyethylene-glycol-PEG (currently the most widely used technique to detect macro-TSH) vs. gel-filtration-chromatography (expensive and not available most Hospitals). Heterophilic-antibodies (HAMA) and Rheumatoid-Factor: negatives. An exceptional finding, not described to date and, on many occasions, forgotten or underestimated, since can lead to incorrect diagnoses and treatments. Thyroid function should not be assessed in seriously ill patients unless there is a thyroid dysfunction. The thyroid dysfunction caused in COVID-19 presents a dynamic evolution with a tendency towards progressive recovery. It is essential to take into account this fact that allows an adequate quality of care and patient safety in the context of COVID-19. Screening macro-TSH should be developed before hormone replacement therapy by discordant results.

Patient-Sample-2	Results
TSH	40.036
Post-PEG (monomeric-TSH) %	15.008 37.5%
Post-PEG (control-sample) %	 88.5%
Dilutions 1:2 1:5 1:10 Control-sample 1:2	 41.525 43.423 39.009 21.60 43.20
TSH Heterophilic-blocking-reagent (HBR)	47.70
Other analyzer** TSH (0.5–4.8 µU/ml) FT4 (0.9–1.76 ng/dl)	 10.54 1.13
Glomerular-Filtration-Rate-eGFR	>90

*Architect-i4000SR; **ADVIA-CentaurXP

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PEP14.6

Higher incidence of COVID-19 in patients with adrenal insufficiency compared with background statistics

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Introduction
Worldwide, 100 million people have been diagnosed with COVID-19. Patients with adrenal insufficiency (AI) are assumed, on the basis of expert opinion, to be at higher risk of infection.
Aim
To determine the patient reported incidence and potential risk factors of infection with COVID-19, for patients diagnosed with AI.
Method
A 42 item questionnaire (inclusive of AI diagnosis, COVID-19 symptoms, testing and concomitant diseases in 2020) was vetted by a panel of endocrine specialists and patients with AI from Patient Advocacy groups worldwide and distributed via associated websites and social media. Participation was voluntary and anonymized. Descriptive and crosstabs (Chi-squared) analysis was performed using SPSS27.
Results
Completed surveys included $N = 1292$ participants from 43 countries. 40/494 patients (screened for COVID-19) tested positive (31 female (78%): mean age 39.9 years (range 1.0–68.0). Highest incidence $N = 19$ (47.5%) was found in those 40–60 years, with a mean duration of AI of 12.7 years (range 0.17–42.0) years. Reported ethnic composition Caucasian + European 35 (87.5%), Hispanic in 3 (7.5%), African-American in 1 (2.5%) and in 1(2.5%) who did not declare this. The positive tests largely correlated with those with the greatest number of participants: UK (35%), USA (35%) and Brazil (17.5%), whereas, the total positive tests from the combination of Finland, Sweden, Estonia, Australia and Netherlands represented (12.5%) patients. COVID-19 positive patients were found to have pre-existing cardiovascular disease (16.6%) and

pulmonary disease (27.7%). Of the COVID-19 positive cohort, participants with congenital adrenal hyperplasia (CAH) reported a significantly higher incidence of COVID-19 (12.9%, $P = 0.001$) compared with other diagnoses.
Discussion
At the time of the survey, 100 million patients worldwide were diagnosed with COVID-19, whereas 1292 participants with adrenal insufficiency completed the questionnaire, representing 12.9% of the expected numbers of respondents, based on an average prevalence of adrenal insufficiency of 100 per million. Of those who completed the questionnaire, 494 participants had been screened for COVID-19 and only 40 (8%) who tested positive, representing an annual incidence of 3.1%, which is slightly higher than the worldwide incidence of COVID19 of 1.25%.
Conclusion
Although this survey is biased by self-election, we detected a slightly higher than background incidence of COVID-19 infection for patient with AI. This may be concerning as patients with adrenal insufficiency are potentially at greater risk from respiratory illness due to impaired natural killer cell function. In particular, patients with CAH may be at especially greater risk for COVID-19.

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PEP14.7

Psychological distress in patients with hypocortisolism during mass quarantine for Covid-19 epidemic in Italy

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Beyond the huge impact on physical health, coronavirus disease-19 (COVID-19) epidemic represents a significant psychological stressor, causing effects on mental health. The psychological distress of the epidemic and consequent mass quarantine on patients with hypocortisolism, particularly frail and vulnerable to infections and stress, is unknown. The current multicentre, web-survey-based, case-control study evaluated the psychological impact of COVID-19 quarantine in a large cohort of patients with hypocortisolism. The study was performed on 478 patients with hypocortisolism adequately treated with glucocorticoids, of which 363 with adrenal insufficiency (AI)(215F, 148M, 47.61 ± 12.44 years) and 115 with congenital adrenal hyperplasia (CAH)(75F, 40M, 38.84 ± 13.23 years), matched with 478 Italian healthy controls. Major disabilities, ongoing/recent hospitalization, psychiatric illnesses/medications, COVID-19 infection/suspicion represented exclusion criteria. All patients with hypocortisolism were informed on required glucocorticoid dose adjustments in case of intercurrent illnesses and stress conditions. AddiQoL, General Anxiety Disorder-7 (GAD-7), Perceived Stress Scale (PSS), Patient Health Questionnaire-9 (PHQ-9), Specific Psychotic Experiences (SPEQ), Ego-Resiliency Revised Scale (ER89-R), and 18-items Psychological Well-Being (PWB) questionnaires were telematically and anonymously administered to participants during the last 3-weeks of quarantine, lasted 2 months in Italy; higher scores of GAD-7, PSS, PHQ-9 and SPEQ indicated higher anxiety, perceived stress, depression, and psychosis, whereas lower scores in AddiQoL, ER89-R and PWB indicated lower QoL, resiliency and psychological well-being. In the whole cohort of patients, GAD-7 ($P < 0.001$), PHQ-9 ($P < 0.001$) and PWB-environmental mastery ($P = 0.043$) scores appeared significantly higher, whereas ER89-R related to openness to life experience (ER89-R-OL) ($P = 0.003$) and PWB-self-acceptance ($P = 0.004$) scores significantly lower in patients than in controls. AI patients reported significantly lower AddiQoL ($P < 0.001$) scores than CAH patients, with significantly higher PSS ($P = 0.022$) scores in AI than CAH females, and higher ER89-R-OL ($P = 0.035$) scores in AI than CAH males. During quarantine, 64 (13.4%) patients, 53 (14.6%) AI and 11 (9.6%) CAH patients required glucocorticoid dose increase, with females reporting a significantly higher prevalence of glucocorticoid dose increase than males (16.9% vs 8%, $P = 0.0057$). In conclusion, patients with hypocortisolism suffered increased anxiety and depression, associated with a dissatisfaction feeling of self and a reduced resiliency, although reporting a higher sense of mastery in managing the environment, being able to choose contexts suitable to personal needs. Moreover, AI patients reported a worst QoL than CAH patients, with higher perceived stress in females, and higher resiliency in males. Therefore, an empowerment of psychological counseling for these vulnerable patients during COVID-19 should be considered by national health-care services.

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PEP14.8

Simulation via Instant Messaging – Birmingham Advance (SIMBA) model helps improve clinicians' confidence to manage various endocrine conditions during the COVID-19 pandemic

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Introduction
In response to the COVID-19 pandemic, delivery of medical education has transitioned from predominantly in-person teaching to virtual platforms. Simulation-based learning is a successful teaching modality to develop clinicians' knowledge and skill, while safeguarding patients. Simulation has traditionally been performed via face-to-face role play, however many of its principles can be adapted for remote use. We explored the effectiveness of the Simulation via Instant Messaging - Birmingham Advance (SIMBA) model as a method of delivering virtual, simulation-based medical education during the COVID-19 pandemic.
Methods
Six SIMBA sessions were conducted between July 2019 and October 2020, focussing on different topics in the field of endocrinology (namely adrenal, pituitary ($n = 2$), thyroid and diabetes ($n = 2$)). In each session, transcripts based on real-life anonymised data were used to simulate clinical cases. During simulation, participants interacted with moderators (trained medical students and junior doctors) through WhatsApp and assessed patients as they would in real life, formulating a diagnosis and management plan. Simulation

was followed by an interactive discussion with experts in the relevant field, delivered by Zoom. Wilcoxon Signed Rank test was used to investigate the effect of SIMBA on participants' self-reported confidence in approaching clinical scenarios, measured using Likert scale. Acceptance and relevance of the simulated cases were also analysed.
Results
236 participants completed pre- and post-SIMBA evaluation forms and were included in analysis. Self-reported confidence in participants' approach to the simulated cases was significantly improved following SIMBA: [overall (n = 236) (P <0.001); pituitary 1.0 (n = 24) (P <0.001), diabetes 1.0 (n = 17) (P <0.001), adrenal (n = 33) (P <0.001), thyroid (n = 37) (P <0.001), pituitary 2.0 (n = 79) (P <0.001), diabetes 2.0 (n = 46) (P <0.001)]. 94.5% (n = 207/219) strongly agreed/agreed SIMBA sessions accommodated their personal learning style and 90.9% (n = 199/219) strongly agreed/agreed the sessions were engaging. 96.4% (n = 188/195) and 93.8% (n = 183/195) strongly agreed/agreed that the content was impactful at both a personal and professional level respectively. Participants felt that SIMBA improved their clinical competencies in patient care [57.4% (n = 112/95)], professionalism [32.3% (n = 63/195)], patient management [86.2% (n = 168/195)], systems-based practice [45.6% (n = 89/195)], practice-based learning [71.8% (n = 140/195)] and communication [25.1% (n = 49/195)].
Conclusion
SIMBA is an effective virtual teaching model which improves clinicians' confidence in managing various conditions in endocrinology. Participants felt the simulated cases were relevant to their clinical practice and suited their learning style. Further research is needed to explore whether this increased confidence level translates to better real-life performance.

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Late Breaking

PEP15.1

Diabetic euglycemic ketoacidosis in newly diagnosed type 1 diabetes mellitus during A ketogenic diet

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Background
Diabetic ketoacidosis (DKA) is one of the most serious complications of diabetes. It is characterised by the triad of hyperglycemia (blood sugar >250 mg/dl), ketosis and metabolic acidosis (arterial pH <7.3 and serum bicarbonate <18 mEq/l). Rarely these patients can present with blood glucose (BG) levels of less than 200 mg/dl, which is defined as euglycemic DKA.
Case
A 22-year-old female patient applied to the primary care physician with tingling and numbness in the hands. Fasting blood glucose was 205 mg/dl with normal renal and liver function tests in the first laboratory evaluation and then suggested to apply to the endocrinology clinic. After learning about high blood sugar level, she avoided foods containing carbohydrates and followed a ketogenic diet. She is 160 cm tall and 45 kg heavy. The patient referred to the endocrinology clinic with nausea two weeks later. Her plasma glucose level was 86 mg/dl with an HbA1C of%10.3. HbA1C measurement was repeated and confirmed to be high. She was diagnosed with diabetes. Her laboratory assessments revealed an elevated anion gap of 20.9, increased urinary and plasma ketones, and metabolic acidosis. Low hCG values excluded pregnancy The diagnosis of euglycemic DKA was made, and treatment with intravenous fluids and insulin was initiated, then the patient improved.The C-peptide level was 0.42 μg/l (n:0.81–3.85 low normal). Anti-glutamic acid decarboxylase and anti-insulin antibodies were negative, while the anti-islet cell antibody was positive. There was no one with diabetes in her family. She was screened for liver diseases and glycogen storage diseases, and no pathological condition was detected.
Conclusion
We present a type 1 diabetic patient diagnosed with euglycemic DKA. The possible aetiology of euglycemic DKA includes decreased caloric intake, heavy alcohol consumption, the recent use of sodium-glucose cotransporter 2 inhibitors, chronic liver disease and glycogen storage disorders. DKA in pregnancy has also been reported to present with euglycemia. Our patient had euglycemic DKA triggered by the ketogenic diet. Euglycemic DKA can be missed or inadequately treated in patients presenting with euglycemia on initial presentation. Recognising this condition in newly diagnosed patients can also be a challenge for physicians.

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PEP15.2

Monocarboxylate transporter 8 deficiency leads to autophagy-induced persistent cathepsin-mediated thyroglobulin processing triggered by insufficient L-type amino acid transporter 2 functionality

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The thyroid gland functions in supplying thyroid hormones (TH) to the body periphery, which is enabled by cathepsin-mediated thyroglobulin proteolysis and TH translocation across membranes by the Mct8, Mct10, and Lat2 transporters. Previously, we showed that cathepsin K-deficient mice feature normal thyroid phenotypes which is, in part, due to the functional compensation through cathepsin L upregulation that is independent of the classical hypothalamus–pituitary–thyroid axis. These results imply that intrathyroidal TH-sensing mechanisms exist. Since cathepsin K deficiency correlated with increased Mct8 protein amounts, we aimed to understand if TH transporters are part of such thyroid auto-regulatory mechanisms. Therefore, in a murine model, we analyzed phenotypic differences in thyroid function arising from combined cathepsin K and TH transporter deficiencies, i.e. in *Ctsk*$^{-/-}$/*Mct10*$^{-/-}$, *Ctsk*$^{-/-}$/*Mct8*$^{-/y}$, and *Ctsk*$^{-/-}$/*Mct8*$^{-/y}$/*Mct10*$^{-/-}$. Our results show that, albeit impaired TH export, *Ctsk*$^{-/-}$/*Mct8*$^{-/y}$/Mct10$^{-/-}$ mice feature thyrotoxic stress-triggered autophagy induction, which results in persistent thyroglobulin proteolysis due to enhanced lysosomal biogenesis. Furthermore, we aimed to elucidate what triggers autophagy in *Ctsk*$^{-/-}$/*Mct8*$^{-/y}$/*Mct10*$^{-/-}$ thyroid glands. Lat2 has been implicated as a sensor of amino acids in kidney and muscle, where it is believed to activate mTORC1, a negative regulator of autophagy. Since TH as iodothyronines are amino acid derivatives, we propose that Lat2 might be involved in sensing of intrathyroidal cytosolic TH states in *Ctsk*$^{-/-}$/*Mct8*$^{-/y}$/*Mct10*$^{-/-}$ mice, thereby inducing autophagy when TH export is lacking. Although no significant changes were observed in Lat2 mRNA levels in the triple-deficient thyroids in comparison to wild-type controls, Lat2 immunoblotting showed significantly reduced protein amounts. In addition, immunofluorescence staining demonstrated decreased Lat2-specific signals, while Lat2 sub-cellular localization in thyrocytes of *Ctsk*$^{-/-}$/*Mct8*$^{-/y}$/*Mct10*$^{-/-}$ mice remained unaltered, suggesting a direct link between diminished Lat2 and autophagy induction in *Ctsk*$^{-/-}$/*Mct8*$^{-/y}$/*Mct10*$^{-/-}$ mice. To support this hypothesis, we investigated autophagy-mediated lysosomal biogenesis in Lat2 deficiency. Indeed, Lat2 deficiency was accompanied by enhanced cathepsin levels and activity, increased autophagosome formation, and enhanced autophagic flux. Collectively, we conclude that insufficient Lat2 functionality in triple-deficient mice leads to a reduction in intrathyroidal TH sensing capabilities, thereby failing to activate mTORC1, and consequently triggering autophagy. In addition, autophagy induction results in the biosynthesis of lysosomal proteins which could explain the enhanced cathepsin-mediated thyroglobulin degradation and Lat2 protein instability in *Ctsk*$^{-/-}$/*Mct8*$^{-/y}$/*Mct10*$^{-/-}$ mice.

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PEP15.3

TGF-β increase caspase activation and migration in typical bronchial carcinoids

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Introduction
Typical bronchial carcinoids (TBC) are rare well-differentiated neuroendocrine neoplasms (NEN) of the lung whose management can still be very challenging. In fact, the gold-standard treatment for TBC is total resection of the primary tumour; however, in case of metastatic disease adjuvant therapy with the mTOR inhibitor everolimus (eve) might

be recommended. Unfortunately, prognosis may be very poor in cases showing moderate response rates to eve, since resistance to treatment is not uncommon. Previous studies have reported TGF-β's ability to activate mTOR pathway and induce epithelial to mesenchymal transition (EMT) in cervical cancer. Moreover, preliminary results from our lab showed an overexpression of TGF-β/SMAD signalling and caspase activation in TBC cells, as well as an interplay between this pathway with the PI3K/mTOR pathway.
Aims
The present study focused on understanding how TGF-β signalling could interfere with TBC pathophysiology, which might possibly explain the reduced sensibility of these neoplasms to eve.
Materials and Methods
In vitro functional assays such as cell viability, migration, and caspase 3/7 activation were performed in the TBC cell line NCI-H727. Cell viability and caspase activation were performed by using specific kits, whereas migration was assessed through wound healing assay. Cells were treated with the mTOR inhibitor eve and TGF-β alone or combined with IGF-1 and paclitaxel (pac), considered as positive and negative controls, respectively.
Results
TGF-β or eve treatment alone had no effect on cell viability, whereas their combination reduced it by >10% vs. control (P = 0.009). TGF-β increased caspase activation by 14% vs. control (P = 0.04) and this effect was not accompanied by apoptosis induction. TGF-β also induced migration by 40% vs. control, whereas combined treatment with eve abrogated this effect by reducing it by 27% vs. control (P <0.0001). Moreover, combined treatment of TGF-β and pac significantly increased migration by >50% vs. pac treatment alone (P = 0.03), indicating that TGF-β was responsible for the observed increased migration in these cells, whereas combination with IGF-1 had no further effect vs. IGF-1 treatment alone.
Conclusions
TGF-β-induced caspase activation and cell migration could explain EMT and associated malignancy features found in many TBC. Given the interplay between TGF-β and mTOR, inhibition of both pathways could represent an alternative for the treatment of these NEN, which are orphans of an effective therapeutic algorithm.

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PEP15.4

Selection of the most effective genetic tests for the diabetes mellitus risk prediction in Belarus

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Introduction and background
According to world diabetes-focused organizations (EASD and IDF) the number of patients with type 2 diabetes mellitus (T2DM) and obesity is increasing tremendously all over the world. The FTO gene (Fat mass and obesity-associated gene) was noticed during GWAS-study at 2007, when it's multiple polymorphic variants were detected, many of which were associated with obesity and T2DM. Significant differences in allele prevalence in between populations were observed. So minor allele rs9939609 polymorphic variant is found in 34–44% of European, 11–20% of Asian and 17% of Latin-American population. There are no similar data on Belarusian population.
Aims
The aim of the study was the detection of the most relevant genetic marker for the prediction T2DM.
Methods
We have formed 2 groups of patients to determine FTO allele frequency and it's association with T2DM. 1st group – 116 patients with T2DM (72 female, 44 male), with an age of 51.2±8.2 years, and BMI 32.6±7.4 kg/m^2. 2nd – Control-group (151 female, 96 male) with an age of 34.9±9.5 years, BMI 24.1±3.9 kg/m^2. Peripheral blood lymphocytes were used for DNA extraction using Nucleosorb-A ("Primetech", Belarus) kits. Genotyping of 13 FTO-gene polymorphic variants (rs10852521, rs11075990, rs1121980, rs1421085, rs1477196, rs17817449, rs3751812, rs4783819, rs7206790, rs8047395, rs9939609, rs9940128, rs9941349)was made using TaqMan® probes (Applied Biosystems, USA).
Results
The minor allele rs9939609 prevalence was 41.3% in or study, that corresponds with European population data. The strongest association with the T2DM was detected for rs9941349 (P = 0.007) plymorphysm. For minor T/T variant carriers odds ratio (OR) was 2.74, and for heterozygos – OR = 1.96. Also highly associated with T2DM were G/G rs11075990 (OR = 2.36), A/A rs1121980 (OR = 2.35), T/T rs3751812 (OR = 2.26), A/A rs9939609 (OR = 2.49), C/C rs1421085 (OR = 2.09) and A/A rs9940128 (OR = 2.19). There were no other significant associations.
Discussion
The analysis of linkage disequilibrium block showed high linkage of rs11075990, rs1121980, rs1421085, rs17817449, rs3751812, rs9939609, rs9940128, rs9941349 polymorphisms (P <0.001, r2 0.92–0.97). These variants form 2 highly prevalent haplotypes – A/G/T/T/G/T/G/C (51.4%) č G/A/C/G/T/A/A/T (42.9%), other variants do not exceed 2%, what allows genetic testing only by rs9941349 polymorphism.
Conclusion
Stable haplotype prevalence allows effective prediction of the FTO-gene polymorphism through detection of rs9941349 variant, what is highly predictive for T2DM estimation.

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PEP15.5

Pheochromocytoma secreting IL-6; an atypical presentation

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Pheochromocytoma (PCC) is a rare tumor that arises from the adrenal medulla, usually presents with headache, sweating and palpitations due to excessive catecholamine release. However, PCC may secrete neuropeptides, hormones and cytokines, such as interleukin-6 (IL-6)) resulting in unusual clinical manifestations. A 48-year-old woman with a previous history of type 1 neurofibromatosis (NF1) and hypertension was referred to discarded PCC. Laboratory tests revealed leukocytosis and thrombocytosis with increased erythrosedimentation rate (ESR) and elevated urinary metanephrine (table 1). Abdominal CT revealed a left bilobed adrenal tumor 33 × 32 mm in the largest dimension (40 HU). Oncohematological and myelodysplastic disease were discarded (mutation JAK2- V617F, trasloc 9-22 and bcr-abl were negative). She had no fever but cytokines secretion was suspected and IL-6 was elevated (table1). Uneventful laparoscopic adrenal surgery was performed. After surgery all biochemical parameters were within the reference range and blood pressure normalization was achieved.
Discussion
It has been previously described that PCC may secrete cytokines with systemic inflammatory response syndrome (SIRS). IL-6 is a multifunctional molecule that plays an important role in hematopoiesis and immune and inflammatory responses. IL-6 over-production can be either ascribed directly to the tumor or indirectly accounted for tumoral production as a consequence of the high levels of circulating catecholamines. Symptoms relief, inflammatory marker and hematologic parameters normalization following the decrease in IL-6 level after tumor resection strongly supports the role of IL- 6 in the unusual presentation of our case. Our patient had mild hypertension despite high catecholamine levels and could be explained by the increased nitric oxide synthesis due to IL–6 activity, which might have led to vasodilation.
Conclusion
PCC may be a cause of paraneoplastic syndrome with marked increase in the levels of inflammatory markers. IL-6 appears to be the primary mediator. PCC has to be considered in the vast differential diagnosis of oncohematological and myelodysplastic syndromes when common causes are ruled out.

Table 1	At diagnosis	After surgery	Reference range
White blood cells account (WBC)	20530	9300	4000–10 000
Neutrophilia	81%	60%	40–65
Platelets(uL)	635000	339000	150 000–400 000
ESR (mm/h)	50	15	0–22
Urinary Metanephrine (ug/24hs)	673	67	30–180
Urinary Normetanephrine (ug/24hs)	119	202	< 451
Urinary Adrenaline (ug/24hs)	53	<2	< 20
Urinary Noradrenaline (ug/24hs)	265	34	< 80
IL-6 (pg/ml)	11.4	<2	LSN 5.9

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PEP15.6

Association between diabetic retinopathy, telomere length and serum proteasome concentration in type 1 diabetes: cross-sectional study in Latvia and Lithuania

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Background
Diabetic retinopathy is the leading cause of blindness in working-age adults in developed world. Derangements of ubiquitine-proteasome system and telomere length have been associated with microangiopathy in diabetes. Until now, limited data are available on above markers in diabetic retinopathy in type 1 diabetes (T1D).
Aim
The aim of this work was to compare serum proteasome concentration and telomere length in patients with different stages of diabetic retinopathy and T1D in Latvia and Lithuania.
Methods
186 Latvian and 120 Lithuanian patients with type 1 diabetes were enrolled. Patients were stratified according to severity of diabetic retinopathy. Group of severe retinopathy included patients with proliferative retinopathy and status post laser-photocoagulation. "No retinopathy" group included patients with nonproliferative/no retinopathy. Proteasome concentration was measured by ELISA. Telomeres were evaluated by real-time qPCR with a relative telomere length method using a reference gene and expressed as (□CT). Statistical analysis was performed in programme R. Wilcoxon rank sum test followed by Ancova on ranks was used to compare the locations of biomarkers distributions between the groups of retinopathy and to adjust for covariates (diabetes duration, waist/hip ratio, serum triglycerides, estimated glomerular filtration rate (eGFR), country).
Results
Subjects in the group of severe retinopathy (n = 119) compared to "no retinopathy" (n = 187) were statistically significantly older (44 (35–53.5) vs. 31 (24.5–44) years), had longer duration of diabetes (28 (22–36) vs. 16 (12–21.5) years), higher serum creatinine concentration and lower estimated glomerular filtration rate, higher serum triglyceride and waist–hip ratio, as well as higher prevalence of other complications of diabetes. We observed lower serum proteasome concentration in the group of severe retinopathy (130 (90–210) ng/ml, vs. "no retinopathy" 150 (100–240) ng/ml), difference was significant after adjustment for covariates, P = 0.024. Median telomere length was higher in the group of severe retinopathy (ΔCT 0.21 (0.12–0.28 vs "no retinopathy" 0.18 (0.1–0.28), difference was significant after adjustment for covariates, P = 0.036.
Conclusion
In this study, we demonstrated differences in proteasome concentration and telomere length between patients with different stages of diabetic retinopathy.
Acknowledgements
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PEP15.7

Adherence to levothyroxine treatment and factors related with adherence in hypothyroid patients

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Objectives
Adherence to treatment is one of the most important parameters that affect the success of the treatment in hypothyroidism. We aimed to evaluate the use and adherence to treatment and determine the factors that are related to adherence in patients on levothyroxine therapy.
Materials and Methods
Patients older than 18 years old and using levothyroxine for hypothyroidism were recruited. Demographical, sociocultural and clinical statuses of patients were determined. The practices of using levothyroxine and compliance were evaluated through a questionnaire. Thyroid hormones and antibodies were obtained from medical records. Those who answered the frequency of not using/skipping the drug as never/rarely, sometimes and frequently/often were grouped as high, medium and low adherence, respectively. Data of high, medium and low adherence patients were compared.
Results
A total of 335 patients – 282 (84.18%) female and 53 (15.82%) – male were included. Mean age was 47.36±12.50. 330 (98.50%) patients were taking levothyroxine in the morning and 332 (99.10%) were taking fast. The period between the drug and meal was 15 min in 66 (19.88%), 30 min in 170 (51.20%), 45 min in 25 (7.53%), at least 1 h in 63 (18.98%) patients, while 8 (%2.41) patients were taking it just before or during the meal. Among 145 (45.03%) patients who use a medication that may interfere with the absorption of levothyroxine, 66.66% were using it in less than 2 h of levothyroxine. There were 218 (65.08%) high, 98 (29.25%) medium and 19 (5.67%) low adherence patients. Drug adherence was not associated with sex, age, marrital and working status, smoking, alcohol use, the cause and duration of hypothyroidism, presence of comorbid disease and thyroid hormones. The rate of patients graduated from primary school was higher in low adherence and rate of patients graduated from university was higher in high adherence groups (P = 0.008). Familial history of thyroid disease was associated with high adherence (P = 0.013).
Conclusion
We showed that drug adherence is medium or low in 34.92% of hypothyroid patients, and education level and familial thyroid disease were related with high adherence. Although majority of patients take levothyroxine at fast, 22.29% eat less than 30 min after taking the drug. In addition, a considerable amount of patients using medications that inhibits the absorption of levothyroxine did not leave required time between two medications. For effective treatment of hypothyroidism, it is important to increase drug compliance and inform patients about hypothyroidism and levothyroxine.

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PEP15.8

Aggressive follicular thyroid carcinoma in a patient with Carney complex

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Introduction
Carney Complex is a rare syndrome characterized by lentiginosis cutis and/or blue nevi, multiple endocrine neoplasia and non-endocrine tumors (cutaneous, mucosal, mammary or cardiac myxomata, bone osteochondromyxoma, psammomatous melanotic schwannoma, multiple ovarian cysts, multiple mammary ductal adenoma). Most cases are familiar, with autosomal dominant heredity and penetrance close to 100%. It is caused by a variety of mutations that activate the PKA (Protein Kinase A) pathway, inactivating mutations of the PRKAR1A gene being the most frequent. The endocrine manifestations may include PPNAD (primary pigmented nodular adrenocortical disease) Cushing syndrome, acromegaly (rarely gigantism), hyperthyroidism and LCCSCT (large cell calcifying Sertoli cell tumors). Most of the Carney Complex-associated neoplasms are benign, but in a few patients a particularly aggressive variant of follicular thyroid carcinoma has been described. Malignant tumors such as ovarian, pancreatic, gastric or hepatic carcinoma are also associated with the Carney Complex.

Methods
Review of the patient's Clinical Record and of the relevant literature.
Clinical Case
A 56 year old man of black African descent was referred to the Endocrinology Clinic due to a cervical mass in the context of Carney Complex. No relatives of his have been diagnosed. Since his adolescence he had intense facial lentiginosis and scattered blue nevi. The diagnostic workup revealed bilateral nodular adrenocortical disease, small myxomata in both atria, with normal pituitary, adrenal and thyroid function and normal glucose tolerance. The atrial myxomata were resected without complications and the cardiac function is normal. The thyroid ultrasonography revealed multinodular goiter with dominant nodules measuring 3.5 cm (craniocaudal) in the left thyroid lobe adjacent to the isthmus, and 2.7 cm in the right lobe, with multiple cervical adenopathies. Ultrasound guided FNAC was performed, with both dominant nodules and 4/7 adenopathies positive for non-oncocytic follicular thyroid carcinoma (Bethesda IV, ATA stage IV-A, T2(m)N1bM0), Total thyroidectomy with radical cervical lymphadenectomy was performed, but plasma thyroglobulin was 97 ng/ml with negative antithyroglobulin antibodies. A rhTSH stimulated radioiodine scan was performed and the patient received 100 mCi of ^{131}I but the response was poor and plasma thyroglobulin remained high (78 ng/ml). A PET-CT scan did not reveal abnormal activity beyond the cervical region. The patient has been referred to Oncology for kinase inhibitor therapy.
Conclusions
Although most of the tumors associated with Carney Complex are benign, the existence of malignant tumors of diverse origins must be ruled out. An aggressive variant of follicular thyroid carcinoma is a particularly ominous possibility.

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Audio ePoster Presentations

Adrenal and Cardiovascular Endocrinology

AEP1

Adrenocortical carcinoma treatment in the Netherlands: An analysis from the Netherlands Cancer Registry from 2014 to 2019

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Background
Adrenocortical carcinoma (ACC) is a rare disease with often poor prognosis. Previous research has shown that surgery in a Dutch Adrenal Network (DAN) center increases the chance of survival. We aim to explore the determinants and survival of patients with ACC recently treated in the Netherlands both within and outside DAN centers.
Methods
We analyzed retrospectively collected data from 172 adult patients with newly diagnosed ACC and 97 patients with recurrence or new metastases, registered between 2014 and 2019 in the Netherlands Cancer Registry. Differences in survival were analyzed with cox-regression analysis.
Results
More than half of the new cases presented with advance disease (25.7% stage III, 34.6% stage IV) and the median survival was 29 months. The majority of treatments occurred within a DAN center (87.2% of surgery, compared to 50% between 1999 and 2009; and 94.5% of medical treatment). There were no differences in patient characteristics between the centers apart from a relatively high number of patients with stage IV disease outside DAN centers (47.2% vs. 28.7%). Adrenal resection and mitotane therapy both resulted in a significant survival benefit (resection HR 0.29, CI95%[0.17–0.49]; mitotane HR 0.61, CI95%[0.37–0.99], corrected for stage). Still, a remarkable proportion of patients with advanced disease received no mitotane treatment (23.8% DAN, 89.5% non-DAN, 39.0% total). Due to the small number of patients treated outside DAN centers, survival benefits could not be tested.
Conclusions
Centralization of ACC care in the Netherlands has improved since the previous report, but a further improvement in centralization of surgery can be made. Adrenal resection and mitotane treatment remain the main form of treatment, with a clear survival benefit. Further research is necessary to determine why mitotane treatment is withheld a large proportion of patients with advance disease.

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AEP2

Characteristics of pheochromocytomas/paragangliomas in Flemish population

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Introduction
Pheochromocytomas (PHEO) and paragangliomas (PGL) are rare neuroendocrine tumors of the autonomic nervous system, originating from neural crest. Despite the same embryological origin, there are some differences between them.
Aim
We searched for differences in method of discovery, clinical and biochemical phenotype, of sporadic vs hereditary PHEO/PGL in a cohort of Flemish patients.
Material and methods
A retrospective analysis of electronic medical records of sixty-seven consecutively registered patients diagnosed or treated with hereditary or sporadic PHEO/PGL in a tertiary care center from Belgium between 2002–2020, was performed. Patients were divided according to anatomic location (PHEO vs. PGL) and according to presenting with sporadic or hereditary PHEO/PGL.
Results
We identified 38 women and 29 men, aged 50 ± 19 years (range 13–85). At diagnosis, 42(63%) had PHEO, 25(37%) had PGL. Patients with PHEO presented more frequently with sporadic than hereditary disease [34 (81%) vs. 8 (19%)] than patients with PGL [9(36%) vs.16 (64%)] respectively. Mean age at diagnosis was significantly higher in PHEO patients (55 ± 17 years in PHEO vs.40 ± 18 years in PGL, $p = 0.001$). The diagnosis was done either due to PHEO/PGL related symptoms [PHEO:21(50%);PGL:13(52%)], discovered incidentally (27) or due to genetic screening (6) [PHEO: 21(50%); PGL: 12(48%)]. In our patient cohort, following CV events were known at diagnosis: myocardial infarction(MI)[PHEO: 8(19%); PGL:1(4%)], Takotsubo cardiomyopathy [PHEO:2; PGL:2], arrhythmias [PHEO:3; PGL:0] and stroke [PHEO:1; PGL:0]. All PHEO and about two-thirds of PGL were hormonally functional. Metanephrine levels were higher in PHEOs than in PGLs ($P < 0.02$). Tumor diameter was 44 (17–200) mm in PHEO vs. 30 (11–110) mm in PGL. Metanephrine levels were correlated with tumor diameter in PHEOs vs. PGLs. ($P < 0.02$).An interesting aspect is related by the differences in tumor localization of sporadic vs hereditary PPGLs. 61.7 % of sporadic PHEOs and 77.7% of sporadic PGLs and had right lateralization while 62.5% of hereditary PHEOs and 50% of hereditary PGLs had left lateralization. PGLs were mostly HNPGLs (12), followed by abdominal(16), pelvic(16) and thoracic(1) PGLs.
Conclusion
PGLs have a higher hereditary predisposition, therefore are diagnosed at younger age than PHEOs. Although both PHEO and PGL in about half of cases were diagnosed due to related symptoms, patients with PHEO more often presented with cardiovascular co-morbidities which is presumably related to their hormonal activity.

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AEP3

Effective metyrapon treatment of a case of neonatal cushing syndrome of unknown origin

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Neonatal Cushing syndrome (CS) is a rather rare disease. The majority of these few cases are of ACTH dependent origin or caused by a unilateral adrenal tumour (carcinoma or adenoma), however ACTH independent bilateral hyperplasias stand for only a few percent of all cases. The management of neonatal CS depends on the underlying cause – if found in time - of the disease. In the past the survival rate of children with CS was low, new and renewed medical attempts have improved this over the last decades. Our patient was born in March 2020 after an apparently uneventful pregnancy on 35. gw with 1850 g birthweight. At 4 weeks an excessive weight gain was recognized, and the first laboratory findings indicated severe hypercalcaemia (3,27 mmol/l), extremely high cortisol (1777,7 nmol/l) and suppressed ACTH level. These findings altogether indicated an ACTH-independent form of neonatal CS. Abdominal MRI revealed a bilateral micronodular hyperplasia of the adrenal gland. As his clinical condition was quite unstable due to consequences of hypercortisolism present (severe hypercalcaemia, hyperglycaemia, hypertension, ventricular hypertrophy, hepatopathy, muscle weakness) an asap conservative treatment administration was decided. Metyrapon has a long history in endocrine diagnostics, but its use as a therapeutic option is newfangled. An oral solution was induced in our case which proved to be effective in decreasing the cortisol levels; in order to avoid hypadrenia a 'block&replace' method was started. As the oral tolerability of Metyrapon was poor, after a few attempts we switched to rectal administration. Some of the consequences of hypercortisolism resolved in days/weeks/months, but hypertension, tachycardia, muscle weakness and slow weight gain is still present. At the age of 3 months café-au-lait spots appeared on the back and in the perianal region indicating a possible presence of McCune-Albright syndrome which concurred the MRI finding. To have the proper diagnosis both the blood sample and the skin biopsy was investigated for the presence of GNAS/PRKAR1A mutations, but no mutations were found. As the patient still needs a proper diagnosis of his condition, meaning that the prognosis of the disease (e.g. the self-limiting nature as seen in some cases) is still unknown his care is planned to be conservative with all supporting treatments needed (beta-blocker, physiotherapy) and thorough screening of all possible symptoms of diseases causing neonatal CS.

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AEP4

Biomarkers of cardiovascular disease and inflammation in autoimmune addison's disease with residual adrenocortical function

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Background
Residual adrenocortical function (RAF) is present in one third of patients with autoimmune Addison's disease (AAD), yet its clinical significance remains unknown.
Objective
To investigate if biomarker profiles of cardiovascular disease and inflammation are different in patients with AAD and RAF compared to patients without RAF and healthy controls.
Material and methods
24 patients with autoimmune Addison's disease and 24 healthy controls matched for age, sex, and body mass index were included. Blood was sampled at 8 h. Before sampling, patients with AAD had abstained from any GC replacement for at least 18 hours. Nine of the 24 AAD patients had RAF, defined as detectable levels of serum cortisol and 11-deoxycortisol in a medication fasting morning blood sample (1). Blood samples were analyzed for 176 unique plasma proteins (biomarkers) using two 92-plex Olink Proteomics panels: Cardiovascular disease II (CVD II) and Inflammation.
Results
Biomarker expression significantly differed for 13 of the 92 biomarkers of CVD and 11 of the 88 biomarkers of Inflammation (two of which were included in both panels) between AAD patients with RAF, without RAF, and healthy controls (Kruskal-Wallis test, $P \leq 0.010$). The 13 CVD biomarkers were ADM, CEACAM8, FGF-23, GAL-9, HAOX1, IL-6, LOX-1, RAGE, SRC, STK4, THBS2, TNFRSF10A, and XCL1. The 11 inflammation biomarkers were CCL-19, CXCL-10, CXCL9, FGF-23, IL-10, IL-6, LAP TGF-beta1, MCP-1, ST1A1, TNFRSF9, and TRAIL. For nine of the 13 CVD biomarkers and ten of the 11 Inflammation biomarkers, the difference in biomarker expression was only significant between patients without RAF and healthy controls, in which patients with RAF had expression levels in between the two other groups. All but three of the 13 CVD biomarkers (LOX-1, SRC, STK4) and two of 11 inflammation biomarkers (LAP TGF-beta1, ST1A1) had higher expression in patients with and/or without RAF compared to healthy controls. For two of the 13 CVD biomarkers (STK4 and RAGE), expression levels significantly correlated with medication fasting morning cortisol (STK4 $r = 0.477$, $P < 0.025$ and RAGE $r = 0.495$, $P < 0.019$) in patients with AAD. No significant correlations were found between the 11 inflammation biomarkers and cortisol levels.
Conclusion
In AAD, patients with RAF have distinct biomarker profiles of cardiovascular disease and inflammation compared to patients without RAF as well as healthy controls. The findings suggest that RAF in AAD may be clinically significant and warrants further investigation.
Reference
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AEP5

The role of Chchd2 protein in adrenal tumorigenesis

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Background
Recent data have shown the anti-apoptotic effect of Chchd2 mitochondrial protein through the Bcl-2/Bax pathway in various cancers. Bax is regulated primarily by proteins-members of Bcl-2 family and mainly the Bcl-2 protein, which has been found to prevent Bax from accumulating in mitochondria. In response to apoptotic stimuli, Chchd2 decreases and loses its mitochondria localization accompanying by decreased Bcl-2/Bax interaction and increased Bax homo-oligomerization. Thus, Chchd2 negatively regulates the apoptotic cascade upstream of Bax oligomerization. Although, the direct interaction of antiapoptotic Bcl-2 with Bax protein has already been studied, data on the regulatory role of Chchd2 on the expression of Bcl-2/Bax are scarce.
Aim
We aimed to study the expression of *CHCHD2, BCL2* and *BAX* genes at mRNA and protein level in human adrenocortical neoplasms.
Methods
Twenty-four fresh frozen human adrenal tissues including 7 cortisol-secreting adenomas (CSAs), 9 non-functional adrenal adenomas (NFAs) and 8 adrenocortical carcinomas (ACCs) samples were collected. *CHCHD2, BCL2* and *BAX* mRNA and protein expression were determined by qPCR and immunobloting, respectively. The expression of the abovementioned genes was compared with the paired adjacent normal adrenal tissues used as control group.
Results
BCL2 mRNA expression was significantly up-regulated in ACCs compared to benign adrenocortical neoplasms and adjacent normal tissues. *BCL2* mRNA expression was up-regulated in all benign adrenocortical neoplasms compared to their paired adjacent normal tissues without reaching however statistical significance. *BAX* mRNA expression was significantly down-regulated in ACCs compared with benign adrenocortical neoplasms and adjacent normal adrenal tissues. *BAX* mRNA expression was also down-regulated in all benign adrenocortical neoplasms compared with their paired adjacent normal tissues, although not statistical significant. *CHCHD2* mRNA expression was significantly up-regulated in ACCs compared to normal adrenal tissues. *CHCHD2* mRNA expression was also up-regulated in all benign adrenocortical neoplasms compared with their paired adjacent tissue although not statistical significant. Western Blot analysis confirmed the results of qPCR analysis.
Conclusions
This study showed that the expression of both *BAX* and *BCL2* apoptotic genes was altered in adrenocortical neoplasms compared to adjacent normal tissues implying a disturbance of the apoptotic pathway in these neoplasms and perhaps in adrenal tumorigenesis. Moreover, the significant overexpression of *CHCHD2* in ACCs could contribute to the understanding of its role in the clinical behaviour of these neoplasms although functional studies with a larger sample size are required.

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AEP6

Salivary profiles of 11-oxygenated androgens follow a diurnal rhythm in patients with congenital adrenal hyperplasia

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Background
Routine biochemical assessment in patients with congenital adrenal hyperplasia (CAH) includes measurement of serum 17–hydroxyprogesterone (17OHP), androstenedione (A4) and testosterone (T) and their metabolites in urine. Several studies have also described 11–oxygenated 19–carbon (110 × C19) steroids as a clinically relevant androgenetic source and highlighted their potential as markers for evaluation of adrenal androgen excess in patients with 21-hydroxylase deficiency (21OHD).
Methods
Cross–sectional single center study including 34 patients with classic 21OHD (men = 14; women = 20) and 32 BMI- and age–matched controls (men = 15; women = 17). Saliva was collected at five different timepoints throughout the day adjusted to intake of glucocorticoid medication. Salivary concentrations of the following steroids were analyzed by LC–MS/MS: 17OHP, A4, T, 11β–hydroxyandrostenedione (11OHA4) and 11–ketotestosterone (11KT).
Results
Similar to the previously described rhythmicity of 17OHP, 11OHA4 and 11KT concentrations followed a distinct diurnal rhythm in both patients and controls with highest concentrations in the early morning and declining throughout the day (11OHA4: male patients Δ_{mean} = 79%; male controls Δ_{mean} = 81%; female patients Δ_{mean} = 33%; female controls Δ_{mean} = 91%; 11KT: male patients Δ_{mean} = 64%; male controls Δ_{mean} = 60%; female patients Δ_{mean} = 49%; female controls Δ_{mean} = 81%). Significant correlations between the area under the curve (AUC) for 17OHP and 11KT ($r(P)_{male}$ = 0.741**; $r(P)_{female}$ = 0.842****), and 11OHA4 ($r(P)_{male}$ = 0.385^{ns}; $r(P)_{female}$ = 0.527*) were observed in patients but not in controls. P-value ≤ 0.05 (*), ≤ 0.01 (**), ≤ 0.001 (***), ≤ 0.0001 (****).
Conclusions
This study is the first to describe the diurnal rhythm of 11oxC19 steroids in salivary profiles in both healthy controls as well as patients with CAH due to 21OHD. Adrenal 11oxC19 androgens are clearly secreted following a diurnal pattern. This should be considered when evaluating their utility for monitoring treatment control.

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AEP7

Unnecessary cosyntropin stimulation tests for nonclassic congenital adrenal hyperplasia (NCAH) – shall the cut-off value of 17-hydroxyprogesterone be revised?

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Cosyntropin stimulation test is the gold diagnostic standard used to test for NCAH. Genetic testing is not currently considered to be the primary diagnostic tool for NCAH. Still, it may be helpful in establishing a diagnosis if other results are unequivocal or for genetic counselling purposes. The study aimed at verifying the currently accepted threshold of 17-hydroxyprogesterone (17OHP) level (≥ 2.0 ng/ml) at which a cosyntropin stimulation test should be performed.
Material and methods
The retrospective study included 343 patients referred for a cosyntropin stimulation test due to suspected NCAH. Serum 17-OHP was measured with ELISA assay using Ledect96 Microplate Reader before, 30 minutes and 60 minutes after a 250 µg of cosyntropin intravenous injection. CYP21A2 gene sequencing by the Sanger method was performed in 30 patients of the group. NCCAH diagnosis was made if cosyntropin-stimulated 17OHP level exceeded 10.0 ng/ml. Detection of a pathogenic variant was considered a positive result of the genetic test. The ROC curve was determined, and the cut-off point with the highest sensitivity and specificity was established in both groups. The study was approved by the Ethics Board of JUMC. Results. A total of 79 patients were diagnosed with NCCAH based on cosyntropin stimulation test results (22 patients in the genetically screened group). The baseline 17OHP cut-off value that qualified patients best for testing was 2.79 ng/ml in the whole group, with sensitivity and specificity of 77.2% and 91.3%, respectively. The sensitivity and specificity for a guideline-recommended cut-off point (17OHP ≥ 2.0 ng/ml) was 86.1% and 76%, respectively. Pathogenic variants of the CYP21A2 gene were found in 9 patients. If a pathogenic variant was found, baseline 17OHP cut-off which qualified subjects best for testing was 2,88 ng/ml with 77.8% sensitivity and 47.6 % specificity. However, for 17-OHP cut-off ≥ 2.0 ng/ml, these values were 77.8 and 35.7%, respectively. Conclusions. Our results suggest considering an upward shift in the 17OHP threshold at which patients suspected for NCAH should be referred for further evaluation. This may reduce the number of unnecessary cosyntropin stimulation tests, particularly since patients with a mild phenotype (or asymptomatic) frequently may not require any treatment.

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AEP8

Zona glomerulosa derived Klotho does not regulate aldosterone synthesis in young mice

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Klotho (Kl), initially identified as an antiaging gene, plays a critical role in the regulation of renal and adrenal dependent fluid homeostasis. A previous study reported that haplodeficiency of Kl in mice resulted in increased aldosterone synthase (CYP11B2) expression, elevated plasma aldosterone and high blood pressure. This phenotype was presumed to result from diminished Kl expression in zona glomerulosa (zG) of the adrenal. To examine whether Kl expressed in zG is indeed a critical regulator of aldosterone synthesis, we generated a tamoxifen-inducible, zG-specific mouse model of KI deficiency by crossing Kl-flox mice with Cyp11b2-CreERT mice (zG-Kl). Tamoxifen-treated Cyp11b2-CreERT animals (zG-Cre) served as controls. Rosa26-mTmG reporter mice were used for Cre-dependent lineage-marking. Two weeks after tamoxifen induction, the specificity of the zG-Cre line was verified using immunofluorescence analysis to show that GFP expression was restricted to the zG. RNAScope *in situ* hybridization revealed a 65% down-regulation of Kl mRNA expression in zG of zG-Kl mice at 12-weeks of age compared to control mice. Despite this, zG-Kl mice exhibited no difference in adrenal Cyp11b2 expression or plasma aldosterone levels compared to control mice independent of sex. These results suggest that zG-derived Kl *per se* does not significantly regulate aldosterone synthesis in young adult mice. Further studies are required to investigate the role of adrenal Kl in aldosterone synthesis in aged mice.

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AEP9

Effects of adrenalectomy on arterial hypertension, glucose and lipid metabolism in patients with mild autonomous cortisol secretion: preliminary results of a Randomized Clinical Trial

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Introduction
The management of patients with adrenal incidentaloma (AI) and mild autonomous cortisol secretion (MACS) is debated. This randomized study aimed to evaluate the effects of adrenalectomy on arterial hypertension (AH), glucose and lipid metabolism.
Methods
We consecutively evaluated 626 AI patients (referred to 3 Italian Centers between 06/2016 and 02/2020). According to the inclusion criteria, we

enrolled 61 patients (45 F) with MACS (cortisol level after 1mg overnight dexamethasone suppression test, 1 mgDST, between 1.8 and 5 µg/dl). Patients were randomized in surgery (Group 1, n = 29) or conservative follow-up groups (Group 2, n = 32). Three patients from Group 1 withdrew their consent. Blood pressure (BP) and glyco-metabolic parameters were evaluated at baseline and after 6 months. The study is ongoing.
Results
So far, 40 patients (15 in Group 1 and 25 in Group 2, mean age 64.4 ± 10.4 years, adenoma diameter 2.8 ± 0.7 cm, 1 mgDST 3.3 ± 1.6 µg/dl) have completed the 6 months follow-up. At baseline the two groups were comparable for all characteristics. In particular, 8 patients from Group 1 and 16 from Group 2 were hypertensive; 11 from Group 1 and 14 from Group 2 were dyslipidemic; 3 and 6 patients, respectively in Group 1 and in Group 2, were diabetic. After 6 months, in Group 1, 8 patients (57.1%) improved BP (in particular 2 hypertensive patients passed from a grade 1 AH to a high-normal BP and other 2 hypertensive patients passed from a grade 2 to a grade 1 AH), only 2 (14.3%) worsened BP control; in Group 2, BP improved in 5 patients (20%), but worsened in 8 (32%), (P = 0.05). Glycemic control improved in 1 patient of both groups, but worsened in 4 patients of Group 2 and in 1 of Group 1 (16% vs 6.7%); in the subgroup of diabetic patients, only 2 non-operated patients worsened glycemic control at follow-up. Insulin-resistance, evaluated by HOMA-IR, remained steady in Group 1, while it showed a worsening trend in Group 2: 2.7 ± 2.1 at baseline vs. 6.0 ± 10.2 at 6 months (P = 0.07). LDL-cholesterol levels improved in 4 patients of Group 1 (26.7%) and in 2 patients of Group 2 (8.3%); on the other hand, they worsened in 4 patients of Group 1 (26.7%), and in 4 patients Group 2 (16.7%).
Conclusion
These preliminary data suggest that, in MACS-patients, adrenalectomy has a beneficial role on glucose and lipid metabolism, but above all on AH.
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AEP10

A very rare case of extranodal lymphoma with adrenal and heart involvement

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Background
Extranodal non-Hodgkin lymphoma (NHL) is a rare condition that accounts for less than one-third of patients with NHL at diagnosis. The heart or the endocrine organs (adrenals) involvement is extremely rare.
Objective
We report an unusual case of extranodal B-cell NHL: DLBCL (diffuse large B-cell non-Hodgkin lymphoma) presenting with heart and bilateral adrenal involvement.
Design-results
A 72-year-old male patient presented to our Endocrinology Unit for investigation of 3.8 cm right adrenal mass, diagnosed by abdominal ultrasound and thereafter by computed tomography (CT) because of abdominal pain. On admission, a repeated adrenal CT scan identified bilateral adrenal masses of 6.7 cm on right adrenal gland compressing the inferior vena cava and 3.7 and 3.6cm on left adrenal gland. Thorax CT scan revealed a 4.6cm mass in the right atrium wall extending from the drainage of the superior vena cava to the drainage of the inferior vena cava. Heart MRI confirmed the previous finding. Left ventricular ejection fraction was 55%. Adrenal hormonal baseline and dynamic investigation [cortisol post-overnight dexamethasone suppression test and aldosterone post-saline infusion test] excluded autonomous cortisol or aldosterone secretion. Urinary metanephrine and normetanephrine excretion were normal. Cortisol response after a short synacthen test excluded adrenal insufficiency. A CT-guided adrenal biopsy revealed the presence of a DLBCL, with triple expression of bcl2, bcl6, C-MYC(+70%). Cell proliferation index Ki-67 was 99%. Positron emission tomography scan (PET-CT) showed hyper-metabolic infiltrative masses involving the right atrium (SUVmax 21.2) and both adrenal glands (SUVmax 20.5). Virology tests for Epstein Barr virus and HIV were negative. Bone marrow aspiration, trephine biopsy and cerebrospinal fluid analysis were negative for lymphoma infiltration. Karyotype was normal and MRI brain spectroscopy was negative for CNS lymphoma detection. The patient was asymptomatic. Under the care of the haematology team systemic immunochemotherapy with R-DA-EPOCH (rituximab, dose adjustment etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) and high dose methotrexate for CNS prophylaxis were administrated. After the completion of six cycles of immunochemotherapy, a marked decrease of lymphoma infiltration in the post-chemotherapy imaging CT and MRI scans was found. Left ventricular ejection fraction was 66%. The treatment was complicated with reversible paralytic ileus, due to vincristine neurotoxicity, which was omitted from the next immunochemotherapy cycles.
Conclusions
An extremely rare case of an extranodal DLBCL stage IVE with both adrenal and heart involvement is described. The selection of the appropriate treatment modality can lead to profound response and improve patient's outcome.
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AEP11

The role of estimated glucose disposal rate as a predictor of insulin resistance, NAFLD and major adverse cardiovascular events in type 1 diabetes mellitus

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Background and Aims
People with type 1 diabetes (T1D) have an increased risk of cardiovascular disease (CVD) despite insulin therapy to treat hyperglycaemia. Insulin resistance may be a contributing factor to CVD. Insulin resistance is strongly associated with NAFLD, which is increasingly linked to CVD. The estimated glucose disposal rate (eGDR) correlates well with the euglycemic clamp, which is the gold standard to assess insulin resistance in T1D, but is unsuited for clinical practice or large studies. This study aimed to assess the association between eGDR, NAFLD and CVD.
Methods
Adult T1D subjects were consecutively screened for liver steatosis using ultrasound (US), the Fatty Liver Index (FLI) and controlled attenuation parameter (CAP). Secondary causes of liver steatosis were excluded, implying that liver steatosis was due to NAFLD in all cases. The eGDR was calculated based on hypertension, HbA1c and waist circumference. CVD was assessed based on documented major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal ischemic stroke or peripheral vascular disease in need of therapeutic intervention).
Results
CVD was present in 34 out of 355 subjects. Divided into tertiles (<5.39,5.39–7.79,>7.79), 36.6% expressed low eGDR; 32.7% intermediate eGDR and 30.7% high eGDR. The eGDR is inversely associated with insulin resistance. There was moderate correlation between eGDR and FLI (r = 0.68, P < 0.001) and weak correlation with US (r = 0.33, P < 0.001) and CAP (r = 0.50, P < 0.001). In the low eGDR group (= insulin resistant group) was not only steatosis (38.5% vs. 11.2% (intermediate eGDR) and 12.8% (high eGDR)), but also composite CVD (18.5% vs. 6.0% and 2.8%) significantly more present (P < 0.001 for both). Low eGDR (OR: 4.2 [2.2–8.2], P < 0.001), but not BMI or dyslipidaemia was independently associated with US-defined NAFLD. Low eGDR was also independently associated with FLI-determined NAFLD (OR: 5.5 [1.7–17.6], P = 0.004) together with BMI (OR: 1.6 [1.4–1.9], P < 0.001). Low eGDR (OR: 8.0 [2.3–27.4], P = 0.001) and NAFLD (OR: 2.7 [1.2–6.1], P = 0.022 (US-defined), OR: 2.9 [1.4–6.0], P = 0.005 (FLI-defined)) were independently associated with CVD, but presence of metabolic syndrome, dyslipidaemia and BMI were not.
Conclusions
Insulin resistance, as assessed by eGDR, is prevalent in T1D. eGDR correlates with the presence of NAFLD. Both eGDR and NAFLD correlate with major cardiovascular adverse events.
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AEP12

Niemann-Pick disease and endocrine disorders: A case report

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Introduction
Acid sphingomyelinase-deficient Niemann–Pick disease (NPD) is a lysosomal lipid storage disorder. We report a new case of Hashimoto thyroiditis associated to primary adrenal insufficiency (PAI) likely of infiltrative process occurring in NPD type B patient.
Observation
A 24-year-old Tunisian female patient was followed up in our endocrinology department for Hashimoto thyroiditis. Two years later, she was diagnosed with PAI. Laboratory studies showed elevated serum ACTH concentration (165 pg/ml), low morning serum cortisol concentration, and an abnormal cosyntropin stimulation test. PAI investigations were ensued. The patient had negative adrenal antibody test. Computed tomography imaging demonstrated a left adrenal mass of 3 cm with a density of 31 HU associated to a hepatosplenomegaly and diffuse infiltrative lung disease. Multifocal systemic tuberculosis was highly suspected. However, therapeutic test showed no response. The endocrine work up showed no hormonal secretion of the adrenal lesion that remained stable. Laboratory data showed prediabetes, dyslipidemia and cytolysis with thrombocytopenia and anemia. A bone marrow aspiration was in favor of NPD. On the grounds of these results the diagnosis of NPD type B was confirmed.
Conclusion
No cases of the coexisting of NPD with PAI and Hashimoto thyroiditis have been reported to our knowledge. Further studies are needed to ascertain whether multiple glandular dysfunction should be anticipated in NPD type B.

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AEP13

Epidemiology, clinical course, and genetic analysis of pheochromocytomas/paragangliomas: A single centre tertiary care experience over 16 years from crete-greece

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Background
Pheochromocytomas (PHOEs) and paragangliomas (PGLs) are rare neuroendocrine tumors originating from chromaffin cells. PHEO/PGL incidence ranges between 2–8/million, with 10–49% of these tumors being detected incidentally during imaging performed for other reasons. Up to 40% of PHEOs/PGLs patients have disease-specific germline pathogenic variants. This study aimed to investigate the epidemiology, clinical course, and genetic background of PHEOs/PPGLs in a Greek tertiary reference centre.
Methods
We retrospectively reviewed the data of 21 PHEOs/PGLs patients seen at the Endocrine Clinic of the University Hospital of Heraklion, Crete, Greece, between 1998–2020. Demographic, histopathology and follow-up data were collected. Germline DNA, extracted from patients' peripheral blood, was subsequently analyzed by a 94-cancer gene panel, followed by MLPA. All participants have signed informed consent.
Results
In total, 21 patients with a mean age of 46.52 ± 18.34 years were included. There was a male predominance (men, n = 15 [71.4%]; women, n=6 [28.6%]). Sixteen patients (76.2%) had PHEO, 4 (19%) had PGL and one patient (4.76%) had both PHEO/PGL. Ten patients (62.5%) had right-sided PHEO, 5 (29.41%) left-sided and 2 (11.76%) bilateral. PGL locations included: retroperitoneum (40%), head/neck (20%), multiple organs (20%), pericardium (20%). Twelve patients (57.1%) presented as an incidentaloma, 8 (38%) as a suspected PHEO and 1 (4.8%) was screened because of neurofibromatosis-1 syndrome. The mean age at presentation did not differ between patients with incidentaloma and suspected PHEO (47.5 ± 14.22 vs 57 ± 14.59 years, P = 0.16). PGLs patients tended to be younger, compared to PHEO (33.4 ± 25.63 vs 51.5 ± 14.32 years, ns). Overall, 15 patients (71.42%) had hypertension: 58.33% of incidentaloma group and 87.5% of PHEO suspected group. Males more frequently presented with incidentaloma (66.66%), and females with PHEO suspected symptoms (60%). Most patients had secreting PHEO/PGL (71.42%). Eighteen patients (85.71%) were operated, while 3 (14.28%) preferred conservative management. The mean tumor maximum diameter was 6.3 ± 2.4 (range 3–11 cm). In most cases the Pheochromocytoma of Adrenal Gland Scaled Score was <3 consistent with benign potential. Although the genetic analysis is still ongoing, primary results revealed the presence of germline pathogenic variants in five patients and more specifically, three in succinate dehydrogenase (SDHx) subunits, all of which developed metastatic disease, and one in each of RET and NF1. Fourteen patients (66.66%) are in remission, four patients (19.04%) have stable disease and three patients (14,28%) showed disease progression. This is the first attempt to collect, report and characterize PHEO/PGL in Greece.

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AEP14

Differential phenotype of bilateral macronodular adrenal hyperplasia and other bilateral adrenal lesions with associated subclinical hypercortisolism. Study of 98 patients

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Purpose
To evaluate the prevalence of bilateral macronodular adrenal hyperplasia (BMAH) in patients with adrenal incidentalomas (AIs) and analyse the differential phenotype of patients with BMAH compared to other bilateral adrenal lesions which do not meet BMAH definition (non-BMAH), with associated possible or confirmed autonomous cortisol secretion (ACS).
Methods
Retrospective study of patients with AIs diagnosed between 2013 and 2019 in the Hospital Ramón y Cajal (n = 730). Patients with bilateral disease and associated possible or confirmed ACS were included (n = 98). Possible ACS was defined as a DST > 1.8 µg/dl without specific clinical signs of Cushing syndrome, and confirmed ACS when cortisol post-DST was > 5.0 µg/dl. BMAH diagnosis was established in patients with hyperplasia and bilateral adrenal nodules > 1 cm and associated possible or confirmed ACS.
Results
Inclusion criteria were fulfilled by 98 out of the 730 patients with AIs included in the RCUH ADRENAL INCIDENTALOMA database. BMAH was confirmed in 31 patients (4.2% of AIs and 31.6% of bilateral AIs with possible or confirmed ACS). Patients with BMAH presented a higher prevalence of ACS (OR 4.1, 95% CI 1.38 to 12.09, P = 0.010), but differences disappeared after adjusting by tumor size and total adenomatous mass (adjusted OR 2.3, 95% CI = 0.65–8.27, and OR 2.3, 95% CI 0.47 to 11.21, respectively). However, no significant differences in the cardiometabolic profile of both groups were observed. Tumor size and total adenomatous mass were significantly higher in patients with BMAH (30.2 ± 12.16 vs 24.3 ± 8.47, P = 0.010 and 53.9 ± 20.8 vs 43.3 ± 14.62, P = 0.023). After a median follow-up of 33.7 (range 3.7 to 194.8) months, no differences in the risk of developing comorbidities was observed between BMAH and non-BMAH. Aberrant receptors study was performed in 5 patients with BMAH, being positive in three patients (in the metoclopramide test in two patients and in the metoclopramide and mixed food test in another). Two patients with BMAH underwent unilateral adrenalectomy, with improved of cardiometabolic and hormonal alterations, one patient (study positive for mixed food test) was treated with lanreotide with no response and other (one of the patients with a positive metoclopramide test) with amitriptyline, without response neither.
Conclusion
BMAH is relatively common in patients with incidentally detected bilateral adrenals lesions with associated subclinical hypercortisolism. The higher prevalence of ACS in BMAH compared to non-BMAH is related with the higher tumor size and total adenomatous mass in patients with BMHA, but no differences in the cardiometabolic profile was observed between both groups.

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AEP15

Effect of retinoic acid on adrenal primary cultures from patients with Cushing's disease

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Retinoic acid, a major modulator of adrenal development and differentiation, has also been shown to inhibit ACTH secretion by tumoral corticotropes. Recent clinical trials in patients with Cushing's disease revealed that retinoic acid exerts beneficial effects in these patients (1,2). Of note, the decrease in cortisol secretion during retinoic acid administration was more pronounced than the change in ACTH levels (1) suggesting a direct action at adrenal level. Aim of the present study was to evaluate the effect of retinoic acid on cortisol secretion and on genes involved in steroidogenesis and retinoic acid action in adrenals from patients with Cushing's disease
Methods.
Adrenal specimens from six patients with Cushing's disease were incubated with retinoic acid with and without ACTH. Cortisol secretion was measured by immunoassay and expression of genes involved in steroidogenesis (*CYP17A, STAR, LIPE, MC2R, DAX*-1, *SF*-1) as well as retinoic acid action (*RARA, RARB, LXR, PPARD, COUP-TF1, SREBP1, mND1, mND6*) were evaluated by real-time RT-PCR.
Results.
Incubation with 10–100 nM retinoic acid increased spontaneous cortisol secretion and expression of *STAR* and *CYP17A*. As expected, retinoic acid increased *RARA*, *RARB* and *SREBP1*. In wells treated with 10 nM ACTH, retinoic acid markedly diminished *MC2R*, thus blunting ACTH receptor upregulation, and no stimulatory effect on cortisol secretion or steroidogenic enzyme synthesis was observed. ACTH itself increased ligand-induced *RARB* expression, possibly enhancing sensitivity to retinoic acid.
Conclusions.
Our results indicate that retinoic acid stimulates spontaneous cortisol secretion but, in presence of ACTH, the decrease in adrenal ACTH receptor overrides this effect. These findings support the hypothesis of a direct adrenal action in patients with Cushing's disease.
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AEP16

Typical obese patient with an adrenal incidentaloma is a menopausal female with an unilateral nonfunctioning tumor – a single centre experience

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Introduction
The connection between obesity and tumorigenesis has been well established.
Aim
The aim of this study was to elucidate if there are any demographic and functional differences in adrenal incidentalomas (AI) with respect to different body mass index (BMI) categories.
Patients and methods
This was an observational, cross sectional study. The AI cohort consisted of 680 patients that underwent functional hormonal assesment in our Clinic. After exclusion of patients with overt adrenal hyperfunction, malignant adrenal tumors, adrenal cysts and metastasis, the total studied group consisted of 560 patients: 385 female and 175 male. Based on BMI, we have stratified them in three groups, 18.5–25 kg/m^2 (135 patients, 22.44 ± 2.03 kg/m^2, 56 ± 11 years), 25–30 kg/m^2 (219 patients, 27.63 ± 1.41 kg/m^2, 58 ± 11 years) and > 30 kg/m^2 (206 patients, 33.91 ± 3.53 kg/m^2, 59 ± 9 years). Based on cortisol level after 1 mg overnight dexamethasone suppression test, AI were identified as nonfunctional AI (NAI) (≤ 50 nmol/l), those with possible autonomous cortisol secretion (PACS) (> 51 nmol/l) or autonomous cortisol secretion (ACS) (> 138 nmol/l).
Results
Female sex was predominant in all BMI groups (M/F %: 22.6/77.4, 40.5/59.5 and 27.1/72.9). However, obese and normal weight patients had significantly higher frequency of females when compared to overweight patients ($P < 0.001$). Obese patients were significantly older then the other two BMI groups ($P = 0.008$). Overweight and obese AI patients were more likely to have NAI ($P < 0.001$) whereas normal weight AIs were more likely to have either PACS or ACS ($P < 0.001$). All three BMI groups had predominantly more unilateral then bilateral AIs (70.7/29.3%, 79.1/20.9% and 77.8/22.2%). There was no difference in frequency between unilateral and bilateral AIs with respect to BMI group ($P = 0.172$). There was a significant positive correlation between patients› age and BMI ($r = 0.097$, $P = 0.022$). There was no significant difference in the size of AI between the groups ($P = 0.292$).
Conclusion
Our results imply that the typical obese patient with an AI is very likely to be a menopausal female with an unilateral nonfunctioning tumor. They also add to the body of evidence that obesity plays an important role in the adrenal tumorigenesis. However, there is yet to be determined which came first: the hen or the egg?

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AEP17

Cost-effectiveness of empagliflozin plus metformin vs metformin alone as first-line therapy in patients with type 2 diabetes mellitus: An australian perspective

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Background
Sodium-glucose cotransporter 2 (SGLT2) inhibitors are potentially an attractive option for initial combination therapy with metformin for type 2 diabetes mellitus (T2DM), which may help patients to achieve adequate glycaemic control and reduce cardiovascular disease (CVD). Empagliflozin has been shown to be superior compared to other SGLT2 inhibitors in reducing all-cause and cardiovascular mortality in patients with T2DM.
Aims
To evaluate the cost-effectiveness of first-line empagliflozin added to metformin vs metformin alone in patients with newly diagnosed T2DM and established CVD in Australia.
Methods
A Markov model was constructed to simulate cardiovascular events occurring in Australians currently aged 50 to 84 years with newly diagnosed T2DM and existing CVD. The cycle length was one year, and the base-case time horizon was five years. The model consisted of two health states: 'Alive' and 'Dead'. Clinical inputs were based on data from Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose. Costs and utilities were extracted from published sources. The analyses were performed from an Australian public healthcare system perspective and from a societal perspective, with the latter ascribing the Australian Government's 'value of statistical life year' (VoSLY, AUD 213,000) to each year lived by a person. The main outcome was the incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year gained (QALY) and years of life saved (YoLS). Future outcomes were discounted at a rate of 5% per anum. Sensitivity analyses were undertaken confirm robustness of the results.
Results
First-line use of empagliflozin in addition to metformin reduced overall cardiovascular events by 0.82% and death by 7.72% over five years, compared to metformin alone. There were 0.2 YoLS per person and 0.16 QALYs gained, at a net healthcare cost of AUD 4,408. These equated to incremental cost-effectiveness ratios of AUD 22,076 per YoLS and AUD 28,244 per QALY gained. The gains in VoSLY equated to AUD 42,530 per person, meaning that from a societal perspective, the intervention was cost saving.

Conclusion
First-line use of empagliflozin added to metformin appears to be a cost-effective strategy for the management of Australians with newly diagnosed T2DM and CVD.

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AEP18

Klinefelter syndrome: Beyond hypogonadism

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Introduction
In Klinefelter syndrome, hypergonadotropic hypogonadism is the most prominent endocrine-metabolic disorder. However, a higher prevalence of cardiovascular risk factors has also been reported.
Objectives
In a sample of individuals with Klinefelter Syndrome (KS): – to document the diagnostic context; – to assess the prevalence of cardiovascular risk factors (CVRF) and compare it with a control group; – to analyse the influence of age at diagnosis and hormone replacement therapy (HRT) on CVRF.
Materials and methods
A sample with KS under 55 years of age and an equal number of age-matched male control subjects were selected.
Results
Study group with 32 KS subjects, mean age 29.5 ± 8.6 years. Diagnosis on average at 17.5 ± 12.3 years of age due to learning/behavioral issues (25.0%), infertility (25.0%), phenotype (21.4%), delayed pubertal development (21.4%) and prenatal diagnosis (7.1%). Karyotype (n = 28): 82.8% 47XXY, 6.9% 46XY/47XXY, 3.4% 48XXXY and 6.9% 49XXXY. All of the subjects had hypergonadotropic hypogonadism, 93.8% decreased testicular volume, 46.2% gyneco/adipomastia and 32.1% cryptorchidism. In those in which it was evaluated (n = 8), the presence of azoospermia was constant. HRT was started in 93.8% at a median age of 15.5 ± 12.0 years. In the last 5 years, these patients had an average of 56.2 ± 37.3% of the total testosterone levels within the reference values, 36.4 ± 35.6% below and 5.9 ± 19.8% above. The vast majority of KS (78.1%) had some CVRF: 15.6% pre-diabetes, 6.3% diabetes, 53.1% dyslipidemia, 46.9% overweight, 18.8% obesity and 6,3% hypertension. The overall prevalence of CVRF was higher than that of the control group (25 vs 15, P = 0.010), with: higher prevalence of dysglycemia (7 vs 0, P = 0.011) and dyslipidemia (17 vs 8, P = 0.021); more overweight/obese individuals without reaching statistical significance (21 vs 32, P = 0.079); similar prevalence of hypertension (2 vs 3, P = 1,000). There was no significant correlation between higher number of CVRF and age at diagnosis (P = 0.333), age at HRT initiation (P = 0.281) or the percentage of testosterone assays within reference values (P = 0.753).
Conclusions
This sample is composed mainly of young patients, with a variable context of diagnosis, but in general precocious. Even so, an elevated prevalence of CVRF was registered, higher than that of the control group. Although sample size is a limiting factor, the data does not suggest an influence of early diagnosis and HRT on CVRF.

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AEP19

Aryl hydrocarbon receptor Interacting Protein (AIP) status in a functional adrenal adenoma occurring in a patient with a germline AIP mutation

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Introduction
Aryl hydrocarbon receptor Interacting Protein (AIP), a pituitary tumour suppressing gene located in 11q13, is the most common predisposing gene for early-onset and familial acromegaly. Fifteen years after its identification, there is little evidence of AIP involvement in non-pituitary tumors. We had the opportunity to study AIP status in a cortisol-producing adenoma operated in an AIP mutation carrier.
Case-report
A 43-year-old woman was followed-up as a carrier of a familial R304X AIP mutation. Her sister, first degree cousin and son had developed acromegaly but she had no evidence of pituitary disease. However, an incidental and asymptomatic right adrenal mass of 26 mm was found on abdominal US, with MRI suggesting an adrenocortical adenoma. The only biochemical abnormality was abnormal suppression of cortisol after a 1mg O/N dexamethasone suppression test. At the age of 46, because of a progressive mass increase with autonomous cortisol secretion confirmed by a I131-norcholesterol scintigraphy, she was operated on by laparoscopic surgery. The diagnosis of adrenocortical adenoma, larger than expected (max 45 mm), without cellular atypia, was confirmed, with multiple foci of mielopoma. The patient gave consent for the study of AIP status in the tumour. RT-PCR amplification of the AIP gene (exon6) on tumour and adjacent normal adrenocortical tissue DNA showed the presence of the wild-type and mutated allele in both samples, as confirmed on leukocyte DNA. AIP-immunostaining was positive on normal and tumour cells. After post-operative corticotroph insufficiency, glucocorticoid replacement therapy was progressively reduced and withdrawn 5 months later. She is currently eucortisolic, and the left adrenal gland is normal. None of her acromegalic relatives had evidence of adrenal abnormalities.
Discussion
Adrenocortical adenomas may be encountered more frequently in acromegalics. To the best of our knowledge, four cases of adrenocortical tumors (1 non-functioning, 3 androgen-secreting) were reported with sufficient details in AIP-related acromegalics and LOH at the AIP locus was found only in a corticosurrenaloma.
Conclusion
The study of tumour AIP status in an unusual cortisol-secreting adenoma developing in a familial context of germline AIP mutations, in the absence of acromegaly, favors the hypothesis that the R304X mutation was not involved in adrenal tumorigenesis. Rather, it suggests LOH at the AIP locus is not an early event in adrenocortical tumors, although AIP expression may be lost due to somatic chromosomal abnormalities, including loss of genetic material in chr 11 and in particular LOH in 11q13.

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AEP20

The association between adrenal adenomas' size, autonomous cortisol secretion and metabolic derangements

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Objective
Autonomous cortisol secretion (ACS) is the most common hypersecretion syndrome present in patients diagnosed with adrenal incidentalomas (AI). ACS is associated with various metabolic derangements. Thus far, very few and mostly inconclusive data exists regarding the association between AI's radiological characteristics and hormonal functionality. In this study we assessed the associations between radiological characteristics of incidentally discovered adrenal findings, ACS, and metabolic abnormalities.
Methods
We prospectively collected data from 77 patients evaluated for adrenal incidentalomas in a large tertiary medical center between December 1st, 2017 and October 31 st, 2020. Post -Dexamethasone suppression test (DST) morning cortisol levels were used to diagnose ACS, and the association between AI's radiological features, post-DST morning cortisol levels and metabolic outcomes was analyzed.
Results
Maximal adenoma diameter linearly correlated with post-DST morning cortisol levels (R = 0.474, P < 0.01.). This correlation translated to a linear correlation between maximal adrenal adenoma diameter and metabolic parameters, mainly fasting plasma glucose and glycated hemoglobin levels (R = 0.58, P < 0.01 and R = 0.56, P < 0.01, respectively). Moreover, we

demonstrate that the linear correlation between maximal adenoma diameter and post -DST cortisol is greatly intensified in patients meeting the criteria for the metabolic syndrome. Additionally, we show that patients with ACS, have larger adrenal adenomas than patients harboring non-functioning adenomas (27 mm, Vs. 20.3 mm, respectively, $P < 0.01$), and that adenomas sized ≤ 13.9 mm are likely to be non-functional with a sensitivity of 90%.
Conclusions
The diameter of incidentally found adrenal lesions is positively associated with ACS and abnormal glucose homeostasis. Our data suggest that initial adrenal adenoma diameter may be an adjunct for the risk stratification for ACS and its associated metabolic morbidity.

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AEP21

Metabolic and Inflammation markers in patients with mild autonomous cortisol secretion: preliminary results of a Randomized Clinical Trial

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Introduction
Irisin is a molecule secreted from skeletal muscle and contributes to maintenance of metabolic homeostasis leading to increased energy expenditure and reducing the risk of obesity and diabetes. Literature data suggest that patients with Cushing disease have lower irisin values than controls and remission of hypercortisolism increases these values. Moreover, other plasma inflammation markers implicated in the pathogenesis of atherosclerosis, including TNF-alpha and IL-6, are increased in Cushing's syndrome patients. Few data are available in mild autonomous cortisol secretion (MACS) patients. In this randomized study we aimed to evaluate the effects of adrenalectomy on circulating irisin, IL-6 and TNF-ήlevels in patients with adrenal incidentaloma (AI) and MACS.
Methods
Among 626 AI patients (referred to 3 Italian Centers between 06/2016 and 02/2020), according to the inclusion criteria, we consecutively enrolled 61 patients (45 F) with MACS (cortisol level after 1mg overnight dexamethasone suppression test, 1 mgDST, between 1.8 and 5 μg/dl). Patients were randomized in two groups: surgery (Group 1, $n = 29$) or conservative follow-up (Group 2, $n = 32$). Three patients from Group 1 withdrew their consent to surgery. Irisine, TNF-alpha, IL-6 levels, anthropometric, and glyco-metabolic parameters were evaluated at baseline and after 6 months. The study is ongoing.
Results
So far, 40 patients (15 in Group 1 and 25 in Group 2, mean age 64.4 ± 10.4 years, adenoma diameter 2.8 ± 0.7 cm, 1mgDST 3.3 ± 1.6 μg/dl) have completed the 6 months follow-up. At baseline the two groups were comparable for clinical and biochemical characteristics. After 6 months we found that only in group 1 irisin levels increased over time (13.1 ± 1.8 ng/ml at baseline vs 26.2 ± 15 ng/ml at 6 months, $P < 0.05$) whereas TNF-alpha and IL-6 levels did not change in both groups. At baseline, TNF-alpha and IL-6 levels were correlated to HOMA-index levels ($r = 0.408$, $P = 0.015$, $R = 0.425$, $P = 0.011$, respectively), that, in turn, significantly correlated with BMI and waist circumference. The TNF-alpha levels were also correlated to the fibrinogen levels ($r = 0.360$, $P = 0.031$). We did not find any correlation between TNF-alpha and IL-6 levels and parameters of cortisol secretion (1 mgDST, ACTH, urinary free cortisol/cortisone and midnight salivary cortisol levels). Unexpectedly, we found a strong positive correlation between irisin levels and 1 mgDST ($r = 0.625$, $P = 0.001$), we suppose for a mechanism of peripheral resistance, but not with other metabolic parameters.
Conclusion
These preliminary data suggest that, in MACS-patients, irisin levels increases after surgery, whereas they remain steady after a conservative follow-up.
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AEP22

Impact of adrenal insufficiency on female sexual function: A preliminary study

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Introduction
Adrenal insufficiency is a clinical condition that leads to depletion of glucocorticoids, mineralocorticoids and androgens. While in men adrenal androgen deficiency is not clinically significant for testicular testosterone synthesis, in women so far androgen treatment is suggested for the reduction of libido and depression. However, no data is currently available on female sexual function.
Primary endpoints
1) To study the prevalence of Female Sexual Dysfunction (FSD) in women with adrenal insufficiency; 2) To compare the obtained data with a healthy control group.
Secondary endpoints
1) To evaluate the correlation between FSD and sexual distress in patients with adrenal insufficiency; 2) To study the impact of different glycoactive-therapies on sexuality; 3) To evaluate the correlation between FSFI-6 total scores and cortisol and ACTH levels.
Patients and methods
22 women with adrenal insufficiency and 23 healthy women were recruited as controls. A clinical investigation was carried out, including anamnesis, physical examination, serum cortisol and ACTH dosage. In addition, Female Sexual Function Index-6 (FSFI-6) and Sexual Distress Scale (SDS) questionnaires were administered to the patients.
Results
The prevalence of FSD (total score < 19) was significantly higher in women with adrenal insufficiency (15/22; 68.2%) compared to controls (2/23; 8.7%; $P = 0.001$). Regarding the questionnaire items, a significantly different score was found for desire ($P < 0.001$), arousal ($P = 0.0006$), lubrication ($P = 0.046$) and overall sexual satisfaction ($P < 0.0001$) in women with adrenal insufficiency compared to controls. A significant inverse correlation was found between FSFI-6 total scores and sex-related distress ($r = –0.65$; $P = 0.0011$), a significant direct correlation was found between FSFI-6 total scores and cortisol plasma levels ($r = 0.55$; $P = 0.035$). No statistically significant differences for any of the FSFI-6 items or total score was found between women treated by hydrocortisone or cortisone acetate and women treated by a modified release hydrocortisone formulation. No statistically significant correlations were found between ACTH plasma levels and total score for the FSFI-6 questionnaire.
Conclusions
A higher prevalence of FSD was found in women affected by adrenal insufficiency compared to the group of healthy women. Desire seems to be the most impaired part of sexual response. Moreover, sexual dysfunction in this population seems to be related to sexual distress and cortisol serum levels. Further studies on larger series are needed to confirm these data on this sensitive issue.

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AEP23

Adrenal cysts – a rare entity

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Introduction
Adrenal cyst lesions are uncommon and only a few large series have been reported. The pathogenesis is unclear. Currently, adrenal cystic lesions are

categorized into endothelial cysts, pseudocysts, epithelial cysts and parasitic cysts. In most cases they are found incidentally in asymptomatic patients or in patients with non-specific gastrointestinal symptoms. We describe three cases of adrenal cysts.
Case report
Case 1: Female patient, 50-year-old, with essential arterial hypertension. An adrenal mass in the right adrenal gland was diagnosed incidentally after an abdominal ultrasound. The CT scan showed a 55 mm cystic lesion with a partially calcified wall, under 20 HU. The laboratory evaluation suggested a non-functional lesion. The patient was submitted to a laparoscopic adrenalectomy. The pathology examination revealed an adrenal cyst with 60 mm of larger axis, with no recognizable epithelial tissue and with a partially calcified wall. Case 2: A 55-year-old female patient, with a previous history of ovarian teratoma, mammary fibroadenomas and arterial hypertension. A nodular cystic lesion in left adrenal gland was diagnosed incidentally after a renal ultrasound that was requested due to recurrent urinary tract infections. The patient underwent a CT scan that showed a cystic lesion, with low density and homogenous content, with 66 mm of larger axis. The laboratory evaluation suggested a non-functional lesion. The patient was submitted to a laparoscopic left adrenalectomy. The pathological examination showed an epithelial cyst with 70 × 50 × 30 mm. Case 3: 56-year-old female patient, with no relevant personal history. An adrenal lesion with 58 mm larger axis, homogenous, with water density, was diagnosed in a lumbar CT scan requested due to a back pain. The laboratory evaluation suggested a non-functional lesion. The patient underwent a MRI that showed a cystic nodular formation with benign characteristics. After 2 years of tight surveillance the cystic nodule is now smaller in size, with 43 mm of larger axis.
Discussion
Adrenal cysts are rare entities, however, due to a significative increase in the demand of imaging exams, the incidence has grown. The choice of treatment is not always clear. In most cases, when the larger axis is above 4 cm the complete excision may be considered an option. In one of the cases described, the patient underwent tight medical vigilance, with a reduction in the size of the cyst and no signs of malignancy 2 years after the diagnosis.

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AEP24

One train may hide another: Scleromyositis in a patient with peripheral adrenal insufficiency

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Introduction
Patients with primary adrenal insufficiency (PAI) may have musculoskeletal symptoms. However, the association of such endocrinopathy with scleromyositis is extremely rare and has not been reported formerly to our acknowledge. Herein we report this association.
Case report
A 32-years old female with one year history of profound global weakness was referred to internal department in April 2006, for suspicion of polymyositis. Diagnosis of PAI was established in endocrinology department in September 2005 in front of clinical signs associating fatigue, muscle weakness, gastrointestinal complaints, weight loss and hyperpigmentation. Moreover hormonal evaluation (Short synachten test revealed baseline morning cortisol at82.5 ngl/mL and at 147 ng/ml at 60th minutes/ normal ACTH = 25 pg/ml). Further investigations excluded tuberculosis infection, adrenal hemorrhage or neoplasia. Anti adrenal antibodies were also negative. Treatment by hydrocortisone substitution (30 mg/day) was prescribed. Nevertheless, musculoskeletal symptoms persisted leading to inability to walk. Three months later, she experienced dyspnea, arthralgia, and dysphagia. Physical examination revealed Raynaud's phenomenon, cutaneous sclerosis in the face and the trunck and digital ulcers. The body temperature was at 38°C, the blood pressure was at140/90 mm Hg, the heart rate was at 100 bpm. She had proximal muscles deficiency. Electrocardiogram revealed right branch block. Doppler-echocardiography found low systolic function (26%) and enlarged right cavities with high pulmonary arterial pressure (76 mmHg). Computed tomography ruled out pulmonary embolism and revealed interstitial lung disease. Biological findings found elevated transaminases (AST/ALT: 200/110 iu/l) and high muscular enzymes (CK:465 iu/l). Immunologic analysis found high anti nuclear antibodies (1/1280). Myositis immunoblot was negative. Electromyography showed a myogenic syndrom. MRI revealed significant bilateral amyotrophic muscles of the thigh with fatty degeneration of posterior and medial muscles. Muscle biopsy was normal. Gastro-duodenal endoscopy showed peptic esophagitis. Manometry demonstrated peristaltic disorder in lower esophagus. Scleromyositis with severe cardiac involvement was retained. Steroid therapy was started (1 mg/kg/day) with 3pulses of methyl prednisolone associated to immunosuppressant (cyclophosphamide) and symptomatic treatment based on diuretics, ACE inhibitors and colchicine. Clinical course was favorable. Control echocardiography after one month revealed improvement of left ventricular function (60%). The patient has been followed up for over 13 years with favorable course.
Conclusion
This case underlines the importance of seeking endocrinopathies in patient with unexplained musculoskeletal symptoms. However, that should not under diagnose autoimmune myopathies disorders like scleromyositis.

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AEP25

Oral and dental manifestation of Allgrove syndrome: A case report

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Introduction
Triple-A syndrome, also known as Allgrove syndrome, is a rare autosomal recessive disorder. It is a multisystemic disease with an estimated prevalence of 1 per 1 000 000 individuals The 3 features of this syndrome are achalasia, adrenal insufficiency, and alacrima. Recently, dental impairment has been the subject of several case reports and reviews. However, this abnormality remains under-diagnosed.
Purpose
This article reports a patient with multisystemic features of the syndrome with particular attention to premature loss of permanent teeth.
Case report
We represent the case of a 23-year-old male patient with no family medical history, born to consanguineous parents. He was diagnosed with adrenal insufficiency at the age of 3 after a hypoglycemic and hyponatremia seizure with low cortisol and elevated ACTH level. He was treated with oral hydrocortisone. Medical examination showed hyperpigmentation, microcephaly, delayed developmental milestones and dysmorphic facial features: narrow face, long philtrum, down-turned mouth. Further examination confirmed achalasia and dysphagia. The Allgrove syndrome was then suspected and confirmed when genetic analysis identified the mutation of the AAAS gene (IVS14 + 1G). He had esophageal dilatation on 2 occasions (2000 and 2011) with real improvement of dysphagia. At the age of 6, the patient started having gingivitis and dental caries. Due to tendency to eating sweet foods and poor oral hygiene, the teeth have decayed rapidly. Also, due to inadequate root length remaining after the removal of decay, all of them were extracted. Because of economic problem, he had implant treatment for only his upper teeth when he was 20-years-old. However, the implant was only successful for 2 years and then the patient started losing his teeth again.
Conclusion
Triple A syndrome is a multisystemic disease needing multidisciplinary management: endocrinology, gastrology, ophthalmology and dentists. The prevention and management of bucco-dental complications associated with xerostomia and achalasia are essential to minimize the loss of permanent teeth and improve the quality of life.

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AEP26

Adrenal steroid profiling in the diagnostics of partial enzyme defects in the adrenals. Establishment of normal cut-off levels using LC-MS/MS

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Background
Non-classical congenial adrenal hyperplasia (NCCAH) is an important differential diagnosis in women with acne, hirsutism, menstrual abnormalities and infertility. To diagnose NCCAH can be challenging, and currently used cutoff levels are based on unstandardized immunological assays, no longer in use.

Objective
Define LC-MS/MS based cut-off levels for steroid hormones, to improve diagnosis of NCCAH and other less common partial enzyme defects in the adrenals.
Methods
Basal and cosyntropin stimulated serum samples were collected from 83 healthy adults (52% women), 23–68 years of age. Twenty-two patients evaluated for possible NCCAH were used as a validation cohort. LC-MS/MS determined cut-offs for basal and cosyntropin stimulated 17-OHP, 21-deoxycortsiol (21-DF), 11-deoxycortisol (11-DF), deoxycorticosterone (DOC), corticosterone (B), 17-hydroxypregnenolone (17-OH Preg), cortisone (E), and dehydroepiandrosteron (DHEA) were defined by the 2.5 and 97.5% percentile in healthy subjects respectively.
Results

Table 1 shows basal (0 min) and cosyntropin stimulated (60 min) lower (2.5%) and upper (97.5%) cut-off levels for the steroid hormones studied.

Steroid (nmol/l)	0 min		60 min	
	2.5 %	97.5%	2.5 %	97.5%
17OHP	0.30	5.5	1.5	9.3
11DF	0.22	2.5	0.91	5.1
21DF	< 0.25	< 0,25	0.26	1.9
DOC	0.07	0.39	0.26	1.3
B	1.4	57	45	142
17OHPreg	3	–[a]	7	33
E	25	74	25	62
DHEA	4	57	8	114

[a]not calculated: many results < mLOQ; No significant differences were found between the genders, or between age groups.

Table 2 shows how these cut-off levels are applied on the validation cohort, consisting of 18 patients classified as healthy and three patients with verified NCCAH. One patient was impossible to classify, and is omitted from **Table 2**.

Steroid (nmol/l)	Patient 1		Patient 2		Patient 3		Healthy validation cohort (n = 18)	
	0 min	60 min	0 min	60 min	0 min	60 min	0 min	60 min
17OHP	< 5.5	> 9.3	< 5.5	> 9.3	< 5.5	> 9.3	All < 5.5	n = 1 > 9.3
21DF	> 0.25	> 1.9	< 0.25	< 1.9	< 0.25	< 1.9	All < 0.25	All< 1.9

All three women with verified NCCAH showed one or more parameters above the defined upper cut-off levels.
Conclusions
We propose that serum steroid profiling by LC-MS/MS should be applied as the initial screening test for NCCAH and other rarer enzyme defects in the adrenals. Our data supports that the cosyntropin stimulation test is still needed in the work-up of this patient group.

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AEP27

Clinical and pathological characteristics of pheochromocytoma and paraganglioma: Single center experience

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Aim
Pheochromocytoma and paraganglioma are rare neuroendocrine tumors, that can be diagnosed incidentally or with symptoms that may be confused with other diseases. In our study, we aimed to demonstrate our clinical biochemical and pathological experiences with pheochromocytoma and paraganglioma cases.
Method
The clinical, biochemical, radiological, and pathological data of a total of 79 patients diagnosed with pheochromocytoma between 2006 and 2021 at Marmara University School of Medicine Endocrinology and Metabolic Diseases Polyclinic were evaluated retrospectively.
Results
The mean age of the 79 patients was 51.7 ± 15.0 years, and 46.8 ± 15.6 years at the time of diagnosis. The majority of patients were female (Female/Male:48/31). The percentage of patients diagnosed incidentally was 53.2%, while 32.9% of patients were diagnosed due to hyperadrenargic symptoms, and 14.0% of them were diagnosed during screening for hereditary conditions. The most frequent symptoms were hypertension (49.4%), palpitation (39.2%) and perspriation (30.4%). Median tumor size in MR imaging was 45.5 mm (range: 7–170 mm) and the lesion size correlated significantly ($P < 0.0001$, $r = 0.5390$) with the urinary normetanephrine levels. Tumor localization was left adrenal in 30.4%, right adrenal in 27.8%, bilateral adrenal in 17.7%, and paraganglioma in 21.5% of patients. Eight patients (10.1%) were Von Hippel-Lindau, three patients (3.8%) were multiple endocrine neoplasia (MEN) type 2A, two patients (2.5%) were MEN type 2B, one patient (%1.3) each was neurofibromatosis type 1 and familial pheochromocytoma. Hereditary pheochromocytomas were diagnosed at younger ages, and bilateral lesions were more prevalent in them (both $P < 0.0001$). 64 patients were operated, others refused the operation or left the follow-up. The mean of tumor size in pathology report was 57.2 ± 27.5 mm. Malign pheochromocytoma was detected in 12 patients (15.2%), half of them was hereditary. Postoperative in the first year, urinary metanephrine, normetanephrine and vanilmandelik acid values of all patients decreased compared to preoperative values significantly (all of them $P < 0.0001$). A total of 5 patients died during the follow-up period, one of them was malignant. Three of the malignant ones received chemoradiotherapy. The clinical and biochemical characteristics of malignant and benign ones were similar. Pathological findings will be re-evaluated.
Conclusion
Hereditary syndromes should be kept in mind in young and bilateral cases. Since there is no clinical or biochemical test to distinguish malignant and bening, malign pheochromocytoma should also be considered, especially in hereditary cases.

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AEP28

Effects of sorafenib, a tyrosin kinase inhibitor, on adrenocortical cancer cell line

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The lack of an effective medical treatment for adrenocortical carcinoma (ACC) has prompted the, search for better treatment protocols for ACC neoplasms. Sorafenib, a tyrosine kinase inhibitor has exhibited effectiveness in the treatment of different human tumors. Therefore, the aim of this study was to understand the mechanism through which sorafenib acts on ACC, especially since treatment with sorafenib alone is sometimes unable to induce a long-lasting antiproliferative effect in this tumor type. The effects of sorafenib were tested on the ACC cell line H295R by evaluating cell viability, apoptosis and VEGF receptor signaling which was assessed by analyzing VE-cadherin and β-catenin complex formation. We also tested sorafenib on an *in vitro* 3D cell culture model using the same cell line. Apoptosis was observed after sorafenib treatment, and coimmunoprecipitation data suggested that the drug prevents formation VEGFR-VE-cadherin and β-catenin proteins complex. These results were confirmed both by ultrastructural analysis and by a 3D model where we observed a disaggregation of spheres into single cells, which is a crucial event that represents the first step of metastasis. Our findings suggest that although sorafenib induces apoptotic cell death a small portion of cells survive the treatment and have characteristics of a malignancy. Based on our data we recommend against the use of sorafenib in patients with ACC.

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AEP29

Incidental detection of adrenal hyperplasia and mortality in patients with suspected SARS-CoV-2 Infection

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Many patients affected by SARS-CoV-2 disease (COVID) have associated comorbidities (arterial hypertension, obesity, diabetes mellitus, thrombophilia) that are also tied to autonomous cortisol secretion. However, the prevalence of diseases of the adrenal glands in COVID patients is presently unknown. Since the visualization of the adrenal glands is almost always available in chest CT performed in patients with suspected or confirmed SARS-CoV-2 infection, the evaluation of adrenal morphological disorders in such patients appears of interest. We assessed a prospective consecutive series of 402 patients (M 222, 55.2%; F 180, 44.8%) with a median age of 76 years (IQR 64–84 years), admitted to the emergency department for suspected SARS-CoV-2 infection. One hundred patients had a PCR-confirmed diagnosis of infection on a nasopharyngeal swab (24.9%). All patients underwent a chest CT study including the adrenal region. We found an altered adrenal morphology in 100 patients (24.9%): 62 subjects (15.4%) had adrenal hyperplasia (67.7% unilateral, 32.3% bilateral) and 38 (9.5%) discrete adrenal nodules (89.4% unilateral, 10.6% bilateral). The median size of adrenal nodules was 16 mm (10–50 mm) with a median density of 10 HU (-41–42 HU). In 17 patients with adrenal hyperplasia, a previous CT was available for comparison: in all cases an increase in thickness was evident at admission (median increase 1.95 mm, range 1–15). COVID patients had a non-significant higher frequency of adrenal nodules and hyperplasia (12% vs 8.6%, P = NS and 17% vs 12%, P = NS, respectively). Sixty-three patients (16%) died. They were older (80 vs 74 years, P = 0.001), had a higher frequency of adrenal hyperplasia (25% vs 14%, P = 0.03), more frequent active cancer disease (37% vs 19%, P = 0.003) and COVID (23% vs 13.2%, P = 0.02). In a multivariate model, adrenal hyperplasia is an independent risk factor for mortality (OR 2.52, 1.15–5.55, P = 0.02), as well as age (OR 1.04, 1.01–1.07, P = 0.005), active oncological disease (OR 3.06, 1.44–6.49, P = 0.004), and COVID (OR 2.88, 1.38–6.01, P = 0.005). This is the first study reporting the prevalence of morphological alterations of adrenal glands in suspected COVID patients. The frequency of discrete adrenal nodules (9.5%) is in line with the high prevalence of adrenal incidentalomas in elder subjects. The finding that adrenal hyperplasia is associated with an increased risk of mortality suggests that it may be the consequence of an exaggerated activation of the HPA axis due to a highly stressful condition.

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AEP30

Repeated hormonal and radiological evaluation of hypertensive patients is necessary for correct primary aldosteronism diagnosis and treatment

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Background

Primary aldosteronism (PA) constitutes the most common form of hormonal hypertension. However, it is very often misdiagnosed and incorrectly managed. Detection rates are inadequately low and the interpretation of hormonal results is impossible in some patients . Subtype evaluation with its several limitations represents another problematic issue. We describe the cases of two young primary aldosteronism patients with complicated history and a few-year follow-up until the final diagnosis.

Case description

CASE 1. 26 year-old female with grade I arterial hypertension, still hypertensive on betaxolol, with hypokalaemia despite potassium supplementation, was admitted for hormonal testing. 4 years earlier she had undergone evaluation for primary aldosteronism with strongly positive screening test results (aldosterone 23 ng/dl, plasma renin activity, PRA 0.312 ng/ml/min, aldosterone-to-renin ratio, ARR 74), but no further conclusions. Abdomen computed tomography (CT) had been normal and she hadn't been given spironolactone because of her reproductive age. She was allergic to iodinated contrast agents, so adrenal venous sampling (AVS) hadn't been performed. We repeated biochemical testing which again confirmed primary aldosteronism. Another abdomen CT revealed left adrenal adenoma sized 7.5 mm in diameter. The patient was finally successfully adrenalectomized with biochemical and clinical remission. CASE 2. 37 year-old male was referred to the Department of Endocrinology due to resistant hypertension despite 4-drug therapy (with thiazide) for the last 2 years, associated with inadequate, deep hypokalaemia. Laboratory work-up revealed medium-high, non-suppressible aldosterone levels, but with repeatedly non-suppressed direct renin concentrations (18–110 μIU/ml). The results didn't change despite drug withdrawal, making PA diagnosis questionable. Renal stenosis was excluded and adrenal glands were described as normal in CT. Two years later, the evaluation was performed again. The hormonal profile changed as direct renin concentrations were substantially lower (2,95–15 μIU/ml). ARR converted to positive and saline infusion test confirmed PA. Another CT revealed left adrenal adenoma sized 9 mm in diameter. NP59 scintigraphy showed nonspecific bilateral radionuclide uptake, so the patient is waiting for AVS.

Conclusions

Hypokalaemia of unknown origin in young patients is very indicative of PA. Non-suppressible aldosterone levels with non-suppressed renin or PRA are the laboratory findings of unexplained significance. In the case 2, they might have represented an early stage of the disease. Regular ambulatory check-up with repeated hormonal screening as well as another radiological evaluation may enable the final diagnosis in high-risk, but somehow unequivocal, cases.

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AEP31

Unilateral extramedullary adrenal plasmocytoma: A case report

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We present the case of an octogenarian with a major history of lambda light chain myeloma which was treated by a first-line lenalidomide and dexamethasone from June 2018 to September 2019. Patient had also hypertension and valvular heart disease (mechanical valve and anticoagulation by acenocoumarol). In September 2019, a right adrenal mass was incidentally discovered by a renal ultrasonography made for acute kidney injury. The abdominal CT-scan confirmed the presence of a large heterogeneous mass (5 cm) of high density (38 UH) on unenhanced attenuation in the right adrenal gland. 18F-FDG PET-CT showed a moderate FDG-uptake in the adrenal mass and two myelomatous bone lesions (one recent vertebral compaction of L2 and a lesion of the anterior arch of the 5th right rib). Adrenal mass showed high signal in T2 ponderation and in diffusion, without significant fat content on MRI imaging. The lesion characteristics allowed to exclude a benign adenoma and were in favor of a malignant nature. Hormonal evaluation did not demonstrate excessive cortisol (midnight salivary cortisol < 2.5 nmol/l) or other sexual steroids secretion [total testosterone 7.92 nmol/l (N: 6.68–25.70), DHEAs 1.56 μmol/l (N: 0.44–3.34), androstenedione < 0.2 ng/ml (N: 0.1–3.0), oestradiol < 25 ng/l (N: 27.1–52.2)]. Dexamethasone suppression test was not performed because of the treatment with methylprednisolone for the myeloma. 24-hours urine fractionated metanephrines and catecholaminesmeasurements were in the normal ranges. The hypothesis of a non-secreting pheochromocytoma was possible while non-secreting adrenocortical carcinoma (ACC) or metastasis were less probable, especially in the absence of autonomous cortisol secretion for a voluminous ACC and the absence of the localization of a primitive elsewhere for a metastasis. After a multidisciplinary discussion, a biopsy of the mass was performed before removing this neoplastic mass. Anatomapathological examination of the specimen concluded to a lambda light chain monoclonal plasmocytoma, as a rare complication of the myeloma. Solitary plasmacytomas occur most frequently in bone but can also be found outside bone in soft tissues. Extramedullary plasmacytoma (EMP) accounts for only 3% of plasma cell malignancies and adrenal plasmocytomas are extremely rare. Indeed, at our best knowledge, this is the tenth reported case of adrenal plasmacytoma.

Among the reported cases, three showed a bilateral gland involving. This case highlights the need of excluding differential diagnoses before surgical treatment of an adrenal neoplasm and the necessity of multidisciplinary input in the management of adrenal tumors.

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AEP32

A rare association of pheochromocytoma, contralateral nonfunctioning adrenal adenoma, and renal angiomyolipoma

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Introduction
Bilateral adrenal incidentalomas represent about 15% of adrenal incidentalomas. Their investigation and management are less discussed and more challenging than unilateral incidentalome. A special attention is required because they are more likely to be pathologic. When associated with a synchronous extra-adrenal tumor, the first diagnosis is adrenal metastasis, but this is not always true. Here we present a rare association of pheochromocytoma, contralateral nonfunctioning adrenal adenoma, and renal angiomyolipoma.
Case presentation
A 69-year-old female, with a history of resistant hypertension, diabetes mellitus and hypercholesterolemia was admitted in our endocrine department for exploration of bilateral adrenal incidentalomas associated with a left renal tumor. She had no family history of endocrine neoplasms. On physical examination, there was no goiter or thyroid nodules. Adrenal insufficiency was ruled out by a normal synachten test. Routine laboratory testing were normal except uncontrolled diabetes. Hormonal investigations showed a high level of urinary fractionated metanephrines (2.3 fold above the upper limit of normal). Basal cortisol level, overnight dexamethasone suppression test, and aldosterone renin ratio were normal. Contrast enhanced computed tomography had shown a typical angiomyolipoma in the upper pole of the left kidney with two adrenal gland masses measuring at right 37 mm with a density of 38 HU and at left 15 mm with a low density (–3 HU). SPECT/CT Metaiodobenzylguanidine (mIBG) scintigraphy was performed and had detected abnormal fixation in the right gland. After 10 days of preoperative preparation, the patient underwent successful right adrenalectomy and the histopathologic features were consistent with pheochromocytoma. After surgery, urinary fractionated metanephrine level was normal and the hypertension was controlled with only monotherapy.
Conclusion
Bilateral adrenal tumors require a meticulous work-up, including hormonal investigation, morphological and functional imaging studies, in order to establish the correct diagnosis and to assess the perioperative risks. The association of adrenocortical and adrenomedullary tumors with renal angiomyolipoma described in our case is not common. It can be sporadic or may result from inherited disorders or multiple neoplasia syndromes.

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AEP33

Initial therapy with empagliflozin in addition to metformin vs standard therapy alone for patients with type 2 diabetes mellitus and cardiovascular disease in qatar. A cost-effectiveness analysis

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Background
Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce deaths and cardiovascular events in patients with type 2 diabetes mellitus (T2DM), but are currently not used as first-line therapy.
Objective
To evaluate the cost-effectiveness of introducing empagliflozin into the current standard care (metformin monotherapy) for patients with newly diagnosed T2DM and existing cardiovascular disease (CVD).
Methods
A lifetime horizon Markov decision analytic model was developed from the perspective of Qatari healthcare system to compare first-line empagliflozin combined with metformin vs metformin monotherapy for patients aged 50 to 79 + years with T2DM and existing CVD. Two health states were considered: 'alive' and 'dead'. Patients entering the model transitioned to non-fatal myocardial infarction, non-fatal stroke, hospitalisation for heart failure, hospitalisation for unstable angina, death from cardiovascular or non-cardiovascular causes. Efficacy, healthcare costs, and health state utilities were ascertained from published sources as well as publicly available sources in Qatar. The main outcome was the incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year gained (QALY) and years of life saved (YoLS). Base-case multivariate uncertainty analysis was considered for this study. Costs and outcomes were discounted at 3% per annum. Sensitivity analyses were conducted to evaluate parameter uncertainty.
Results
Adding empagliflozin to current standard care led to additional 1.9 YoLS and 1.5 QALYs with an incremental cost of QAR 56,869 (USD 15,619), which equated to an incremental cost-effectiveness ratio of QAR 30,675 (USD 8,425) per YoLS and QAR 39,245 (USD 10,779) per QALY. Sensitivity analyses showed the findings to be robust.
Conclusions
First-line empagliflozin combined with metformin appears to be a cost-effective therapeutic option for patients with T2DM and CVD in Qatar.

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AEP34

Metabolic, renal and cardiovascular status in patients with primary hyperaldosteronism

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Introduction
Primary hyperaldosteronism (PHA) is an increasingly prevalent cause of endocrine hypertension. It is characterized by unregulated aldosterone secretion with an excessive activation of mineralocorticoid receptors, inducing volume expansion, hypokalemia, endothelial dysfunction and fibrotic processes in the renal and cardiovascular systems. The aim of this study was to assess the metabolic, renal, and cardiovascular status in patients with primary hyperaldosteronism.
Methods
We conducted a retrospective study in 40 patients with a primary hyperaldosteronism (aldosterone-producing adenoma: n = 24; adrenal hyperplasia: n = 16). Clinical and biological data were collected. Electrocardiogram and cardiac ultrasound were analyzed in all participants. Cardiovascular risk was assessed using Framingham Risk Score (FRS).
Results
There were 24 (60%) women and 16 (40%) men, with a mean age at the diagnosis of hypertension of 40.3 ± 10.9 years. Overweight, obesity, prediabetes, diabetes mellitus, dyslipidemia, and metabolic syndrome were diagnosed in 37, 50, 30, 32, 45, and 70% of cases, respectively. Hypokalemia was present in 30 patients (75%). Kalemia was negatively correlated with plasma aldosterone level (r = –0.387; P = 0.015). Albuminuria and chronic renal failure were found in 53 and 17% of cases, respectively. The average 10-year FRS was 19.6 ± 12.3%. It was significantly correlated with age (r = 0.675, $P < 10^{-3}$), fasting glucose level (r = 0.395, P = 0.012), glycated hemoglobin (r = .503, P = 0.009), triglycerides level (r = 0.485, P = 0.002), and creatinine level (r = 0.502, P = 0.001). However, FRS was not correlated with aldosterone and renin levels. Twenty five percent of patients had a low risk, 20% had a moderate risk and 55 % had a high risk. Thirty percent of cases had a subepicardial ischemia, 63% had a left ventricular hypertrophy and 10% had a low left ventricular ejection fraction. A history of stroke was found in 17% of patients.
Conclusion
Primary hyperaldosteronism is associated with a high prevalence of metabolic disorders and renal disease. These complications are significantly associated with the cardiovascular risk.

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AEP35

24-Hour blood pressure profile in patients with adrenal insufficiency

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Introduction
Retrospective analyses suggest that patients with adrenal insufficiency (AI) have an increased risk for cardiovascular diseases which was mainly attributed to non-physiological cortisol profiles and/or supraphysiological replacement doses.
Material and methods
We analyzed the 24-hour blood pressure (BP) profiles in patients with primary (PAI) and secondary (SAI) AI. BP threshold criteria for hypertension and dipping status of the 2018 ESC/ESH guidelines were used (24-h: ≥ 130 and/or ≥ 80, daytime: ≥ 135 and/or ≥ 85, night-time: ≥ 120 and/or ≥ 70, non-dippers: nocturnal BP drop < 10%). Results were correlated with daily intake of gluco-/mineralocorticoids, serum electrolytes, plasma-renin-concentration (PAI), salivary cortisol (SC) profile (06:00/12:00/16:00/20:00/22:00), 24-hour urinary free cortisol, BMI, waist-to-hip ratio and comorbidities.
Results
Fifty-two patients (30 PAI/22 SAI, age 55 (21–88), 36 females) were included. Twenty-two patients (11 AI/11 SAI) received antihypertensive treatment. Mean 24-h BP values were 124 ± 14/76 ± 10 mmHg (daytime 127 ± 15/79 ± 11, night-time 116 ± 18/69 ± 11). Prevalence of hypertensive 24-h BP was 42% (12% in patients without known hypertension), without differences between AI and SAI. Night-time hypertension was more prevalent than daytime hypertension (50% vs 35% in the whole cohort, 20% vs 8% in patients without known hypertension). Twenty-eight patients (14 AI/14 PAI) were classified as non-dippers. 20:00- and 22:00-SC levels were higher in patients with hypertensive compared to patients with normal 24-h BP (0.062 vs 0.02 $P = 0.01$, 0.054 vs 0.016 $P = 0.004$) regardless of antihypertensive treatment. Daily glucocorticoid intake was higher in patients with hypertensive 24-h BP (22.5(10–60) vs 20(15–30) mg $P = 0.035$).
Conclusion
Ambulatory hypertension and non-dipping were frequent in this small cohort of patients with AI and showed an association with supraphysiological glucocorticoid doses and exposure to glucocorticoids in the late afternoon/evening. However, validation in larger cohorts is warranted.

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AEP36

The acute effects of milk intake on calcium homeostasis and cardiovascular outcome: A randomized, crossover trial in postmenopausal women

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Introduction
The importance of calcium intake from dairy has been investigated in several studies with discrepant results. Meta-analyses have shown beneficial effects of dairy intake on cardiovascular health with an inverse association between intake and cardiovascular disease. However, a recent trial has suggested an increase in blood pressure in the hours following intake of 1000 mg of calcium citrate compared with placebo. So far, it has not been investigated whether milk intake causes similar effects on indices of cardiovascular health.
Materials and methods
We enrolled twenty postmenopausal women with vitamin D insufficiency aged between 60 and 80 years in this randomised crossover trial conducted during winter and spring. With at least ten days washout period in-between, the participants received either 500 ml of water or semi-skimmed milk with 200 µg of cholecalciferol added. Pulse wave analysis and velocity (PWV) were made twice using the SphygmoCor XCEL (AtCor Medical, Sydney, Australia): in the morning with the participants in a fasting state prior to and 4h after the intervention.
Results
Compared to water, milk increased plasma levels of ionized calcium by 1.61 pp ($P = 0.023$) and by 1.83 pp ($P = 0.053$) after 2h and 4h, respectively. Concomitantly, PTH levels decreased by 14.22 pp ($P = 0.005$) after 2 h and by 23.63 pp ($P = 0.001$) after 4 h. However, despite these changes, the two types of intervention did not cause changes as measured 4h after the intervention in indices of cardiovascular health in terms of PVW ($P = 0.557$), central diastolic blood pressure ($P = 0.599$), central systolic blood pressure ($P = 0.403$), mean arterial pressure ($P = 0.671$), pulse pressure ($P = 0.443$), aortic augmentation ($P = 0.915$), aortic augmentation index ($P = 0.782$), heart rate ($P = 0.341$), and pulse transit time ($P = 0.987$). We found no carry-over effect or period effect.
Discussion
The effects of dairy intake on cardiovascular health do not seem to occur acutely. Thus, the inverse relationship between dairy intake and cardiovascular disease seen in previous studies might be owing to long-term intake. Based on this study, milk intake is safe concerning immediate cardiovascular responses.

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AEP37

Natural history of nonfunctioning adrenal incidentalomas: A 10-year longitudinal observational study

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Objective
There are few data on long-term follow-up of patients with nonfunctioning adrenal incidentalomas (NFAIs). We aimed to determine the natural history of NFAI at 10 year follow-up. We also evaluated the associations between baseline body mass index (BMI) and changes of NFAIs' and patients' characteristics at follow-up period.
Design
Longitudinal observational study.
Patients
We included 67 patients (20 (29.9%) males, 47 (70.1%) females, mean age 57.9 (52.3–63.9) years and BMI 27.42 (24.07–30.56) (kg/m^2)) presenting with NFAI. Twenty patients had BMI < 25 kg/m^2, 21 BMI 25–30 kg/m^2 and 26 had BMI > 30 kg/m^2 at the initial presentation. The mean follow-up period was 10.5 (9.1–11.9) years.
Measurements
Clinical, laboratory and computed tomography (CT) characteristics were assessed and compared with baseline.
Results
Progression to mild autonomous cortisol excess (MACE) was observed in 22 % patients. The progression rate was significantly higher in overweight and obese subjects, given that 5% progression rate was observed in patients with baseline BMI < 25 kg/m^2, 33.3% in a group with BMI 25–30 kg/m^2 and 26.7% in a group with BMI > 30 kg/m^2. Clinically significant tumor enlargement ≥ 10 mm occurred in 8.9% patients. Prevalence of cardiometabolic disorders at follow-up was significantly higher than at baseline, especially in groups with initial BMI ≥ 25 kg/m^2. At follow-up, 37.9% of patients had additional CT changes in kidneys, 21.2% in gastrointestinal tract, 18.2% in liver region, and 10.4% in pancreas, mostly cysts. Three patients with BMI > 30 kg/m^2 were referred to further diagnostics to rule out possible malignant disease incidentally found by CT imaging, unrelated to NFAI.
Conclusion
Duration of the follow-up period is an important factor in characterizing the natural history of NFAI. Higher baseline BMI might predict the long-term likelihood of change in hormonal activity and occurrence of metabolic disorders in patients with NFAI. The clinical significance of the highly prevalent concomitant CT findings in this population and the potential role of periodic CT reassessments in obese subjects with NFAI need further evaluations.

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AEP38

Low-renin hypertension with normal or high aldosterone levels is a cause of severe hypertension, and can be diagnosed by applying endocrine society hyperaldosteronism guidelines

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Low-renin hypertension (LRH) with normal or elevated aldosterone levels is considered part of the spectrum of aldosterone-associated hypertension, and can cause poorly-controlled hypertension. We studied patients diagnosed with LRH, comparing their clinical and biochemical characteristics with patients diagnosed with primary hyperaldosteronism (PHA).
Methods
Retrospective. Diagnosis in a general Endocrinology out-patient clinic over 8 years, with strict application of Endocrine-Society Guidelines for PHA screening/diagnosis. Aldosterone/Renin (ARR) screening on medication, except for mineralocorticoid-receptor blockers or amiloride was positive when ≥ 20 (aldosterone and direct renin measured by Radioimmunoassay in pg/ml). Captopril challenge test (CCT) was positive for PHA on doxazosine and/or long-acting verapamil and/or hydralazine if aldosterone level ≥ 130 and/or ARR ≥ 50 2 hours post-25 mg captopril. Patients negative for PHA with normal/high basal CCT aldosterone, together with basal ARR ≥ 50 or low renin throughout CCT, were diagnosed with LRH. Clinical characteristics of both groups were compared. Parametric values expressed as mean (SD); non-parametric values as median [interquartile range]. SPSS 25.
Results
Diagnosis: 46 patients PHA, 80 LRH. Age at diagnosis: PHA: 57.0 (SD:11.2), LRH: 64.7 (SD:12.9), $P = 0.001$. PHA: 21/46 (46%) women, LRH: 16/80 (20%), $P < 0.001$.
Moderate hypertension
PHA: 21/46 (45.7%), LRH: 52/80 (65%), $P = 0.04$. Severe Hypertension: PHA 25/26 (54.3%), LRH: 28/80 (35%), $P = 0.04$. Resistant hypertension: PHA: 16/46 (34.8%) vs LRH: 5/80 (6.3%), $P < 0.0001$. All aldosterone and ARR levels were significantly higher in PHA than LRH, with screening and basal CCT values showing overlap. Renin levels were not significantly different at screening, nor throughout CCT. At screening, PHA vs LRH respectively: Aldosterone: 284.3 (SD:202.1) vs 206.11 (SD:99.3), $P = 0.023$. Renin: 3.8 (SD: 4.9) vs 5.2 (SD:4.6), $P = 0.13$. ARR: 109.9 (SD:8.5) versus: 52.9 (SD: 33.6), $P < 0.0001$. Baseline CCT: PHA vs LRHT respectively: Aldosterone 296.2 (SD: 194.5) vs 146.3 (SD:56.7), ($P < 0,001$). Renin 3.0 (SD:3.7) vs 3.3 (SD: 2.15), $P = 0.54$. ARR: 162 (SD: 126.0) vs 57.7 (SD: 38.9). $P < 0.001$. 2-hour CCT: PHA vs LRH respectively: Aldosterone 221.57 (SD:117.3) vs 80.3 (SD 37.2), $P < 0.001$. Renin: 2.15 [1.25–4.0] vs 3.2 [2.2–4.8] $P = 0.53$. ARR: 69.3 [52.1–165.8] vs 22.6 [12.6–37.0], $P = 0.001$.
Conclusions
LRH can be diagnosed with the CCT when applying Endocrine-Society PHA guidelines. This entity was more frequent in a general Endocrinology out-patient clinic than PHA, and over a third of patients had severe HT. Given LRH's previously-described favorable response to mineralocorticoid-receptor blockers, we believe that LRH should be diagnosed, and specifically treated as an aldosterone-associated hypertension.

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AEP39

Increasing incidence of primary aldosteronism – yet an underdiagnosed disorder

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Context
Primary aldosteronism (PA) is the most common cause of secondary hypertension. Yet, the incidence of PA in the population has not been studied.
Objective
To estimate the incidence of PA in western Sweden.
Design and methods
Patients who had received a diagnostic code for PA between 1987 and 2016 were identified in the Swedish National Patient Registry. Assessment of clinical and biochemical data retrieved from patient records was used to validate the diagnosis. The annual incidence of PA was calculated by using the number of inhabitants in the Västra Götaland County as reference.
Results
Of 570 identified patients, 473 (83 %) had confirmed PA. Eligible for the incidence analysis were 416 patients, 248 (60%) men and 168 (40%) women, diagnosed with PA between 1987–2016. The median (mean) age at diagnoses was 56 ± 12 years. The median (interquartile range) annual incidence was 2 (1–2) cases per million between 1987 and 1996, 6 (4–9) cases per million between 1997 and 2006 and 17 (12–24) cases per million between 2007 and 2016. At the end of the study (December 31st 2016), 386 patients with confirmed PA were alive and living in the Västra Götaland County, giving a prevalence of 231 cases per million (0.022%).
Conclusions
Despite increasing detection rate, PA is still underdiagnosed. Given the serious consequences of untreated PA, the noticeable low prevalence at the end of the study illustrates a need for measures aiming at increasing the awareness of PA among health care providers.

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AEP40

A Clinically silent, non-secretory phaeochromocytoma

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Adrenal incidentalomata are a common finding on cross-sectional imaging of the abdomen. Further assessment is required to differentiate benign adrenal masses from adrenocortical carcinomas and hormone-secreting tumours. Phaeochromocytomas are rare catecholamine-secreting tumours arising from chromaffin cells of the adrenal medulla. They classically present with symptoms and signs of catecholamine excess including headache, sweating, hypertension and tachycardia. However, with increased use of abdominal cross-sectional imaging it is becoming more common to discover asymptomatic phaeochromocytoma through assessment of adrenal incidentalomata.
We describe a 63-year-old man presenting with renal colic. Cross-sectional imaging of his renal tract with CT showed a 5 mm stone in the proximal ureter, but also a 40 mm right adrenal mass with indeterminate characteristics (attenuation value of 30–40 HU). He had no symptoms of catecholamine excess, no family history of phaeochromocytoma and was normotensive. Investigations for adrenal hormone excess, including 24-hour urinary metanephrine excretion, were normal. Interval imaging showed a 5 mm increase in maximum diameter over 6-months and a decision was made, based on size change and imaging characteristics, to proceed to a right laparoscopic adrenalectomy.
Surgery proceeded uneventfully without pre-operative alpha adrenoreceptor blockade. In particular intra-operative blood pressure remained stable between 100–170 mmHg systolic and 60–90 mmHg diastolic. Histological examination of the tumour showed appearances typical of phaeochromocytoma.
This report describes a rare case of a patient with an adrenal incidentaloma who underwent adrenalectomy based on radiological size and appearance criteria and in whom post-operative histology demonstrated a phaeochromocytoma despite normal 24-hour metanephrine levels; a non-secretory phaeochromocytoma. It highlights the changing presentation of phaeochromocytoma from classical symptomatic disease to more incidental asymptomatic disease. However, it is very rare to see asymptomatic disease with no biochemical evidence of catecholamine excess.

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AEP41

A case of adrenergic myocarditis in pheochromocytoma mimicking COVID-19 pneumonia

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Introduction
Pheochromocytomas are rare catecholamine-producing neuroendocrine tumors derived from the sympathetic or parasympathetic nervous system.

The clinical presentation of pheocromocytoma has varying forms, which makes diagnosing it challenging. Here, we report a case of Adrenergic cardiomyopathy mimicking COVID-19.
Case report
A 40-year-old woman with a history of pulmonary edema during cesarean delivery 4 years ago with an ad integrum normalization of cardiac function was admitted to the emergency for acute shortness of breath. Three days before her admission she presented epigastralgia, vomiting and myalgia. On physical examination: temperature: 37.9°C, blood pressure: 100/60 mmHg, HR:100 bpm, peripheral oxygen saturation 100% with oxygen therapy at 15 l/min. The chest CT revealed bilateral asymmetric ground glass opacities extended to the 2 pulmonary fields, lobe and interseptal thickening, that could be compatible with covid-19 pneumonia. The day following the admission, the patient presented an acute chest pain with tachycardia, peripheral oxygen saturation 88% with oxygen therapy at 15 l/min, confusion and eventually a cardiac arrest. The patient was successfully resuscitated, intubated, and mechanically ventilated. The electrocardiogram showed a sinus tachycardia at 110 bpm with ST segment depression in the infero-lateral leads. Transthoracic echocardiography (TTE) revealed left ventricular septal hypokinesis with ejection fraction (LVEF) 40%. Blood examinations returned the following values: troponin: 9 ng/ml;BNP: 1558 pg/ml. The diagnosis of myocarditis was brought up: hypoxemia, localized depolarization disorder, echocardiographic findings and abnormal cardiac biomarkers. A second chest scan has showed the disappearance of ground-glass opacities. The Sars-Cov2 pneumonia was eliminated because of a negative PCR, serologies and the quick disappearance of the ground-glass opacity. An abdominal computed tomography showed a liquid mass on the left adrenal gland, measuring 5.2 × 4.6 cm, with well-defined borders thickened in places. After the improvement of her condition, the patient was extubated and referred to the endocrinology department for further exploration. Holter monitoring of blood pressure has eliminated any hypertensive peaks. Laboratory tests of urine catecholamines metabolites showed increased Normetanephrine (1.3 the standard level), but normal metanephrine. A second TTE revealed a normal heart function: FEVG 70 %. Cardiac MRI, performed 16 days after, was normal. Left surrenalectomy was performed. Histopathological evaluation confirmed the diagnosis of pheochromocytoma.
Conclusion
Pheochromocytoma can present itself with normotensive cardiomyopathy. Adrenergic cardiomyopathy is a rare entity with a variable clinical presentation. This case demonstrates the importance of considering pheocromocytoma in cases of myocarditis without a cardiac etiology.

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AEP42

A case of adrenal tuberculosis mimicking non-functioning adrenal incidentaloma

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A 77 year old gentleman was referred to the endocrinology team following the incidental finding of an adrenal nodule on computer tomography (CT) colonography. Following this, dedicated CT of the adrenal showed a 4cm nodule with an attenuation of 30 Hounsfield Units. Biochemical investigation found no evidence of adrenal insufficiency or functional hormone production. Subsequent imaging by magnetic resonance imaging (MRI) and further CT showed stable appearances in size of the lesion, however concern remained regarding the risk of malignancy. Fluorodeoxyglucose-positron emission tomography was then performed, and this found moderate to intense activity in the area. The patient underwent adrenalectomy. Histopathology of the adrenal mass showed necrotising granulomatous inflammation, raising suspicion of adrenal tuberculosis (TB) and although acid-fast bacilli were not isolated on culture, TB ELISpot was positive. Differential diagnoses included sarcoid and granulomatosis with polyangiitis. The latter was considered unlikely given the clinical history and serum angiotensin-converting enzyme levels were not elevated. Multidisciplinary discussion decided this was likely a case of latent TB. Systemic anti-TB treatment was not initiated due to absence of symptoms and lack of evidence to suggest TB at other body sites. Less than 2% of adrenal incidentalomas are due to isolated adrenal TB[1]. TB is the most common cause of primary adrenocortical insufficiency caused by infection[2]. Adrenal tuberculosis is thought to rarely mimic non-functioning adrenal incidentaloma. Future development of imaging techniques and frequency of imaging will likely increase detection of non-functioning incidentalomas. This case suggests the importance of considering TB as a differential diagnosis whilst investigating non-functioning adrenal incidentalomas.
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AEP43

Evaluation of metabolic profile and thyroid disease in non functional adrenal insidentaloma patients

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Aim
Nonfunctional adrenal incidentalomas (NFAI's) are often associated with a high prevalence of insulin resistance (IR). The relationship between IR and thyroid diseases, as well as, thyroid cancer (TC) in patients with NFAI is not yet understood. The aim of this study is to determine the frequency of thyroid disease and TC in NFAI patients and to investigate any possible association of thyroid disease with IR and metabolic disturbances in NFAI patients.
Material and method
In our study, patients with NFAI and patients with normal adrenal imaging between 2010 and 2020 were evaluated retrospectively. 126 patient with NFAI and 114 patient with normal adrenal imaging were included in the study. Fasting blood glucose (FBG), fasting insulin, lipid profile, C-reactive protein (CRP), serum free triiodothyronine (fT3), free thyroxine (fT4), thyroid stimulating hormone (TSH), thyroid autoantibody (anti-Tg and anti-TPO) levels, thyroid ultrasonography and thyroidectomy results were registered retrospectively. IR was evaluated using homeostasis model assessment (HOMA-IR).
Results
There were no significant differences between NFAI and the control group in terms of age and gender. The average BMI of NFAI group was higher than the control group (29.5 ± 4.9 vs 27.4 ± 4.7, $P < 0.001$). Fasting insulin, HOMA-IR, total cholesterol, LDL cholesterol and serum CRP levels were significantly higher in the NFAI group ($P < 0.05$). FBG, HDL cholesterol, triglyceride, TSH, fT3 levels were similar in both groups. NFAI group had lower mean fT4 levels than the control group ($P = 0.027$). NFAI group had higher prevalence of positive anti-TPO and anti-Tg antibodies than the control group (%36.5 vs 23.7% and 29.4% vs 17.5%, respectively) ($P = 0.031$, $P = 0.032$, respectively). At least one thyroid nodule was detected in 89 (70.6%) NFAI group compared to 48 (42.1%) in the control group ($P < 0.001$). In NFAI group; there were 3 patients (2.4%) with diffuse goiter, 6 patients (4.8%) with uninodular goiter, 34 patients (27.0%) with multinodüler guatr (MNG), 3 patients (2.4%) with toxic MNG, 1 patient (0.8%) with Graves disease.TC was detected in 9 (7.1%) of NFAI group. MNG and TC were significantly more common in patients with NFAI ($P < 0.001$, $P = 0.046$, respectively).
Conclusion
In our study it was found that patients with NFAI had an elevated risk of IR and metabolic disturbance. Also it was detected that patients with NFAI have increased risk of autoimmune thyroiditis, nodular thyroid disease, MNG and TC. Therefore, it would be appropriate to screen NFAI patients with thyroid function test and thyroid ultrasonography as well as metabolic parameters.

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AEP44

Bilateral adrenal masses caused by extramedullary hematopoiesis detected by 18F-FLT PET/CT

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Introduction
Extramedullary hematopoiesis (EMH) refers to hematopoiesis occurring outside the bone marrow. Pathologic EMH can be caused by thalassemias or disorders in the hematopoietic system. Sites of EMH can be widespread however, most common localizations are in the spleen, liver, and lymph node
Case report
A 22-year-old male patient was referred to the endocrinology department for bilateral adrenal masses found on computed tomography (CT). The patient had been followed up at the hematology department for thalassemia major with 2 units of erythrocyte suspension replacement per month, occasionally less frequently because of patient's incompatibility. Splenectomy was done at the age of 6. Abdominal CT revealed a 50 × 35 mm mass in the right adrenal gland and 45 × 33 mm mass in the left adrenal gland. The patient had no symptoms and signs compatible with functioning adrenal adenoma such as involuntary weight gain, hypertension, etc. There was no anorexia, weight loss, smoking history associated with malignancy. The patient's height was 161 cm, weight was 68 kg, and BMI was 26.2 kg/m^2. Blood pressure was 125/75 mmHg and pulse was 65 beats/min and rhythmic. Leucocyte: 11 900, Hb:10.7 g/dl, Htc: 34%, PLT: 76 7000, Ferritin: 700 ng/ml. Adrenal functioning tests revealed no functioning. Abdominal MRI showed a 34 × 46 mm, well-circumscribed, solid mass in the right adrenal gland and 33 × 44 mm solid mass in the left adrenal gland, in out-of-phase sections without significant signal loss. The signaling feature might be compatible with an low-fat-content adenoma or non-adenomatous mass. Positron emission tomography (PET) with fluorodeoxyglucose (18F-FDG) done for malignancy exclusion showed mild FDG uptake in both adrenal masses (SUVmax for the left and right adrenal masses 2.3 and 2.4, respectively) with no other pathological uptake. Bilateral adrenal masses were thought to be due to EMH. Fluorothymidine (18F-FLT) PET imaging was performed. FLT-PET demonstrated peripheral nonhomogeneus increased FLT uptake in both adrenal glands with SUVmax 8.2 in the left adrenal gland and SUVmax 6.7 in the right adrenal gland. EMH was confirmed by adrenal biopsy from the periphery of the left adrenal gland where intense FLT uptake was observed.
Conclusion
Bilateral adrenal masses due to EMH are very rare in the literature. 18F-fluoro-3-deoxy-L-thymidine (18F-FLT) is a DNA precursor and its uptake is related to the proportion of DNA synthesis in hematopoietic cells. 18F-FLT PET/CT offers a unique and non-invasive method for three dimensional localization and quantification of functional bone marrow. It can be used to differentiate masses that could be due to EMH in atypical locations.

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AEP45

The role of E47 in patients with endogenous cortisol excess

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Context
E47 is a transcription factor mostly known for its role in B and T cell lineage commitment. Recently E47 was identified as a modulator of glucocorticoid receptor target genes, its loss protecting mice from metabolic adverse effects of glucocorticoids. Patients with Cushing's syndrome (CS) suffer from an endogenous glucocorticoid excess due to tumour formation associated with a variety of metabolic comorbidities seriously affecting patients' health status.
Objective
To analyze the role of circulating E47 in blood of patients with endogenous glucocorticoid excess.
Design, setting, and participants
Retrospective cohort study including 120 female patients with CS (ACTH-dependent=79; ACTH-independent = 41) and 26 healthy female controls. Whole blood samples were drawn in the morning after over-night fast.
Outcome measures
E47 mRNA expression levels in whole blood samples of two different CS subgroups, pre- and post-surgery as well as after ACTH stimulation and dexamethasone suppression test in controls and correlation analysis between E47 gene expression and complications of CS.
Results
Mean E47 gene expression levels were significantly lower in patients with overt CS (n = 29) compared to patients in remission (n = 91; P = 0.0391). E47 gene expression in the pre-surgery subgroup of patients (n = 18) with CS was significantly lower than post-surgery (n = 102; P = 0.0215) also in pre /postsurgery data sets of the same patients (P = 0.0166, n = 14). Gene expression also showed significant differences in overt vs. remission (P = 0.016) and pre vs. postsurgery (P = 0.008) subgroups in patients with ACTHindependent (adrenal) CS. Administration of 1 mg dexamethasone overnight did not change E47 mRNA expression. Stimulation with Synacthen resulted in a significant decrease of E47 mRNA expression 30 minutes after i.v. injection compared to baseline measurements. E47 gene expression showed a positive correlation with total serum cholesterol (P = 0.003), low density lipoprotein cholesterol (P = 0.015) measurements and waist-arm-ratio (P = 0.014) in the subgroup of patients with CS in remission.
Conclusions
Generally, the level of E47 mRNA presents with a high level of dispersion both in CS patients and controls. E47 appears to be a GC-dependent gene that is upregulated in situations with endogenous GC excess potentially aiming at reducing metabolic glucocorticoid side effects.

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AEP46

High-normal serum uric acid levels in Type 2 diabetes patients with atherosclerotic cardiovascular diseases

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Background and aim
Hyperuricemia is linked to a variety of diseases such as atherosclerotic cardiovascular disease (ASCVD). There are controversial data concerning the significance of high-normal values of serum uric acid (SUA) in patients with T2DM and cardiovascular disease. The aim of the study is to assess SUA levels in Type 2 diabetes mellitus (T2DM) patients with ASCVD.
Patients and methods
This retrospective study was performed in 70 T2DM patients. All patients had treated hypertension and hypercholesterolemia. Participants were divided into 2 groups: Group1(G1) consists of 35 patients with ASCVD, Group2(G2) consists of 35 patients without ASCVD ASCVD includes previous acute coronary syndrome (myocardial infarction or unstable angina), coronary revascularization, stroke, transient ischaemic attack and peripheral arterial disease. Diabetes duration, SUA, glycosylated hemoglobin (HbA1c), LDL-cholesterol (LDL-C), triglyceride (TG), systolic and diastolic blood pressure and body mass index (BMI) were assessed.
Results
G1 consists of 22 men and 13 women. G2 consists of 22 women and 13 men. The mean age of the patients presented with and without ASCVD was 58.5 and 54.5 years respectively. SUA levels in ASCVD patients were higher compared to patients without ASCVD (341.5 µmol/l vs 272 µmol/l, P = 0.09). Diabetes duration was longer in G1 compared to G2 (13.5 vs 11.6 years, P = 0.06). HbA1c level and BMI did not statistically differ (11.15 % vs 11.08 %, P = 0.63; 36.31 vs 33.1 kg/m^2, P = 0.7 respectively). Values of systolic and diastolic blood pressure did not statistically differ in study groups (135 mmHg vs 129 mmHg, P = 0.5; 75 vs 80 mmHg, P = 0.26 respectively). TG levels were higher in G2 (3.44 mmol/l vs 1.9 mmol/l, P = 0.06) while LDLC levels did not statistically differ between two groups (2.99 vs 2.44 mmol/l, P = 0.9).
Conclusion
T2DM patients with ASCVD have higher SUA levels compared to group 2.HbA1c level, BMI, systolic and diastolic blood pressure and LDL-C did not statistically differ between two groups. Further studies are necessary to assess significance of SUA as an independent risk factor for development of ASCVD in T2DM patients.

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AEP47

Associations between the atherogenic index of plasma, cardiovascular and metabolic risk in patients with primary hyperaldosteronism

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Introduction
Primary hyperaldosteronism (PHA) represents the most common cause of secondary hypertension. It is associated with a high risk of cardiovascular diseases (CVD), suggesting that aldosterone is implicated in the development of early atherosclerosis. Clinical studies have shown that atherogenic index of plasma (AIP) predicts cardiovascular risk. The aim of this study was to assess the associations between atherogenic index of plasma and cardiovascular and metabolic risk in patients with PHA.
Methods
We conducted a retrospective study including 37 patients with PHA. Clinical data and lipid profiles were obtained from patient's medical file. AIP was calculated as $\log_{10}$ (TG/HDL-C). It was categorized into low risk: < 0.1, moderate risk: [0.1–0.24] and high risk: > 0.24. The cardiovascular risk was assessed using Framingham Risk Score (FRS).
Results
There were 23 (62%) women and 14 (38%) men, with a mean age of 56.8 ± 12.6 years. Smoking, obesity, diabetes mellitus, dyslipidemia and metabolic syndrome were present in 27, 49, 32, 46, and 68% of cases, respectively. Low HDLc level, hypercholesterolemia, and hypertriglyceridemia were found in 65, 19, and 41% of cases, respectively. The mean level of AIP was 0.20 ± 0.25 in all patients, 0.26 ± 0.21 in patients with metabolic syndrome vs 0.07 ± 0.27 in those without metabolic syndrome (P = 0.014). AIP was positively correlated with age (r=0.372, P = 0.023) body mass index (r = 0.445, P = 0.006), total cholesterol level (r = 0.402, P = 0.014), triglycerides level (r = 0.708, $P < 10^{-3}$), FRS (r = 0.437, P = 0.007), and negatively correlated with HDLc level (r = 0.628, P < 10–3). No association with aldosterone level (P = 0.305) or aldosterone-to-renin ratio (P = 0.942) was found. According to AIP category, 32% (12) were in low risk group, 30% (11) were in moderate risk and 38% (14) were in high risk of CVD. An AIP level > 0.24 was positively associated with a FRS > 20% (Odds Ratio = 5.7, P = 0.022).
Conclusion
PHA is involved in atherosclerotic process because of endothelial dysfunction, myocardial fibrosis and lipid metabolism alteration. Our study underlines the power of AIP as a predictive biomarker of cardiovascular and metabolic risk, independently of aldosterone levels.

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AEP48

Lipid paradox in acute myocardial infarction

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Introduction
Some studies have shown low-density lipoprotein cholesterol (LDL) and triglyceride (TG) levels were significantly lower in high-Killip (III + IV) patients compared with low-Killip (I + II) patients and in those who died after acute myocardial infarction (AMI) compared with those who survived beyond 30 days, which they called lipid paradox. Elevated levels of LDL and triglycerides are important risk factors for cardiovascular disease, and there appears to be a minor role in the acute phase of AMI. In fact, triglyceride fatty acids are the main source of energy, LDL appears to be critical for cell membrane synthesis and both are essential for cell synthesis.
Material and methods
In an attempt to demonstrate whether total cholesterol (TC), LDL, a high density lipoprotein (HDL) and TG can influence Killip's classification, as well as early post-AMI mortality, we reviewed the clinical processes of patients with type 1 diabetes. 2 admitted by EAM to our hospital. We performed a statistical analysis using SPSS version 25.0. A value of P < 0.05 was considered statistically significant.
Results
In a total of 129 patients with type 2 diabetes, they were admitted to our hospital with AMI. Of these, 65.9% were male and their ages vary between 35 and 90 years, with an average age of 68.27 ± 10.71 years. The median HbA1c at admission was 7.5% (AIQ = 1.5). Of the sample, 18.6% had current smoking habits, 20.9% had previous smoking habits and 21.7% had chronic kidney disease. Regarding other co-morbidities, we verified the occurrence, in most patients, of arterial hypertension (86%) and overweight / obesity (72.9%). TG levels were lower in those who died compared to those who survived beyond 30 days (P = 0.04), however there was no association between this and patients classified as high Killip compared to patients with low Killip (P = 0.75). As for the level of TC, LDL and HDL, its influence on early mortality and Killip's classification was not found. High Killip severity was associated with in-hospital mortality in 30 full days (P = 0.013).
Conclusion
Lower levels of TG were related to a higher rate of early mortality. The small sample size may have constituted a bias, impeding the demonstration of a relationship between LDL and the other variables under study. Other studies with more patients need to be carried out to clarify these data.

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AEP49

Hair cortisol levels in patients with adrenal incidentalomas compared to healthy controls

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Background
Adrenal incidentalomas (AI) are present in 3–10% of the general population. Up to 20% of them may have autonomous cortisol secretion (ACS). However, subclinical hypercortisolism isn't clearly defined. The 1mg dexamethasone suppression test (ODST) is the most widely accepted for the screening of these patients. Recent data suggest that hair cortisol should be considered as a routine test for the screening of Cushing syndrome.
Aim
To compare hair cortisol levels in patients with AIs and healthy controls along with the 'classical' functional diagnostic tests.
Methods
Twenty-nine consecutive patients with AIs followed in the 1st Department of the Endocrine Unit of Laiko Hospital were included in our protocol. Hormonal functional tests were analysed and compared to 29 matched healthy controls. Primary or secondary adrenal malignant lesions were excluded. Hair cortisol measurement was also performed and compared with baseline morning (8.00) cortisol, adrenocorticotropic hormone (ACTH), and 1-mg ODST. Hair cortisol samples (2 cm length) were collected according to SoHT guidelines and measured by liquid chromatography tandem–mass spectrometry (LC–MS/MS). ACS was defined in patients displaying at least two biological abnormal markers including increased urinary free cortisol, or suppressed plasma ACTH, or 1 mg-ODST > 1.8 μg/dl in patients with adrenal tumors.
Results
Age, sex and BMI didn't differ between two groups. Hypertension, hyperlipidemia and diabetes mellitus prevalence was similar in both groups. The studied population included 22 cases of non-functional AIs (NFAIs), 6 cases with ACS and 2 cases with aldosterone-producing adenomas (1 patient had concomitant secretion of cortisol and aldosterone). Although mean baseline blood cortisol levels were found higher and ACTH levels lower in patients with AIs compared to controls, no statistical significant difference was reported. 1-mg ODST was not statistical significant different between patients with NFAIs and controls groups. However, DHEAS levels were statistically significant suppressed in patients with AIs compared to controls. Mean hair cortisol levels were within the normal range and found similar in both groups. Hair cortisol showed no correlation with blood cortisol levels, ACTH and 1 mg ODST.
Conclusions
Our series didn't find significant differences in baseline blood serum cortisol, ACTH and post-1 mg-ODST cortisol levels between patients with AIs and healthy controls. Hair cortisol levels confirmed blood analyses and were similar in patients with AIs and controls. Hair cortisol could be a simple and low-cost routine test for screening and follow-up patients with AIs and studies with larger sample size should be conducted.

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AEP50

Incidentally diagnosed bilateral pheochromocytoma accompanied by urothelial carcinoma of the bladder

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Introduction
Adrenal abnormalities can be detected incidentally during the imaging performed for malignancies. These abnormalities may include adrenal pathological conditions independent of primary malignancies. Pheochromocytomas detected as part of some familial syndromes are often bilateral.In this report, we present a case of isolated sporadic bilateral pheochromocytoma that was incidentally detected during malignancy workup and staging, which is a rare occurrence.
Case presentation
The 51-year-old female patient was referred to our clinic due to the detection of bilateral adrenal mass on positron emission computed tomography (PET-CT) that was performed following the surgery for urothelial carcinoma of the bladder. The patients 24-hour urine and plasma catecholamines indicated approximately 30 times higher values of metanephrine and normetanephrine (Table 1). Fundus examination indicated grade 1–2 hypertensive retinopathy. On 24-h Holter monitoring, mean blood pressure was 152/98 mmHg. Abdominal magnetic resonance imaging (MRI) showed a lesion that was isointense in T1-weighted images and slightly hyperintense in T2-weighted images without signal loss in the external phase sequence, measuring 43 × 23 mm in the right adrenal gland and 26 × 29 mm in the left . Based on these findings, the patient was diagnosed as bilateral pheochromocytoma and the patient was negative for Von Hippel-Lindau (VHL) and RET gene mutations. Bilateral cortex-sparing surgery was performed .The catecholamine levels of the patient decreased postoperatively. The pathological result was reported as pheochromocytoma, with a diameter of 4.5 cm on the right side and 5 cm on the left, which was positive for s-100, synaptophysin, chromogranin, and neuron-specific enolase (NSE) and had a low ki-67 index. The PASS (pheochromocytoma of the adrenal gland scaled score) score was 1 and 3 for the right and left glands, respectively. No pathological lesion was detected in the adrenal glands in follow-up imaging.
Conclusion
Almost 5–10% of pheochromocytomas occur bilaterally. Although bilateral masses are rare, they do not have any syndromic features. Nevertheless, the number of pheochromocytoma cases detected in the presymptomatic stage is increasing due to the growing use of advanced imaging techniques and genetic tests.
Keywords: Bilateral pheochromocytoma, adrenal incidentaloma, urothelial carcinoma

Table 1. Clinical characteristics

TEST	Preoperative value	Reference value	Postoperative value
Plasma Metanephrine	608.71 pg/ml	≤ 90	15.5
Plasma Normetanephrine	5877.92 pg/ml	≤ 180	177.68
Plasma Adrenaline	168.81 ng/l	≤ 90	66.86
Plasma Noradrenaline	895.32 ng/l	≤ 500	189.72
Urine Metanephrine	1496.51 µg/24 h	50–250	88.95
Urine Normetanephrine	8370.15 µg/24 h	100–500	369.96
Urine Adrenaline	51.6 µg/24 h	0–20	7.32
Urine Noradrenaline	145.76 µg/24 h	15–80	45.83

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AEP51

Occult aldosteronoma mimicking degenerative spine disease

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68 years old Caucasian women presented to the emergency department (ED) with complains of stiffness, intolerable pain in lumbosacral region and inability to walk for last two days. The common pain-relieving medications did not subdue her pain. The patient had experienced similar episodes for two years, provoked by remaining in fixed position or after having carbohydrate rich meal. Pain usually persisted for a few minutes and symptoms disappeared after light exercise. Her complains were attributed to lumbar spondylosis and treated with analgesics. Her medical history revealed that she had been admitted to ED due to hypertensive crisis and epistaxis 7 times over last 8 years. She was on maximal dose of perindopril and amlodipine. Further neurological examination revealed asymmetrically decreased strength in lower extremity muscles and asymmetrical proximal leg paraparesis, more pronounced on the left side. Deep tendon reflexes in lower extremity were similar, without pathological reflexes. Sensitivity and the rest of the examinations were normal. Magnetic resonance imaging of the spine ruled out a compressive–expansive condition, CT of the brain showed no relevant changes. Nerve conduction study revealed bilateral carpal canal syndrome dxt > sin, severe grade; sensory-motor polyneuropathy in the legs, axonal-demyelinating; chronic, old L3-L4 sin root damage. BP was 128/80 mmHg. In laboratory tests serum potassium was 3.2 mmol/l, sodium 138.0 mmol/l, creatinine 56.0 µmol/l. ECG showed normal sinus rhythm, heart rate was 70 beats per minute and patient denied any history of dysrhythmias. Due to family history of multiple gastrointestinal cancers, abdominal CT scan with contrast was performed, thus concurrently left side adrenal adenoma of 2 cm in size was detected. The patient was consulted by endocrinologist, plasma aldosterone concentration (PAC) and direct renin concentration (DRC) was assessed. PAC was 9.47 ng/dl, DRC was 0.59 ng/l. PAC/DRC ratio was 15.8 ng/dl/ng/l. According to Endocrine Society Clinical Practice Guidelines 2016 the lowest range of PAC/DRC ratio for diagnosis of primary hyperaldosteronism is 3.8–7.7 ng/dl/ng/l. A council of endocrinologist, endocrine surgeon and radiologist decided to perform left side laparoscopic adrenalectomy. Histopathological examination determined tumour with large compact cells with lipid rich cytoplasm, sign of adrenal cortex clear cell adenoma. After surgery patient improved rapidly with significant reduction of presenting symptoms. She had no further episodes of spine and leg stiffness. We are reporting the unusual case of primary hyperaldosteronism with hypokalemic periodic paralysis mimicking lumbar spondylosis and treated ineffectively with analgesics for several years.

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AEP52

Oligosymptomatic positive SDHB gene mutation paraganglioma

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Introduction
Endocrinopathies represent about 1–3% of secondary hypertension.The non-head-neck paragangliomas are rare neuroendocrine tumors that arise from the ganglia of the sympathetic nervous system. About 75% are intra-adbdominal,thus they are often mistaken for adrenal pheocromocitoma.They usually secret normetanephrine and chromogranin A, which are responsible of 0.2–0.6% of secondary hypertension.
Objective
A case report of a young man with a 6 years history of paroxysmal, well tolerated hypertension.
Case report
A 26-year-old male presented in our clinic with a long-term history of hypertension crisis associated with palpitations, headache, cold sweats and tremor, triggered by physical effort and mental stress, that attenuated spontaneously in the last two years. Abdominal MRI performed 2 years ago suggested a vascular tumor on the left adrenal gland (40/42/46 cm). The urinary metanephrines were elevated. No treatment was performed at that time.
Results
Current laboratory studies point out both an elevated plasma and urinary normetanephrine level as well as chromogranin A. Matinal cortisol and ACTH were normal. The MRI revealed one tumoral node (48/44/47.5 cm)

without demarcation in relation to the pancreas, left paraaortic, focally adjacent to the splenic and left renal vascular pedicle. Paraganglioma was suspected and treatment with alpha1-selective adrenergic receptor blockers was initiated, followed by beta-adrenergic receptor blockers. This treatment has been prescribed for 2 weeks as preoperative preparation. Laparoscopic surgery was performed without any complications. Postoperative, the blood pressure values were maintained in normal range. Immunocytochemical analysis showed that tumor cells were positive for chromogranin A, S100, synaptofisin and Ki67 3%, with a GAPP score =3/10. The histologic features combined with the immunocytochemical and ultrastructural findings confirmed the diagnosis of paraganglioma. Genetic testing showed a germline mutation in the SDHB gene. Follow-ups after the 1st, 3rd, 6th, 12th, 24th months after surgery revealed normal hormonal profile and negative PET-CT scan.
Conclusion
Although our patient has multiple negative risk factors (young age, voluminous tumor, SDHB gene mutation), the clinic was oligosymptomatic and the evolution was favorable, without any recurrence at the present.

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AEP53

Pheochromocytomas: Diagnosis, treatment and clinical outcomes

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Introduction
Pheochromocytomas originate in the adrenal medulla. Although rare, they can be lethal through their cardiovascular complications. They may be sporadic or come in the context of hereditary syndroms. The aim of our work is to describe the clinical, biological and radiological features of these tumors and assess the clinical outcomes after surgical treatment.
Materials and methods
Our study is retrospective descriptive, involving 21 patients presenting pheochromocytomas, followed in our Endocrinology-Diabetology and Nutrition Department.
Results
The mean age of our patients was 46.3 ± 16.3 years with a sex ratio H/F of 0.4. History of hypertension was present in 52.3% of cases and diabetes in 46% of cases. In 52.3% of patients the pheochromocytoma was discovered while exploring adrenal incidentaloma, 4.7% in the context of inherited disorders, especially multiple endocrine neoplasia type 2, and 42.8% in the course of symptoms. 52.6% of cases presented with the complete Menard Triad, 36.8% reported abdominal pain, and only 26% experienced weight loss. All of them had elevated 24-h urinary fractionated metanephrines, varying from 4 up to more than 100 times the normal value, with an average of respectively 12 and 11 times the normal value for metanephrine and normetanephrine. Abdominal CT scan was performed for all patients revealing unilateral tumors in 79% of cases and bilateral in 21% of cases. The mean size of the tumor was 42.1 ± 26.2 mm (11–103). Before surgery, 38% of our patient received α1blockers preparation 15 days before surgery. During the intervention, only 37% presented hypertensive peaks without further complications. In post-operative follow-up, a good blood pressure control was achieved and antihypertensive treatment was reduced in all of our hypertensive patients. As for glycaemic control, the mean HbA1c dropped from 8.1% ± 1.7 before surgery to 6.6% ± 1.3 three months after. Antidiabetic treatment was permanently stopped in 22% of cases concluding to the diagnosis of secondary diabetes mellitus, and significantly reduced in the rest. In our series, 71.4% of pheochromocytomas were sporadic, 23.8% secondary to MEN1 and only 4.7% in Van Hippel Lindau Disease.
Discussion–conclusion
Pheochromocytomas are rare but dangerous tumors due to the catecholalmines over production and the potential cardiovascular complications. The preoperative treatment with α1blockers at least 10–14 days before surgery prevents and limits peroperative hypertensive peaks, arrhythmia and circulatory complications. Surgery remains the gold standard treatment with good post-surgical outcomes. Pheochromocytomas may be associated with familial syndroms like NEM2 and VHL or hereditary mutations of succinate dehydrogenase subunits (SHD). Therefore, genetic testing seems relevant especially if the patient present a familial history of pheochromocytomas.

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AEP54

Adrenal function recovery after successful surgery for Cushing

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Background
Cushing syndrome (CS) is caused by prolonged exposure to elevated cortisol levels and it's classified as either ACTH-dependent or ACTH independent CS. The most common form of endogenous ACTH CS is Cushing disease (CD); ACTH-independent CS is caused by various adrenal abnormalities. First-line therapy in CS is the resection of the underlying tumor in all cases. After surgical cure of CS, most patients develop transient secondary adrenal insufficiency (SAI) requiring postoperative glucocorticoid (GC) replacement. The aim of this study is to review the time to normalization of adrenal function after surgical cure of CS.
Patients and Methods
This study is based on the review of 34 patients cured by surgery, after being diagnosed either with CD (15) or ACTH-independent CS with overt CS (19) in our endocrinology department between 2010–2020. All patients were declared cured of CS with postoperative SAI. GC replacement was started for basal plasma cortisol < 5 mg/dl or a stimulated plasma cortisol < 20 mg/dl, using synthetic ACTH with follow-up at 3, 6, 9 months and 1 year or more in selected cases in order to see the duration of SAI.
Results
Data showed that they received GC replacement for a period of time that ranged from 4 to 27 months, 2 of them with permanent SAI. The decision of ceasing therapy was based on a stimulated cortisol value ≥ 20 mg/dl, without any evidence of SAI symptoms after that. Patients with CD required a longer period of substitution (a mean of 17.5 months) than patients with ACTH-independent CS (a mean of 13.3 months).
Conclusions
Successful surgery in CS leaves behind SAI, requiring a long term steroid substitution. The decision of whom to treat is based on many clinical and biochemical data, besides absolute cortisol values.

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AEP55

Pulmonary metastasis of a pure oncocytic adrenocortical neoplasm after a 2 years follow up

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Oncocytic adrenocortical neoplasms (OAN) were first described by Kakimoto *et al*. in 1986. Since then, only 160 cases have been reported in the literature. There are 3 categories of OANs: pure oncocytic, mixed oncocytic and ordinary adrenocortical with focal oncocytic changes. Although the majority of OANs are considered benign tumors, certain OANs may present similar characteristics to adrenocortical carcinoma, correct histological caractherisation is therefore crucial. OANs should be assessed using the Lin-Weiss-Bisceglia (LWB) score as the Weiss score may overestimate the malignant nature of these tumors.
We report the case of a 52-year-old man without medical history, addressed for exploration of a large adrenal mass discovered on self-palpation. The patient was completely asymptomatic, with no clinical sign of hormonal hypersecretion. Hormonal testing showed very high DHEAS levels and slightly elevated 17-OH progesterone. CT scan found a 17 × 16 × 11 cm, heterogeneous left adrenal mass, with calcifications and 34 HU spontaneous density. Open left adrenalectomy was performed, with an anatomopathological examination in favor of a 25 × 16.5 × 15 cm OAN weighing 2800 g, considered malignant according to the LWB score. After 2 years of CT scan monitoring every 6 months, a 8 mm pulmonary nodule was detected. The FDG-PET-CT was consistent with increased uptake in the micronodule and in an infracentrimetric lumbo-aortic lymphadenopathy. Biopsy of the pulmonary micronodule confirmed the metastatic origin of the initial OAN.

After discussion in the COMETE multidisciplinary meeting, radiofrequency ablation of the pulmonary nodule was performed and the patient was started on adjuvant Mitotane treatment. CT and PET-FDG assessment carried out 4 months later did not find any increased uptake in the lumbo-aortic lymph node previously described. Pure functional OAN diagnosis, management and follow-up are still controversial. Due to the uncertain evolution profile of these tumors, close monitoring is still recommended in order not to ignore local or distant recurrence. Given the rarity of these tumors, no studies concerning adjuvant therapies have been performed. Each case must be discussed in multidisciplinary meetings of expert networks.

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AEP56

Paraganglioma in pregnancy: The need for a multidisciplinary approach

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Introduction
Paragangliomas (PGL) of the urinary bladder are an extremely rare entity. During pregnancy, PGL can carry higher risk of foetal and maternal mortality, which can be significantly reduced when the diagnosis is made antepartum and adequate multidisciplinary management and surveillance is started. However, despite clinical stability, delivery complications rates are still higher than in the general obstetric population.
Case description
We present a 29-year-old SDHB mutation carrier with a functional urinary bladder PGL diagnosed at the age of ten. She had a past history of hypertension, cardiomyopathy and retinopathy and experienced several recurrences of the disease, requiring two surgical interventions. In 2008, she presented uncontrolled high blood pressure and began treatment with an α-adrenergic receptor antagonist (αAA). Concurrently, vertebral bone lesions were identified and she was submitted to radiotherapy. A year later αAA was withdrawn as she was asymptomatic, with persistently normal metanephrines and stable vertebral bone lesions. Considering the patient's desire for pregnancy and after explaining the risks inherent to her clinical condition, she was referred to maternity unit for close monitoring. She was followed regularly throughout pregnancy and ambulatory blood pressure (BP) monitoring at 15 weeks revealed slightly high diastolic BP but no medical therapy was required. Repetitively normal levels of free plasma metanephrines, 3-methoxytyramine and chromogranin A were observed. She delivered vaginally at 36 weeks and during labour presented with significantly high BP requiring labetalol bolus. Aminotransaminases were elevated (10 times above reference value) and thrombocytopenia (< 20 000/ul) was detected. She was admitted to the intensive care unit with the diagnosis of HELLP syndrome and progressed satisfactorily afterwards. Her postpartum recovery was uneventful.
Discussion
We present a challenging case of a pregnant woman with known metastatic PGL. Even though she presented a HELLP syndrome, there is no data regarding the relationship between these two entities. PGL is not an absolute contraindication, but it does represent a risk factor for potential complications during pregnancy. It is important for the clinician to respect the maternal wiling, after adequate information of the risks involved. The decision to treat with an αAA requires a fine balance between reducing the risk of hypertensive peaks and the risk of uteroplacental insufficiency.

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AEP57

The prevalence of metabolic and cardiovascular complications in patients with pheochromocytoma

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Introduction
Phaeochromocytomas are rare neuroendocrine tumors secreting high levels of catecholamines, able to exert serious metabolic and cardiovascular effects. Glucose intolerance are common complications that require an early recognition and treatment.
Methods
A retrospective study was conducted to assess the prevalence of metabolic and cardiovascular complications in 35 patients diagnosed with pheochromocytoma in the endocrinology's department of Rabta hospital from 2006 to 2020.
Results
The average age was 47 ± 11 years [23–72]. glucose tolerance disorders were diagnosed in 51.7% of cases; 44.8% had type 2 diabetes, one patient had moderate fasting hyperglycemia and one had glucose intolerance. 72% of the patients had dyslipidemia. For the cardiovascular complications, hypertension was found in only 20 patients (76.9%). An ultrasound myocardium imaging was practiced in 21 patients. myocardial amyotrophy was detected in only 9.1% of patients with all having a conserved left ventricular ejection fraction.
Conclusion
The recognition of early catecholamine-induced alterations in patients with pheochromocytoma is important to prevent at least morbidity and mortality before surgical treatment.

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AEP58

Diabetes and adrenal incidentaloma

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The term adrenal 'incidentaloma' is referring to an adrenal mass discovered incidentally during an abdominal imaging exam not motivated by the exploration of an adrenal pathology. The prevalence of diabetes in incidentaloma is high therefore a cortisol secretion should be searched. This is a retrospective study conducted on 100 patients with adrenal incidentaloma. These patients are divided into two groups; the first group is made up of diabetics (G1: $n = 31$) and the second of non-diabetics (G2: $n = 69$). The clinico-biological profile in the two groups was compared. The diabetics were older (64 vs. 56 years; $P = 0.03$). There was a slight female predominance in both groups (74% vs 52%; $P = 0.03$)). The majority of diabetics with incidentaloma had dyslipidemia (51% vs 22%; $P = 0.04$). Arterial hypertension was significantly more frequent in the diabetic group (74% vs. 47%; $P = 0.01$). Non-secretory adenoma was slightly more frequent in non-diabetic group (79% vs 70%). Cushing and Conn adenoma were more frequent in diabetic group. There was no pheochromocytoma in that group. The search for the secretory character of an adrenal mass is strongly recommended. Diabetes is common and is frequently secondary to the secretion of catecholamines and mineralocorticoids and cortisol.

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AEP59

Computed tomography in diagnosis of non-functional adrenal adenoma

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Background
Adrenal incidentaloma (AI) is an adrenal mass discovered accidentally during abdominal or chest imaging techniques not aimed to adrenal gland assessment. The management of non-functional adrenal adenomas (NFAI) at least 4 cm is still a matter of debate as it is unclear whether imaging can be used to characterize their potential malignancy. Moreover, the risk of new hypersecretion in nonoperated tumors is uncertain. Our aim was to better characterize these large NFAIs.
Objective
Description and assessment the radiological parameters of NFAI on computed tomography (CT).
Materials and methods
We performed a retrospective study in City Hospital No. 40 in Yekaterinburg from January 2009 to December 2019, involving 89 operated patients NFAI. For all patients, we assessed history, physical examination, radiological

parameters of NFAI by CT scan (native Hounsfield unit [HU]), maximum diameter and blood investigations (glycated haemoglobin, adrenocorticotropic hormone, aldosterone, renin, aldosterone/renin ratio, normetanephrine, metanephrine, dehydroepiandrosterone sulphate, cortisol and 1 mg overnight dexamethasone suppression test).
Results
Criteria for the diagnosis of malignant NFAI were: a combination of size and HU. 89 operated patients NFAI consist of 3 groups. 1 – the group with native CT < 10 HU (*n*-44): adrenal mass 5.87 ± 2.98 cm (95% CI 4.99–6.75 cm), aged 46.16 ± 12.02 years (95% CI 42.61–49.71 years), observation time before surgery 2.21 ± 3.13 years (95% CI 1.28–4.05 years); 2 – the group with native CT inhomogeneous density (*n*-14): adrenal mass 5.60 cm (IQR 4.0–6.75 cm), aged 60.5 years (IQR 47.5–63.25 years), observation time before surgery 0.5 years (IQR 0.38–1.44 years). 3 – the group with native CT ≥ 10 HU (*n*-31): adrenal mass 6.0 ± 3.13 cm (95% CI 4.9 – 7.1 cm), aged 45.39 ± 13.52 years (95% CI 40.63 – 50.15 years), observation time before surgery 2.27 ± 3.02 years (95% CI 1.21 – 3.34 years).
Conclusions
Patients treated by adrenalectomy had tumors > 5.6 cm, high or different density areas CT ($P < 0.05$).
Keywords: Adrenal incidentaloma, non-functional adrenal adenoma.
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AEP60

Assessment of glucolipid metabolism in patients with nonfunctional adrenal incidentaloma

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Backgrounds
The study aimed to explore the characteristics of glucolipid metabolism in patients with nonfunctional adrenal incidentaloma(NFAI). And investigate the relationship between these factors and insulin resistance, islet beta cell function.
Methods
This study enrolled eight patients with nonfunctional adrenal incidentaloma and five healthy controls(HCs). These data were recorded including body measurements, blood biochemical indicators, and the body composition measured by double energy X-ray absorptiometry(DEXA) technique. In addition, blood glucose levels were indicated by flash glucose monitoring system, which better showed blood variability(GV) according to calculating related parameters and analyzinyg several period times including nocturnal, fasting, and postprandial periods. Furthermore, the correlation between glucolipid metabolism and insulin resistance, islet beta cell function were analyzed in the NFAI group.
Results
As compared with HCs, NFAI group showed higher BMI, larger waistline and wasist hip rate(WHR), and lower HDL-c(all $P < 0.05$). Besides, related indicators with regard to indicators of glucose metabolism and body fat distribution showed no significant difference compared with those of HCs. As for FGMS, all indices indicating GV were not found significant differences compared with those of HCs except lower PT1(the percentage of blood glucose values less than 3.9 mmol/l during the day). Furthermore, the correlation analysis revealed that HbA1c% and FINS were positively correlated with HOMA-IR index, while BMI, neck circumference and lean weight of trunk were negatively correlated with HOMA-β cell function(all $P < 0.05$).
Conclusion
Compered with HCs, there are abnormalities glucoliqid metabolism and fat distribution changes in patients with NFAI. And fat distribution affect function of islet cells.

Table 1. Parameters with statistical sense in NFAI and HCs

Parameters	NFAI	HCs	P value
BMI(kg/m^2)	26.44 ± 1.93	23.20 ± 1.82	0.012
Waistline(cm)	92.89 ± 5.61	75.56 ± 4.57	0.000
Hipline(cm)	102.15(101.28.103.78)	94.50(91.50.102.55)	0.127
Wasist hip rate(WHR)	0.89 ± 0.04	0.79 ± 0.02	0.000
HDL-C(mmol/l)	1.09 ± 0.23	1.63 ± 0.18	0.001
PT1	1.05 ± 1.15	6.76 ± 5.98	0.031

Table 2. The correlation analysis

HOMA-IR		
	R value	**P value**
HbA1c(%)	0.771	0.025
FINS(mmol/l)	0.684	0.006
HOMA-β		
	R value	P value
BMI(kg/m^2)	–0.890	0.003
Neck circumference(cm)	–0.767	0.026
Trunk lean mass(g)	–0.851	0.007

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AEP61

Cushing's syndrome induced galactorrhoea in a non - lactating female: clinical case

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Introduction
It has been observed that in patients with depression and anxiety disorders dopamine secretion is suppressed, therefore prolactin secretion increases. Prolonged hypercortisolemia causes a variety of psycho-emotional changes that may affect dopamine secretion.
Case
A 36-year-old woman was admitted to the Hospital of Lithuanian University of Health Sciences Kauno Klinikos due to a 10-year-lasting galactorrhoea, sleep disorder, mood swings, anxiety attacks, menstrual cycle disorder, and a high blood pressure (BP). Gestational diabetes, preeclampsia, and eclampsia were confirmed in 2010, during the pregnancy. After the childbirth the state has gotten worse, the discharge from the nipples has not disappeared after stop of breastfeeding. Breast ultrasound and biopsy, head MRI were performed because of the galactorrhoea – no pathology were observed. Three groups of antihypertensive drugs were prescribed, but hypertension was still poorly controled. There was no history of other medication, head or chest trauma. No physiological or organic causes of hyperprolactinemia were found.
Physical examination
BMI – 29.76 kg/m^2, central distribution of adipose tissue. Facial hyperaemia. Pink stretch marks were observed: 1.5 cm wide on the arm, thigh, and abdomen area. Hirsutism based on the Ferryman-Gallwey score – 8. Milky white nipples discharge was observed. Thyroid I°- firm, uneven. BP 158/103 mmHg, HR 83 bpm. Other systems: no abnormalities detected.
Laboratory tests
Metanephrine, normetanephrine, aldosterone, renin, thyroid hormones - all in normal ranges. Prolactin 914 mu/l (n.r. 105–548), macroprolactin 78 proc. Head MRI - pituitary area without pathology. Overnight 1 mg Dexamethasone suppression test (DST) - pathological, cortisol after DST 382.9 nmol/l (*n.* < 50). Low-dose Dexamethasone suppression test (LDDST) - pathological, no cortisol suppression. ACTH 0.4 pmol/l (1.63–14.15). Abdominal CT scan: in the left adrenal gland an oval, well-defined 5.8 × 3.8 cm mass, heterogeneous with calcifications, very vascularized, accumulates contrast. Patient was diagnosed with ACTH-independent Cushing's syndrome. A laparoscopic left adrenalectomy was performed. Histological results - adrenocortical adenoma. Post-operative treatment included Hydrocortisone 30 mg/p replacement therapy. Patient's sleep quality and psycho-emotional state improved, galactorrhoea subsided completely within 1 week post-operation. Prolactin 352–294 mu/l.
Conclusion
Physiological and organic causes of hyperprolactinemia were not identified. Since the patient suffered from long-term psycho-emotional alterations dues to hypercortisolemia and cessation of galactorrhoea were observed after the surgical treatment of adrenal adenoma, galactorrhoea can be considered as

Cushing's syndrome complication. To our knowledge, a few similar clinical cases have been reported where galactorrhoea was attributed to psycho-emotional disorders in the context of the other diseases.

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AEP62

Patients with congenital adrenal hyperplasia show an adverse cardiovascular risk profile compared to patients with autoimmune adrenalitis

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Background
Despite adequate hormone replacement therapy, evidence suggests an increased mortality in patients suffering from primary adrenal insufficiency, mainly because of cardiovascular diseases. Congenital adrenal hyperplasia (CAH) and autoimmune adrenalitis (AI) are two entities with a different pathophysiological background and might therefore show divergent cardiovascular risk profiles.
Methods
9 patients with CAH (female $n = 4$; age: 39 ± 11years; weight: 71 ± 12 kg; equivalent dose of hydrocortisone:19 ± 7 mg/day) and 9 patients with AI (female $n = 4$; age: 43 ± 9years; weight: 73 ± 15 kg; equivalent dose of hydrocortisone: 24 ± 7 mg/day) under stable glucocorticoid substitution therapy were investigated. Fasting blood was drawn to evaluate glucose- and lipid metabolism. Standardized blood pressure measurements and magnetic resonance imaging and spectroscopy measurements were performed to assess cardiac function, myocardial (MYCL) & hepatic lipid content (HCL) and abdominal fat mass.
Results
Fasting glucose (91 ± 10 vs 80 ± 7 mg/dl; $P = 0.021$), HbA1c (5.44 ± 0.3 vs 5.1 ± 0.4%; $P = 0.044$) and blood pressure (124 ± 8/80 ± 6 vs 113 ± 10/71 ± 6; $P = 0.031$) were higher in CAH compared to AI. This was paralleled by an increase in HCL (5.8 ± 5 vs 1.8 ± 1%; $P = 0.0549$) and abdominal fat mass (251 ± 130 vs 378 ± 119 mm^2; $P = 0.047$). No differences in heart function (Ejection fraction: 56 ± 4 vs 59 ± 8%; P = n.s) and MYCL (0.28 ± 0.2 vs 0.25 ± 0.1%; P = n.s.) were observed. Patients with CAH were treated more frequently by evening doses of glucocorticoids (6/9 vs 1/9) or others than hydrocortisone (5/9 vs 0/9).
Conclusions
CAH is associated with an adverse cardiovascular risk profile compared to AI, despite a comparable dose of daily glucocorticoid substitution. This might be explained by a more unphysiological timing of replacement therapy or the more frequent use of longer-acting glucocorticoids in patients with CAH, as well as by the adverse metabolic effects of hyperandrogenemia in women.

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AEP63

Prognostic factors in Adrenocortical Carcinoma: A single institution case-series

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Background
Adrenocortical carcinoma (ACC) is a rare but very aggressive endocrine malignancy with poor survival. Histopathology is important for diagnosis, while in some cases immunohistochemical markers and gene profiling of the resected tumor may be superior to current staging systems to determine prognosis.
Aim
Herein, we aimed to present the 20year experience at a tertiary Hospital in patients with ACCs and correlate the immunohistochemical characteristics of ACCs with the clinical and morphological characteristics of the tumors and the survival of the patients.
Material and methods
45 patients with ACC operated in a single center were included in the study. The tumor size and weight and the disease stage (ENSAT classification) were examined along with Weiss score and Helsinki score. Immunohistochemical expression of Inhibin-a, Melan A, Calretinin, Ki67, Synaptophysin, p53, Vimentin, CKAE1/AE3 was also examined.
Results
45 patients were diagnosed with ACC. The male to female ration was 1:1.37. The median age at diagnosis was 55.5 years (IQR 19–77). ENSAT stage I, II, III and IV was 6.6%, 62.3%, 26.7% and 4.4%, respectively. The median size of ACCs was 9 cm (IQR 3.5–22 cm) and the median weight 127 gr (IQR 18–1400 gr). The median follow up period was 18 months (IQR 1–96). Twelve patients (31.58%) had ≤ 1-year survival and 17 (44.74%) demonstrated ≤ 5-year survival. Survival was significantly higher in patients with stage I–II as compared to patients with stage III–IV ACC (62 ± 8.7 months vs 31 ± 12.1 months, $P = 0.02$). A significant correlation between tumor volume ($P = 0.011$, $r = 0.418$), diameter ($P = 0.005$, $r = 0.449$), weight ($P = 0.04$, $r = 0.339$) and Weiss score was observed. An association between Weiss score and the expression of vimentin ($P = 0.02$) was also observed. A larger tumor diameter > 10 cm ($P = 0.007$), tumor volume > 500 cm^3 ($P = 0.0003$), tumor weight > 300 gr ($P = 0.03$), Ki-67 index > 4% ($P = 0.04$), Weiss score > 5 ($P = 0.001$), Helsinki score > 8 ($P = 0.06$) were significantly associated with shorter overall survival (OS) in the univariable analysis. The expression of Melan A and lower expression of Ki-67 (≤ 4) were independently associated with longer OS time ($P = 0.01$). No statistical significance was observed regarding the correlation between IHC markers and ENSAT staging (I/II vs III/IV).
Conclusion
Adrenocortical carcinoma is a rare and very aggressive endocrine malignancy. The most important factors that determine long-term prognosis of ACC are the disease stage at diagnosis, the Weiss score, and the Ki67 index. Immunohistochemical markers such as Melan A could also serve as prognostic factors.

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AEP64

The clinical, paraclinical, etiological and therapeutic profile of adrenal incidentalomas

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Objective
Describe the clinical, paraclinical, etiological and therapeutic profile of adrenal incidentalomas.
Material and methods
Retrospective study, conducted on 100 patients previously hospitalized in the endocrinology department of the university hospital center RABTA, following the fortuitous discovery of an adrenal mass over a period of 10 years.
Results
The mean age of the patients was 58 years (24–82 years), the sex ratio (M/F) was 0.69 and the mean BMI was 30.05 kg/m^2 (16.18–48.00 kg/m^2). The most frequent finding circumstances of adrenal incidentaloma were abdominal pain (36 cases) and lumbar pain (17 cases). Bilaterality was objectified in 33.7% of the cases. The size of the AIs varied between 3 mm and 120 mm on the right with an average of 31 mm, and between 6 mm and 110 mm on the left with an average of 24 mm. Hormonal assessment revealed hypercorticism in 10 patients (11.5% of patients), pheochromocytoma in 6 patients (6.9%), Conn's adenoma in 4 patients (4.6%), and a non-secretory nodule in 67 patients (77% of patients). Only sixteen (16) patients underwent adrenalectomy.
Discussion
Due to the development of medical imaging techniques, the incidental discovery of adrenal masses has become increasingly common. Adrenal incidentalomas constitute an entity with varied, sometimes even serious, etiologies, the exploration of which must be rational and well codified.

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AEP65

Nephrotic syndrome following resection of an adrenal incidentaloma: A case report

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A 69 year old man had a 5 cm right adrenal lesion discovered incidentally while being investigated for a deterioration in previously well-controlled hypertension. Routine investigations including serum albumin were normal. Further investigation confirmed a non-functioning adrenal lesion. MRI revealed a 'non-fat-containing T1 hyperintense indeterminate adrenal lesion with speckling of T2 hyperintensity, not typical for adenoma, hyperplasia, myelolipoma, haemangioma or pheochromocytoma'. An uncomplicated laparoscopic adrenalectomy was performed. Histology revealed a 118 g adrenal neoplasm, modified Weiss score 0, with abundant hyaline deposits. 3 months later the patient complained of peripheral oedema. Investigations revealed a serum albumin of 24 g/l and 14 g of proteinuria in 24 hours. Serum protein electrophoresis revealed a monoclonal IgA type lambda band. Renal biopsy revealed amorphous material displaying apple green birefringence on staining with Congo Red, which stained with antibodies to lambda light chains, confirming AL amyloid. Therefore the patient's resected adrenal specimen was retrieved and stained with Congo Red, revealing apple green birefringence in the walls of the blood vessels, confirming the presence of amyloidosis. Although adrenal gland involvement in secondary amyloidosis is common, adrenal involvement in primary amyloidosis is less well described. This case illustrates the indolent nature of primary amyloidosis, prior to the development of often catastrophic symptoms. Consideration should be given to Congo Red staining of resected pathologic specimens containing hyaline deposition, to potentially allow for earlier recognition of this devastating disease. A pathophysiologic link between the patient's incidentaloma, adrenalectomy, and onset of nephrotic syndrome remains a matter for conjecture.

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AEP66

Recurrence of a malignant corticosadrenaloma

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Introduction
The adrenal cortex is a rare malignant tumor at the expense of the adrenal gland, very aggressive because of its invasion, its metastatic potential and its five (5) year survival at 40% with a high risk of locoregional relapse.
Case presentation
We report the case of a 17-year-old patient with a history of long-term corticosteroid therapy over 3 years and secondary amenorrhea for 2 years, who was admitted in April 2019 for the management of hyper androgenism. On clinical examination, the general condition was preserved with a notion of moderate weight gain, she presented a severe hirsutism rated at 32 on the Ferriman and Gallway score without signs of virilization, signs of hypercorticism with a cunshingoid facies.. The hormonal balance noted a CLU raised to 3 times the normal, i.e. 616 nmol/24 h (30–200), SDHEA > 27 µmol/l (1.3–8), testosterone at 20 nmol/l or 6 times the normal, methoxylated derivatives were normal. The cervico-thoraco-abdomino-pelvic CT scan performed revealed the presence in the right adrenal gland of a hypodense tissue mass with areas of necrosis measuring 6 × 6 × 7 cm, pushing back the IVC and the upper pole of the right kidney, with multiple cervical nodes. A right adrenalectomy with detachment of the adhesions and conservation of the right kidney was performed, the postoperative was complicated by acute adrenal insufficiency for which the patient was substituted. The pathological examination was in favor of a malignant adrenal cortex classified as stage 3 by ENSAT with an intermediate prognostic risk. At 6 months of follow-up there was a clear regression of clinical signs, at 12 months there was a reappearance of hirsutism, the control of the abdomino-pelvic CT noted a hypodense formation of 41 × 36 mm at the expense of the right adrenal gland. in connection with a local recurrence. Iterative adrenalectomy was performed, with confirmation on pathological examination of a recurrence of adrenal cortex associated with fibromyxoid changes.
Discussion and conclusion
The malignant adrenal cortex has a poor prognosis with a high risk of recurrence especially at stage 3 and 4 of ENSAT, wide surgical excision appears to reduce the risk of relapse according to some authors but treatment with mitotane or poly chemotherapy should be considered.

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AEP67

Diagnosing Cushing's syndrome due to Ectopic ACTH secretion warrants high Index of Suspicion- phenotypical features may not always present

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Patients with Cushing's syndrome usually have characteristic phenotypical features but this is not always true in case of Ectopic ACTH secretion. This is mainly because this develops more acutely and underlying malignancy can cause significant weight loss. We report a 71 years old male with background of Prostatic malignancy who was found to have new profound hypokalaemia which was resistant to treatment. There were no signs of Cushing's syndrome but index of suspicion was high given persistent hypokalaemia on background of known malignancy, metabolic alkalosis and hypertension. Random cortisol came significantly elevated which failed to supress after overnight 8 mg Dexamethasone suppression test. ACTH was significantly high. He was planned for medical management given progression of malignancy and was started on metyrapone which resolved the hypokalaemia. Unfortunately patient died within 2 months due to progression of underlying malignancy. It is important to recognise such cases of hypokalaemia early, to appropriately deal with excess cortisol production.

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AEP68

Primary hyperaldosteronism. A clinical profile of the disease without arterial hypertension

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Primary hyperaldosteronism may be due to an adrenal adenoma and is an increasingly recognized cause of secondary arterial hypertension. The disease causes hypokalemia and is usually treated surgically by excision of the adrenal adenoma. However, it appears that it may present with a clinical profile without arterial hypertension. The aim was to describe three cases of primary hyperaldosteronism who presented with hypokalemia and an adrenal adenoma with normal blood pressure. A cohort of three patients is described who presented with hypokalemia in all cases and mild diabetes mellitus in one case. All patients were female, aged 51, 54 and 72 years at the time of diagnosis. Diagnostic evaluation revealed the presence of a small adenoma in the left adrenal gland in two cases and in the right adrenal in one case. Aldosterone levels were elevated while renin was suppressed. In all patients blood pressure levels were normal. Spironolactone was administered in small doses for the management of hypokalemia. During follow up all patients continued to have hypokalemia, however blood pressure levels remained within the normal range. Primary hyperaldosteronism may present with severe arterial hypertension, persisting even after surgical excision of the adrenal adenoma which causes the disease. In many cases surgical treatment is considered successful if drug treatment for hypertension is reduced post surgically. Additionally, the disease may cause significant damage in the target organs affected by hypertension, namely, the heart and kidneys. It appears that although primary hyperaldosteronism is a cause of secondary arterial hypertension, the disease may present with a clinical phenotype without hypertension. This poses new therapeutic alternatives to the clinician. The disease may be managed by follow up, surgical excision of the adenoma being an option, if the clinical profile of the disease changes and creates new problems for the patient.

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AEP69

Quality of life in children diagnosed with non-classic congenital adrenal hyperplasia

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Introduction
Non-classical congenital adrenal hyperplasia (NC-CAH) is a chronic disease characterized by excessive androgen production. Affected children may have their quality of life negatively affected by the awareness of a medical condition, symptoms of hyperandrogenism and the burden of daily medication administration. Pediatric Quality of Life Inventory 4.0 (PedsQL) is a validated tool to assess health-related QoL (HRQoL).
Methods
Cross-sectional study involving 16 patients with NC-CAH followed in the pediatric endocrinology department. NC-CAH patients whose parents were literate and who agreed to participate were included. Anthropometric data was collected and PedsQL was applied to the patients and their parents. Patients were divided into five different groups according to age: 2–4, 5–7, 8–12 13–18 years-old. Control group consisted of healthy individuals from the instrument's validation studies for the Portuguese population (for children aged 5–7 and 8–12) and the standard control population used in the PedsQL validation study (for children aged 2–4 and 13–18).
Results
Overall, there were no differences between the study population and control groups, with the exception of the parent's score results of children aged 8–12. Its results showed physical health and emotional dimension' scores significantly higher, while psychosocial health's score and total scale score were significantly lower than the control group.
Conclusion
HRQoL scores are not negatively affected by NC-CAH on most group ages, with the exception of the parents' reports on HRQoL of children aged 8–12. Further studies with a greater number of patients are needed to determine the impact of this chronic disease on the HRQoL of children.

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AEP70

Metabolic profile and cardiovascular risk assessment in subclinical cushing's syndrome

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Introduction
Subclinical Cushing's syndrome (SCS) is an endocrine disorder characterized by an autonomous cortisol secretion in patients bearing adrenal adenomas in the absence of specific signs of hypercortisolism. The cortisol excess is known to be associated with metabolic comorbidities such as obesity, hypertension, glucose intolerance, and dyslipidemia increasing the incidence of cardiovascular events. The objective of this study was to describe the clinical and biochemical features in patients diagnosed with SCS and assess their metabolic and cardiovascular risk (CVR).
Methods
Medical charts of 40 patients diagnosed with SCS and who had been hospitalized between 1990 and 2020 in the Endocrinology Department of Hedi Chaker University Hospital, Sfax, Tunisia were reviewed. Clinical, biological, and radiological data were analyzed. The CVR was assessed using the SCORE charts.
Results:
Among our 40 patients, 57.5% were female. The average age of diagnosis was 56.82 ± 14.94 years. The 2-day low-dose Dexamethasone suppression test was adopted as a confirmatory endocrine work-up showing mean cortisol and ACTH levels of 68.93 ± 63.56 µg/l and at the 31.34 ± 34.47 pg/ml, respectively. The adrenal incidentalomas were unilateral in 76.4% and at the left side in 58.4%. The most common adrenal lesions were adenomas (73.7%) and hyperplasia (23.7%). The mean adenomas size was 3.17 ± 1.79 cm. A marked metabolic phenotype and insulin-resistance were featured in 82.5% of patients with 12.8% overweighted and 51.3% obese. Conspicuous abdominal fat distribution was noted in 75% of men and 90.9% of women with mean waist-circumferences of 97.88 and 104.82 cm respectively. Hypertension was encountered in 62.5% with a mean systolic blood pressure of 142.2 ± 12.11 mmHg. As for the glucose intolerance: 32.5% had type 2 diabetes mellitus and 35% presented with pre-diabetes. The mean fasting plasma glucose was 6.61 ± 1.77 mmol/l. Dyslipidemia affected 42.5%. The mean total-cholestérol and triglycerides levels were 5.51 ± 1.42 and 2.14 ± 1.98 mmol/l respectively. Considering the SCORE risk, three CVR categories were characterized: low, moderate, and high risk groups representing 37.5%, 30%, and 32.5% consecutively. Adrenalectomy was undergone in 40% of cases.
Conclusion
The SCS is linked to several pronounced metabolic comorbidities especially worsen glucose and lipid profile exposing to a higher CVR. The surgical or conservative management of this condition should be discussed on a case-by-case basis regarding the absence of widely accepted guidelines.

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AEP71

The insulin tolerance test (ITT) in the assessment of the adrenal axis

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Introduction
The insulin tolerance test (ITT) is the gold standard for the assessment of the integrity of the hyopothalamo-pituitray adrenal axis. it's major drawbacks are the mandatory presence of an experienced physician and continuous supervision to detect any complication. Our study aims to evaluate the indications and the outcomes of the ITT performed in our department.
Patients and methods
We conducted a retrospective study of 38 patients with suspected adrenal insufficiency (AI) who underwent the ITT over two years (2018–2019) in our endocrinology department. The patients had 12 hours fasting prior to the test. Intravenous insulin (actrapid) was administrated. The insulin dose was determined from body weight and adjusted based on insulin resistance: 0.2 IU/Kg if the patient was considered to be insulin resistant and 0.1 IU/Kg in other cases. Four blood samples for glucose and cortisol measurements were taken: before the insulin injection (T0), at blood glucose < 50 mg/dl (T1), at 15 min (T2) and at 30min (T3) after achieved hypoglycemia. A meal was given at the moment of hypoglycemia after T1 measurements.
Results
The ITT was performed in 38 patients (10 male, 28 female). The mean age was 40.6 ± 16.4 years (range 10–72 years). Fourteen patients underwent the test for underlying pituitary adenoma, 14 patients for clinical symptoms (7 patients) or biological assessments (7 patients) (hypoglycemia, low cortisol levels.) suggesting an AI, 2 patients for a traumatic brain injury, 2 for pituitary surgery, 2 for bilateral adrenalectomy and 2 for associated autoimmune disease. Adequate hypoglycemia (venous plasma glucose < 50 mg/dl was achieved in 36 patients (94, 7%), of that 8, 7% had no symptoms, while only 2 patients had neuroglucopaenic symptoms. There were no significant adverse events recorded. Eight patients showed an adequate cortisol response (> 18 µg/dl) with a mean serum cortisol 12.5 ± 3.8 µg/dl (T0), 15.9 ± 3.5 µg/dl (T1), 19.11 ± 2.8 µg/dl (T2) and 20.6 ± 1.9 µg/dl (T3). Twenty-eight patients showed an inadequate cortisol response, their levels of serum cortisol were: 8.3 ± 2.9 µg/dl (T0), 7.9 ± 2.7 µg/dl (T1), 10.9 ± 2.8 µg/dl (T2) and 12.4 ± 3.9 µg/dl (T3).
Conclusion
The ITT is a safe test when conducted in optimal settings. The insulin dose should be well determined to obtain appropriate hypoglycemia. Additional time and number of sampling are required to avoid misclassification and to increase the specificity of the test.

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AEP72

Metabolic impact of glucocorticoid substitution in Addison's disease

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Introduction
Recent studies in patients with Addison's disease have shown that this condition, even if treated, is fraught with significant morbidity and even excess mortality. The objective of our study was to determine the deleterious effects of long-term glucocorticoid replacement mainly on the metabolic level.
Methods
Retrospective study, carried out at the Endocrinology and Diabetology Department of Hédi Chaker Sfax University Hospital, which involved 32 patients with Addison's disease that has been evolving for more than 15 years.
Results
The average age was 58.53 years with a predominance of women. The mean duration of follow-up was 17.87 years. The hydrocortisone dose was initially 32.5 mg/d, at the end of 27.9 mg/d. There was gradual weight gain, an increase in body mass index and waist circumference. The prevalence of MS was 3.12% at diagnosis and 35.71% after treatment duration greater than 15 years. At the end of the follow-up, 28.57% of the obese patients against 7.14% at the discovery of the disease were noted, 25% of the hypertensive and type 2 diabetic patients all appeared throughout the follow-up, 42.85% of the dyslipidemic patients. Factors favoring the occurrence of the metabolic syndrome were the duration of the disease and the weight loss on discovery of the disease.
Conclusion
Adjustment of replacement therapy during Addison's disease is an issue in view of the morbidity and mortality associated with overdose. Regular monitoring and a personalized therapeutic approach are necessary to improve the prognosis of his patients.

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AEP73

Late night salivary cortisol and Cushing's syndrome

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Introduction
The thresholds of late night salivary cortisol (LNSC) vary widely among studies due to differences in assay methodologies and in control groups. We aimed to verify the analytical performance of the LNSC by electrochimiluminescence assay (ECLIA) and to establish cut-off values of LNSC for the screening of Cushing's syndrome (CS).
Methods
Patients with suspected CS underwent screening tests including LNSC and 1 mg Dexamethasone Suppression Test (DST). Subjects with abnormal response underwent a 2 mg DST, ACTH assessment and complementary radiological explorations. For the analytical evaluation, the study was performed with guidance from the clinical and Laboratory Standard Institute.
Results
A total of 56 patients with mean age 58.1 years and sex ratio 1.15 were finally enrolled. 22 patients from 56 had clinically CS (group A), 7 patients had subclinical CS (groupB) and 8 patients had a pseudo CS (group C). Goup D (n = 19) was composed of non-functioning adenomas. Reference range for LNSC was 1.06–1.58 ng/ml. LNSC was correlated with nocturnal serum cortisol (r = 0.56, P = 0.004), with serum cortisol after 1 mg DST (r = 0.82, P = 0.04) and after 2 mg DST (r = 0.89, P < 0.001) but not with serum creatinine. BMI was correlated with serum cortisol after 1 mg de DST but not with salivary cortisol. Using a 2.48 ng/ml threshold derived from ROC curve analysis, the sensitivity and specificity of LNSC to identify CS was 84.6% and 69.4% respectively. The intra assay and inter assay coefficients of variation were 9.84% and 10.5% respectively. The detection and quantification limits for salivary cortisol measurement were 0.05 ng/ml and 0.08 ng/ml respectively.
Conclusion
Our data confirm the usefulness of late night salivary cortisol measurement as an initial and simple test for screening for Cushing's syndrome, using an automated ECLIA.

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AEP74

Spontaneous testicular necrosis revealing a pheochromocytoma

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Pheochromocytoma is a rare tumor of the adrenal medulla, responsible for excessive secretion of catecholamines. Symptoms include the classic triad: headache, palpitations and sweating, usually accompanied by hypertension. We report the case of a pheochromocytoma diagnosed following an episode of testicular necrosis. A 72-year-old patient with history of psoriasis and prostate resection underwent emergency surgery for increased testicular pain suspicious of testicular tumor. Pathological examination revealed testicular necrosis due to vascular damage. The patient was addressed to internal medicine consultation for etiological assessment of the vascular lesion. Testing for autoimmune etiology including SAPL, AAN and ANCA antibodies, as well as for a thromboembolic pathology were negative. A full body CT scan found a 14 × 16 mm right adrenal adenoma (60% absolute washout) and a 32 × 29 mm heterogeneous mass of the left adrenal. The left adrenal mass was hyperfunctional in MIBG scintigraphy. Hormonal exploration found plasma normetanephrines increased 3 × normal, with normal plasma metanephrines and normal plasma dopamine and no other abnormality. Chromogranin A was slightly increased. On further interrogation, the patient reported some palpitation episodes several months earlier. A 24 h ECG was performed finding rare atrial and ventricular extrasystoles. First surgery attempt was unsuccessful, with tachycardia followed by bradycardia and cardio respiratory arrest with successful CPR. The patient finally underwent left adrenalectomy by laparotomy with hemostasis splenectomy. Anatomo-pathological examination confirmed a 2 cm left adrenal pheochromocytoma with an estimated PASS score of 6. Normalization of plasma normetanephrines was observed after surgery. This is, to our knowledge, the first case in the literature of a non-traumatic, spontaneous testicular necrosis revealing a pheochromocytoma. There are a few observations of skin necrosis or distal ischemia revealing a pheochromocytoma, however these remain rare. The hypothesis put forward is the appearance of ischemic lesions after adrenergic discharges. Sympathetic hypertonicity would be at the origin of vascular spasms and an alteration of the microcirculation.

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AEP75

Bilateral pheochromocytoma in von hippel-lindau syndrome revealed by a hemangioblastoma

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Introduction
Von Hippel-Lindau (VHL) syndrome is an autosomal dominant disease resulting in a susceptibility to develop central nervous system and retinal hemangioblastomas, endolymphatic sac tumors, renal clear cell carcinoma and pheochromocytoma. Pheochromocytoma occurs usually at a younger age and tends to be bilateral in VHL syndrome. Herein, we describe a case of VHL syndrome with cerebellar hemangioblastoma, bilateral pheochromocytoma and kidney tumor.
Case report
A 34-year-old woman was operated on a cystic axial cerebellar tumor revealed by a high intracranial pressure syndrome, which was confirmed to be a cerebellar hemangioblastoma. She was referred to our department for complementary investigations. On physical examination, she had a triad including headaches, palpitations and diaphoresis. She had a blood pressure of 150/90 mmHg with orthostatic hypotension. On laboratory investigations, she had an iron deficiency anemia, a thrombocytosis, an elevated chromogranin A at 404 ng/ml (4 times normal) and urinary fractionated metanephrines superior to 3 times normal. The adrenal computed tomography scan found a 43 * 49 * 51 mm adenoma in the right adrenal gland and 38 * 44 * 68 mm in the left one, and 123I-metaiodobenzylguanidine (MIBG) scintigraphy detected a bilateral uptake confirming the diagnosis of bilateral pheochromocytoma. The other manifestations of VHL syndrome were assessed, eliminating a retinal hemangioblastoma, endolymphatic sac tumors, and founding a 15 mm kidney tumor. Genetic testing confirmed the diagnosis of VHL syndrome. She was operated on with bilateral

adrenalectomy and histology confirming the complete surgery of a bilateral pheochromocytoma with PASS = 2. In post-operative evaluation, the patient didn't have any symptoms and was no longer hypertensive.
Conclusion
This case highlights the importance of screening all manifestations associated with VHL syndrome to initiate an early treatment for all tumors, cerebellar, adrenal and renal in our patient. The follow-up must be done for the patient and her family, and imaging in our case must reassess any pancreatic mass, especially if chromogranin a remains elevated, considering the possibility of pancreatic neuroendocrine tumor.

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AEP76

Quality of life in patients with classical form of congenital adrenal hyperplasia- deficiency of 21 hydroxylase

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Literary data concerning quality of life in adult patients with classical form of 21 hydroxylase deficiency (21 CAH) are sparse and discrepant. Our aim thus was to explore quality of life in a group of young adults with 21CAH attending regularly tertiary reference care centre. We used WHOQuOL Bref questionnaire and we administered it to 45 21 CAH patients of age 28.6 ± 8 yrs and we compared the results with the data from 111 age matched controls from healthy Czech population. 21 CAH have lower score in the domain of physical health (15.2 ± 2.47,vs 16.14 ± 2.4; $P = 0.036$) and in the domain environment (15 ± 2.16, vs 13.36 ± 2.09; $P = 0.001$). We did not find any correlation between biochemical results (lipids, 17 OH progesterone,androstendion, testosteron) or between BMI and blood pressure and the respective domains of the questionnaire. We did not find any correlation between total dose of used glucocorticoids /hydrocortisone equivalent/and any domain in the questionnaire. Concerning comparison of different steroids used for the treatment, the patients treated with prednison have higher scores in domains of physical health í(16.2 ± 1.7 vs 14.5 ± 2.3 for hydrocortison, $P = 0.038$, and 13.6 ± 2.4 for dexametason, $P = 0.029$) and environment (16 ± 1.6 vs 14.1 ± 2.1 for hydrocortison, $P = 0.01$ and 13.1 ± 2.0 for dexametason, $P = 0.006$). We conclude that young adult 21 CAH patients still have worse quality.of life in the domain concerning physical health than their healthy peers. On the contrary, they have higher quality of life in the domain enviroment, which could be explained by good family support. The best scores of patients treated with prednison could be explained probably by more convenient dose schedule than that for hydrocortison. Supported by Ministry of Health, Czech Republic - conceptual development of research organization (Institute of Endocrinology - EU, 00023761)'

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AEP77

Hyperthermia differentially affects cortisol and aldosterone secretion under stimulated conditions

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Introduction
Primary Aldosteronism (PA) is the commonest secondary cause of hypertension. Mainstay therapy, adrenalectomy resects both hypersecreting and adjacent normal tissue. It is therefore only suitable for patients with unilateral disease (40% cases), whom are surgical candidates. Thermal therapy presents a plausible minimally invasive therapy, to target and disrupt hypersecreting aldosterone producing adenomas (APA), while also preserving adjacent normal adrenal cortex.

Methodology
Adrenocortical cell lines (H295R and HAC15) were treated with hyperthermia for 15 minutes using a water bath at temperatures between 37–65°C. Cell death and apoptosis were analysed immediately and at 24 hours and 48 hours post hyperthermia using Annexin V/Propidium Iodide (PI) (flow cytometry), and Calcein/PI (fluorescence microscopy). Steroidogenesis was analysed following hyperthermia (i) measuring cytosolic calcium flux in response to angiotensin II (ANGII) using Flou-4 staining (flow cytometry); (ii) analysing steroidogenic enzyme expression (RT-PCR/Western Blotting); and (iii) measuring cortisol and aldosterone in cell supernatants (chemiluminescent assays). Cells were also stimulated with forskolin for assays of steroidogenesis.
Results
Hyperthermia induced necrotic cell death without apoptosis. Percentage cell death was significantly higher at 50°C-65°C (95.41 ± 5.74% vs control 9.17 ± 3.01%, $P < 0.0001$). Cytosolic calcium changes in response to ANGII were lower above 55°C-65°C in H295R (−36.33 ± 7.06 Ca + Response vs control 10.67 ± 1.76 Ca + Response, $P < 0.001$) and above 45°C-65°C in HAC15 (−43.33 ± −12.36 Ca + Response vs control 4.43 ± 1.57 Ca + Response, $P < 0.002$). Intracellular stored calcium was also diminished with increasing hyperthermia in both cell lines. CYP11B1 (−31.6 ± 2.8 DDCt vs control, $P < 0.0001$), CYP11B2 (−11.3 ± 4.9 DDCt vs control, $P < 0.0001$), and HSD3B2 (−42 ± 9.8 DDCt vs control, $P < 0.0001$) enzyme gene expression was decreased at 45°C and above in HAC15 cells. CYP11B2 (−9.3 ± 2.5 DDCt vs control, $P < 0.0001$), and HSD3B2 (−15 ± 1.3 DDCt vs control, $P < 0.0001$) enzyme gene expression decreased significantly in H295R cells. Measurement of cortisol decreased with heat treatment ≥ 45°C (22.35 ± 4.49 nmol/l vs control 117.7 ± 25 nmol/l, $P < 0.0001$) while aldosterone output was unaffected at temperatures below 50°C.
Conclusion
Hyperthermia induces necrotic cell death in adrenocortical cell lines at temperatures > 50°C. Cortisol steroid secretion is more susceptible to sublethal hyperthermia when compared to aldosterone. Knowledge of the differential effects of hyperthermia at lethal and sublethal doses on steroidogenesis and steroid secretion is critical when designing thermal ablation systems for adrenal use and warrant consideration during treatment planning for thermal ablation of APA.

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AEP78

Bilateral adrenal leiomyoma mimicking adrenal malignancy: A rare case report

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Background
Adrenal leiomyoma is a rare benign soft tissue tumor, it is even more unusual if presenting bilaterally; 21 cases have been reported in the literature and only six had bilateral involvement; 5 in the pediatric population and only one in an adult patient. Radiological appearance may frequently be confused with malignancy especially if large, calcified and with central necrosis. We report a rare case of bilateral, large, calcified, non-functioning adrenal leiomyoma in a 20-year-old female, who was suspected for a malignancy preoperatively.
Clinical case
A 20 year-old-female presented with chronic abdominal discomfort, fatigue, and inability to gain weight. On examination, she was normotensive, underweight with BMI of 15.6 kg/m^2, and there were no stigmata of Cushing's syndrome, Addison's disease or pheochromocytoma. A contrast CT scan of the abdomen revealed the presence of bilateral well-defined suprarenal lesions measuring 8.5 × 8.5 × 7.2 cm and 4.7 × 4.2 × 3.5 cm on the right and left side, respectively. The lesions showed large central areas of necrosis with multiple punctate calcifications and heterogenous peripheral enhancement. The radiological differential diagnosis included adrenal cortical carcinoma, adrenal metastasis, infectious etiology, and bilateral pheochromocytoma. Her hormonal assays showed normal free cortisol and catecholamine metabolites in the urine and normal serum androgens. The patient underwent a successful right adrenalectomy. Resected specimen measured 10 × 9.5 × 7.5 cm. Histology revealed a well-circumscribed and pseudo-encapsulated smooth muscle tumor comprised of bland, spindle-shaped cells. The panel of immunohistochemical stains supported the diagnosis of leiomyoma. Postoperatively, the symptoms improved, she

gained 4 kg weight over the following 4 months, and short Synacthen test confirmed an intact adrenal function. To avoid lifelong adrenal insufficiency and after discussion with the patient, we agreed to leave the left adrenal mass and follow it by serial imaging. There was only a minimal increase in the size over the following 4 years (5.5 × 4.5 × 3.8 cm).
Conclusion
Adrenal leiomyoma is an extremely rare adrenal tumor and can be confused with adrenal malignancy. Therefore, it should be considered in the differential diagnosis of adrenal incidentalomas. In the case of bilateral etiology, permanent adrenal insufficiency and longterm replacement therapy can be avoided in certain population by removing the larger tumor and continuous follow-up for the other side.

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AEP79

Hypokalemia in a patient with severe SARS-CoV-2 infection

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Hypokalemia has been observed in cases of the new SARS-CoV-2 infection. It has been suggested that hypokalemia may be a sensitive biomarker of disease severity and the requirement for invasive mechanical ventilation requirement in COVID-19 pneumonia. The aim was to describe the case of a patient with severe SARS-CoV-2 pneumonia who developed severe hypokalemia. A patient, male, aged 52, presented with fever and dry cough. He was found to be positive for the SARS-CoV-2 infection. He was hospitalized. During his hospitalization he was found to have hypokalemia, serum K^+ 3.2 mmol/l. His condition stabilized and he was discharged to be followed-up at home. The patient did not have an adrenal adenoma or hyperplasia or history of hypokalemia. However, 2 days later he developed fever and his cough deteriorated. He was hospitalized again. He was found to have pneumonia. K^+ was 2.9 mmol/l, plasma renin 1.0 pg/ml and aldosterone 17 ng/dl. Potassium was administered. A CT of the abdomen was performed which did not show any evidence of an adrenal adenoma or adrenal hyperplasia. Diuretics were not administered. Hypokalemia persisted despite potassium administration and spironolactone was administered along with dexamethasone for the treatment of pneumonia. Following discharge from the hospital the patient recovered and spironolactone was discontinued. The SARS-CoV-2 virus invades cells via a spike which attaches to the ACE2 receptor. The attachment of the virus to the ACE2 receptor causes an imbalance between angiotensin II and angiotensin I systems favoring the angiotensin II system. This imbalance may result in the development of frank hyperaldosteronism in cases of severe SARS-CoV-2 virus infection. This increase in activity of the angiotensin II system causes systemic inflammation and may be involved in the pathogenesis of dry cough characterizing the infection. Hypokalemia has been proposed as a marker of disease severity in the new SARS-CoV-2 infection. However, results are as yet inconclusive and more studies are needed to assess the relationship between SARS-CoV-2 severity infection and hypokalemia.

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AEP80

A giant nonfunctioning adrenocortical carcinoma: A case report

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Introduction
The adrenocortical carcinoma(ACC) is a rare malignant tumor arising from the adrenal cortex, it is usually associated to abnormal hormone secretion, but sometimes it is nonfunctioning, leading to a delayed diagnosis with a locally advanced and/or a metastatic disease.
Observation
We report the case of a 42 year-old woman with no medical history who consulted for chronic epigastralgia. On physical examination, a palpable mass in the right flank was found. Her vital signs were within the normal range and the body mass index was at 25.96 kg/m^2. An abdominal CT-scan revealed a giant retroperitoneal highly vascular tissue mass, encapsulated, well circumscribed and containing areas of necrosis,measuring 18.4 × 13 × 21.5 cm in diameter. Its origin couldn't be clearly defined, it pushes the liver up and to the left, lowers the right kidney, comes into contact with the diaphragmatic dome and rolls the inferior vena cava, suggesting a high potential of malignancy. In front of this giant mass, the biological exploration didn't show any excess of hormone secretion; plasma free normetanephine 0.35 nmol/l < 0.93 mmol/l, plasma free metanephrine < 0.10 nmol/l, cortisol 305 nmol/l, overnight dexamethasone suppression test: cortisol 32 nmol/l < 50 nmol/l, testosterone 0.27 ng/ml, SDHEA 215 µg/dl (normal level 42–307 µg/dl). A tumor biopsy was performed and the histo-pathological examination concluded to an adrenocortical carcinoma. The patient was presented to a multidisciplinary team meeting (endocrinology, urology, oncology), that decided that the tumor was inoperable due to its intimate contact with the vascular structures. As for mitotane treatement, it is not available in our country.
Conclusion
This case is one of the most rare cases of a giant nonfunctioning adrenocortical carcinoma that was reported in the literature. In fact, ACC is an aggressive tumor with poor prognosis.When doable and in the absence of disseminated metastasis, surgery remains the mainstay treatement and has better outcomes than chemotherapy alone. However adjuvant chemotherapy has shown a good effect on the duration of recurrence-free period and on the overall survival.

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Calcium and Bone

AEP81

Bone consequences of high dose denosumab to treat an aneurysmal bone cyst, an example of the European Reference Network support

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Aneurysmal bone cysts (ABCs) are rare pseudotumoral bone lesions with potential aggressive behavior due to the extensive destruction of surrounding bone. Besides surgery, denosumab has been investigated as a treatment for benign fibro-osseous lesions. As for ABCs, pediatric experience is limited, reporting mainly beneficial effects on lesions growth and associated pain. Some reports included well known side effects associated with denosumab, such as the rebound hypercalcemia at discontinuation. In addition, denosumab in young patients may affect both bone modeling and remodeling, even if consequences on the growing skeleton have not been characterized. We describe the case of an 8-year old boy diagnosed with a spinal ABC not accessible to surgery. Denosumab was administered subcutaneously weekly for 4 weeks and then monthly for one year, with optimal clinical response and calcification of the tumor. Six months after the discontinuation of denosumab, the patient developed severe hypercalcemia that required administration of a loop diuretic and intravenous infusion of zoledronic acid to restore normal serum calcium values. Because of tumor recurrence, denosumab was resumed at similar doses and intervals. After a few months, a new episode of hypercalcemia occurred while on denosumab tapering, 3 months after an injection. At this point, the tumor was stable, and denosumab was stopped. The parents and the patient gave their consent to share clinical data on the Clinical Patient Management System (CPMS), an IT platform for clinical consultations between European Reference Networks. The panel of experts from the BOND ERN and the ERN for rare endocrine disease met, and 6 monthly zoledronic acid infusions were initiated in order to control the rebound hypercalcemia post-denosumab therapy. To now, four infusions have been performed, allowing calcium levels to remain below the upper limit of normal. In parallel to rapid changes of mineral homeostasis, we observed an amplified bone remodeling in response to denosumab. After 1 year of treatment, the patient developed sclerotic metaphyseal bands visible on radiographs. Sclerotic lines partially vanished during wash-out periods

or when the injections of denosumab were spaced. Moreover, the patient developed over the years of denosumab therapy lower limb deformities, i.e. genu valgum, which required bilateral epiphysiodesis. Our experience confirms the efficacy of denosumab in treating ABCs, and suggests the importance of monitoring systematically growth, limb deformities, and mineral homeostasis in children and adolescents receiving denosumab. In addition, this report highlights the support of ERNs in the management of patients affected with rare diseases.

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AEP82

Correlation between parathyroid adenoma volume and markers of calcium-phosphate metabolism in patients with primary hyperparathyroidism

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Introduction
In primary hyperparathyroidism (PHPT) the chronic overproduction of parathormone (PTH) is mostly due to a solitary adenoma.
Aim
The aim of our study was to examine the relationship between calcium-phosphate metabolism and the volume of the parathyroid adenoma (PTA) in patients with PHPT.
Material and methods
The study included 195 patients with biochemical data of PHPT and solitary PTA, visualized on ultrasound. Patients with secondary hyperparathyroidism, multiple PTA and familial forms of PHPT were not included in the study. Patients' mean age was 57.9 (± 11.5) and 88.7% were females. Serum calcium, inorganic phosphate, PTH, 25-hydroxyvitamin D, creatinine and alkaline phosphatase (ALP) were measured. Glomerular filtration rate (GFR) was calculated through CKD-EPI equations. In all patients, the PTA was localized and measured by ultrasound. The PTA volume was calculated using the formula of a rotating ellipsoid.
Results
The median PTA volume was 0.49 cm^3; IQ range 0.22–1.19. It correlated positively with serum calcium and PTH (r = 0.33; P < 0.001 and r = 0.34; P < 0.001 respectively) and negatively with serum inorganic phosphate (r = –0.32; P < 0.001). A significant inverse relationship was found between the PTA volume and serum 25-hydroxyvitamin D level (r = –0.339; P < 0.001). The PTA volume was significantly related to BMI (r = 0.29; P < 0.001) and ALP (r = 0.17; P = 0.02) whereas there was no significant correlation with patients' age and GFR (P = 0.52 and P = 0.23 respectively).
Conclusion
In patients with PHPT and a solitary PTA, there is a positive association between PTA volume and the biochemical markers of disease activity.

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AEP83

Efficacy and safety of long-term treatment with monthly calcifediol soft capsules in vitamin D deficient patients

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Background
Vitamin D has shown to play a role in multiple diseases due to its skeletal and extraskeletal actions (such as immunomodulation). In this sense, vitamin D deficiency has become a worldwide health issue. Few supplementation guidelines mention calcifediol treatment, its optimal dosing and treatment duration, despite being the direct precursor of calcitriol and the biomarker of vitamin D status.
Objectives
To assess the efficacy and safety of long-term treatment with calcifediol soft capsules compared to cholecalciferol (vitamin D3) in vitamin D deficiency.
Methods
This was a Phase III-IV, double blind, randomised, controlled, multicentre clinical trial. Postmenopausal women with baseline levels of 25(OH)D < 20 ng/ml were randomised 1:1:1 to calcifediol 0.266 mg/month for 12 months, calcifediol 0.266 mg/month for 4 months followed by placebo for 8 months, and cholecalciferol 25 000 IU/month for 12 months.
Results
303 patients were enrolled, and 298 were included in the ITT population. There were no significant differences in terms of demographic variables, and the mean basal 25(OH)D levels were 13.2 ± 3.7 ng/ml. After 4 months of treatment, 25(OH)D levels over 30 ng/ml were reached by 4.3 times more patients in calcifediol group than in cholecalciferol group. The superiority of calcifediol over cholecalciferol in terms of increasing 25(OH)D levels was shown throughout the 12 months. However, the biggest difference was observed after the first month of treatment (mean change = 9.7 ± 6.7 and 5.1 ± 3.5 ng/ml in both calcifediol groups combined and in cholecalciferol group, respectively). After month 4, the increase in 25(OH)D levels remained fairly stable during the next 8 months of treatment. However, those patients in the group of calcifediol + placebo, despite having mean 25(OH)D levels of 28.5 ng/ml at month 4, went back to basal levels after withdrawal of treatment (16.1 ± 6.0 ng/ml at month 8 and 14.4 ± 6.0 ng/ml at month 12). Regarding safety, no patient reached 25(OH)D toxic levels (> 100 ng/ml), with 64.4 ng/ml being the highest concentration reported during the study. No relevant treatment-related safety issues were reported in any of the groups studied.
Conclusion
Calcifediol is efficient, faster and more potent than cholecalciferol in raising 25(OH)D levels. After 4 months of treatment, calcifediol 0.266 mg/month reaches its maximum efficacy within safe 25(OH)D levels, remaining fairly stable when treatment continues. Discontinuation of calcifediol supplementation lowers 25(OH)D levels back to baseline, suggesting that long-term treatment is safe and necessary.

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AEP84

Non-nuclear cataracts in hypoparathyroidism are associated with biochemical control of the disease

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Introduction
A high calcium-phosphate product is thought to increase the risk of soft tissue calcification in hypoparathyroidism, including cataracts. Based on small case series, cataracts in hypoparathyroidism typically develop in the posterior subcapsular region of the lens. However, the mechanism of cataract formation is still not well understood.
Materials and methods
In a large cohort of 1014 patients with biochemically confirmed hypoparathyroidism diagnosed between 2000 and 2020, we identified those with incident non-traumatic cataracts. Etiology and date of diagnosis of hypoparathyroidism were determined by medical records review. Information on type of cataract, date of surgery and complications after surgery was also collected. Three age- and sex- matched controls with cataracts without hypoparathyroidism were selected for each case.
Results
A total of 96 patients received a new diagnosis of cataracts over this 20-year interval. Of these, 81 had postsurgical and 15 nonsurgical hypoparathyroidism. Median age at hypoparathyroidism diagnosis was 50.0 ± 19.2 years (range, 0–80), and duration of hypoparathyroidism was 17.1 ± 15.0 (0.6–56) years, with no significant differences between postsurgical and nonsurgical groups. Median age at diagnosis of cataracts was 70.4 ± 13.8 (range, 17–88), with older age in the postsurgical group (71.0 ± 10.2 vs. 58.2 ± 22.7, P = 0.028). We identified four categories of cataracts (nuclear sclerosis or age-related, cortical, posterior subcapsular and combined forms)in 57 patients with hypoparathyroidism and 198 controls. Age-related cataracts were the most frequent form in controls (82.8%), while these were less frequent (59.6%) in patients with hypoparathyroidism. Opacities in the cortical and subcapsular portion of the lens were much more common in hypoparathyroidism (40.4% vs. 17.1%), and combinations of the three types were more common in hypoparathyroidism compared to controls (17.5% vs. 2.5%). The lower tertile of time-weighted average of serum calcium (K = –0.244, P < 0.001, N = 191) and the higher tertile of time-weighted average of serum phosphate (K = 0.183, P = 0.026, N = 148) were associated with greater prevalence of cortical, posterior subcapsular and combined forms of cataracts in the total study population. Posterior subcapsular cataracts alone were equally common in patients and controls (8.8% vs. 10.1%, P = NS). Nonsurgical hypoparathyroidism had the highest prevalence of non-age-

related cataracts (8/15, 57%). Hypoparathyroidism did not affect age of diagnosis, type, or complications of cataract surgery, including posterior capsule opacification after surgery.
Discussion
Peripheral damage to the lens is characteristic of hypoparathyroidism and may be correlated with hypocalcemia and hyperphosphatemia. Control of these biochemical abnormalities may reduce the risk of this complication.

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AEP85

Total and free vitamin D metabolites in female primary hyperparathyroidism patients

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Background
Primary hyperparathyroidism (PHPT) is a common endocrine disorder accompanied by low total 25-hydroxyvitamin D [25(OH)D] levels. The 25(OH)D is converted to its biologically active form, 1.25-dihydroxyvitamin D [1.25(OH)$_2$D] that then circulates as bound or free forms. Free 1.25(OH)$_2$D concentrations in patients with PHPT have not previously been examined and understanding this is important to better assess vitamin D status.
Objective
To evaluate total and free 1.25(OH)$_2$D and hormone-to-prohormone [1.25(OH)$_2$D/25(OH)D] 'activation ratio' in patients with PHPT and healthy controls.
Methods
Female patients with PHPT and healthy controls (n = 30/group), matched for age and body mass index, were enrolled. Serum levels of calcium, intact parathyroid hormone (iPTH), vitamin D binding protein (DBP), albumin, total 25(OH)D and 1.25(OH)2D levels were measured. The activation ratio of vitamin D was calculated as total 1.25(OH)$_2$D/25(OH)D. Calculated serum free 25(OH)D and 1.25(OH)2D levels were also reported.
Results
Compared to control subject, patients with PHPT had lower total 25(OH) D and DBP levels (P < 0.001). There were no significant differences in free 25(OH)D or total 1.25(OH)$_2$D levels between two groups; but free 1.25(OH)$_2$D levels were about 26% higher in the PHPT patients compared to controls (P < 0.001). The free (but not total) 1.25(OH)$_2$D level was inversely correlated with DBP (P < 0.01). The activation ratio was significantly higher in patients with PHPT (P < 0.01). The free 1.25(OH)$_2$D levels and activation ratio were positively correlated with iPTH (r = 0.35, P < 0.01) and calcium levels (r = 0.33, P < 0.01). The activation ratio was highly correlated with levels of total and free vitamin D metabolites (P < 0.001).
Conclusion
Patients with PHPT had significantly higher free 1.25(OH)$_2$D levels and activation ratio compared to control subjects. We suggest that total vitamin D levels may not be an accurate estimate of true vitamin D nutritional or functional status. The activation ratio may be a good predictor of free vitamin D levels in these patients.

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AEP86

A rare case of hypercalcemia in pregnancy- a diagnostic conundrum

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Hypercalcaemia in pregnancy is a rare but important finding, given the associated potential risks to mother and baby. These include hypertension, pancreatitis, nephrolithiasis and renal failure in the mother and intrauterine growth restriction, neonatal hypoparathyroidism/hypocalcaemia and stillbirth in the baby (1). We present the case of a 26-year-old female with a background of PTH-independent hypercalcaemia of unknown aetiology. This was initially detected at age 6 months when she was investigated for frontal bossing in Poland. Relevant family history includes that of her two siblings who have chronic kidney disease with renal cysts. Following confirmation of pregnancy, her biochemistry revealed an adjusted calcium of 3.55 mmol/l (her pre-pregnancy levels were 2.62 mmol/l-2.65 mmol/l) (reference range 2.20–2.60 mmol/l) and a PTH of < 0.3 pmol/l (reference range 1.6–7.2 pmol/l). She was initially treated with intravenous fluids, encouraged to establish a low calcium diet and subsequently maintain oral hydration. In view of a creatinine of 122 umol/l (reference range 55–110 umol/l), renal obstetric input was sought, and an ultrasound demonstrated medullary nephrocalcinosis. Further investigations demonstrated the following: 25-OH Vitamin D 250 nmol/l (reference range 70–150 nmol/l), 1.25-OH Vitamin D 267 pmol/l (reference range 55–139 pmol/l) and Fibroblast-Growth-Factor-23 240 H RU/ml (reference range < 100 H RU/ml). PTH-Related-Peptide results are pending. Subsequent targeted genetic testing demonstrated a compound heterozygous mutation in *CYP24A1*, resulting in hypercalcaemia due to excess active vitamin D metabolites (2). To address persistent maternal hypercalcaemia (> 3.00 mmol/l with conservative measures) and reduce the risk of perinatal hypoparathyroidism, she was commenced on subcutaneous calcitonin from 20 weeks gestation (intermittent dosing of 50–100 units repeated when calcium > 2.80 mmol/l). She is now 32 weeks gestation and undergoing close monitoring with regular biochemistry and growth scans, given the risk of growth restriction associated with hypercalcaemia. Here we describe a rare but important cause of hypercalcaemia and its exacerbation and management in pregnancy. Maternal hypercalcaemia was worsened by pregnancy-induced physiological changes, including increased vitamin D-driven calcium gut absorption as well as 1-alpha hydroxylase placental expression (1). An excellent response to calcitonin therapy has resulted in calcium levels safely maintained between 2.55–2.67 mmol/l during pregnancy.
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AEP87

Effect of parathyroidectomy on early diastolic dysfunction assessed with ventricular mass index in patients with primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism (PHPT) is characterized by excessive secretion of parathyroid hormone (PTH) from one or more parathyroid glands. PTH has a central role in the regulation of calcium and phosphate and the classic disorder causes primarily hypercalcemia associated with renal and bone manifestations. Non-classical symptoms are also present including cardiovascular, gastrointestinal, psychiatric, neuro-cognitive disorders. Regarding cardiovascular manifestations it is well established that patients with PHPT experience higher cardiovascular morbidity and mortality. Left ventricular structure has been shown to be affected in PHPT and patients present with increased left ventricular mass, which is regarded as a strong, independent factor of cardiovascular mortality. Both serum calcium levels and parathyroid hormone (PTH) have been reported to be associated with left ventricular hypertrophy.
Aim of the study
The aim of the study was to test whether curative parathyroidectomy (PTX) could contribute in decrease of left ventricular mass, leading to reverse of harmful effects of PHPT on cardiovascular system, in patients suffering from primary hyperparathyroidism.
Methods
We prospectively evaluated 10 patients scheduled to undergo parathyroidectomy for primary hyperparathyroidism (9 women and 1 man, with mean age 59.1 [± 10.5] years, mean BMI 26.4 [± 5.0], PTH at diagnosis 11.93 [± 3.14] pg/ml, and serum calcium 11.13 [± 0.47] mg/dl. Patients had

no history of heart disease (including hypertension, atrial fibrillation, valve disease and diabetes).
Echocardiographic evaluation was conducted by a single investigator with GE Vivid S5 ultrasound instrument and left ventricular end-diastolic dimension (LVEDD), interventricular septal thickness at end-diastole (IVSd) and posterior wall thickness at end-diastole (PWd) were measured. Left ventricular mass (LVM) was calculated as follows: LVM (g) = 0.8 × 1.04 [(LVEDD + IVSd + PWd)3 - (LVEDD)3] + 0.6. Left ventricular mass index (LVMI) was calculated as LVM divided by body surface area. Normal ranges were assumed as 43–95 g/m^2 for women and 49–115 g/m^2 for men.
Results
All patients had a normal LVMI before parathyroidectomy (mean LVMI 67.30 [± 17.04], and they were assessed 2 days before and 3 months after curative surgery. 3 months after PTX mean LVMI was reduced in all patients with mean values of 63.10 [14.16] g/m^2.
Conclusion
LVMI was reduced in all patients 3 months after parathyroidectomy. Despite the fact that LVM was within normal range before surgery the study showed a decrease in the mean LVMI for all patients. This is indicative that an early diastolic dysfunction exists in PHPT patients independent of other risk factors and it is normalized after surgery.

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AEP88

Bone mineral density evolution following long-term simultaneous pancreas-kidney transplantation in type 1 diabetes

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Introduction
Simultaneous pancreas-kidney transplantation (PKT) has a beneficial effect on the evolution of chronic complications in type 1 diabetic (T1D) patients with terminal chronic kidney disease (CKD). However, the CKD-mineral and bone disorder (CKD-MBD) remains a frequent complication. There are a few studies addressing the long-term evolution of bone mineral density (BMD) in these patients.
Aim
To characterize baseline BMD and evaluate its long-term evolution in patients with T1D undergoing PKT.
Methodology
A retrospective cohort, including patients submitted to simultaneous pancreas-kidney transplantation in our tertiary center, between 2000 to 2017. The evolution of BMD was assessed by DEXA. Only patients with baseline value and minimum follow-up of 2 years were included.
Results
Seventy-three patients were included, mostly male (53.4%), with a mean age at transplantation of 35.6 ± 5.9 years. At transplantation, mean T-score of the lumbar spine (LS) and femoral neck (FN) was –1.68 ± 1.12 and –2.15 ± 0.77, respectively. Seventy-five percent presented low bone mass (LBM = osteopenia + osteoporosis) in LS and 90% in FN, with 32.9% having criteria for osteoporosis in LS and 35.6% in FN. On the multivariate analysis, male gender (OR 3.59, P = 0.03) and low BMI (OR 0.78, P = 0.03) were significantly associated with lumbar LBM, but not in the femur. At a long term, BMD significantly improved in LS (ΔT-score + 0.41, P < 0.001) and FN (ΔT-score + 0.29, P = 0.01), in a median time of 4 years after PKT. 57.5% maintained LMO in the LS and 86.3% in the FN, with 12.3% achieving osteoporosis criteria in the LS and 16.4% in the FN. There was a positive correlation between BMI and BMD of LS (r = 0.31, P = 0.02) and FN (r = 0.36, P = 0.005). Pancreas graft failure (P = 0.03) was a predictive factor for osteoporosis in FN, but not in the LS.
Conclusion
In the absence of information available on the Z-score, which is best applicable to most of these patients, the use of the T-score shows more than a quarter of T1D patients undergoing PKT to achieve osteoporosis criteria. The significant improvement in BMD may result from metabolic correction with PKT and physiological mineral capitalization of the skeleton that still occurs at these age groups. The evolution of BMD was positively associated with BMI, due to a greater efficiency of the nutritional balance with transplantation.

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AEP89

Normalization of SIAD-induced hyponatremia stimulates osteoblast function

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Background
Hyponatremia is associated with increased risk of bone fragility and fractures. *In vitro* studies suggest a role of hyponatremia in stimulating osteoclast activation, whereas other studies rather revealed a possible role of acute hyponatremia in impairing osteoblast function. We aimed to assess whether and how correction of hyponatremia in hospitalized patients with the syndrome of inappropriate antidiuresis (SIAD) has an impact on bone metabolism.
Material and methods
This is a pre-defined secondary analysis of 83 hospitalized patients with SIAD undergoing a randomized treatment for 5 days. Biochemical markers of bone resorption (CTX) and bone formation (PINP) were collected in serum at baseline and after the intervention (day 5). Bone formation index (defined as PINP/CTX) was calculated. Patients with steroid therapy (n = 6), fractures (n = 10), or whose data were missing (n = 16) were excluded from the analysis.
Results
Out of 58 patients, 27 (47%) were normonatremic at day 5. These patients showed a 47.9 points higher bone formation index (95% CI 16.7–79.2, P = 0.0035) compared to patients with persistent hyponatremia at day 5. This observation was independent of age, sex, BMI, smoking habits, randomization arm, as well as baseline sodium and cortisol levels. Serum CTX increased similarly in the two groups (P = 0.76), whereas serum PINP increased in patients with normal sodium after intervention (P = 0.04), but not in persistent hyponatremic patients (P = 0.38).
Conclusions
Normalization of hyponatremia in hospitalized patients with SIAD results in an increased bone formation rate, suggesting a stimulation of osteoblast function.

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AEP90

Fibrosis 4 score is associated with bone density measures in postmenopausal women

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Introduction
The routine assessment of postmenopausal women involves screening for cardiometabolic risk factors and bone health. Evaluation of the liver function is not commonly performed, even though this could be easily performed with the use of indirect markers, such as the Fibrosis 4 score. Recent evidence supports an association between liver cirrhosis and bone turnover, affecting both the trabecular and the cortical bone. Therefore, we aimed to explore the possible link between postmenopausal osteoporosis and liver function, expressed according to the values of the Fibrosis 4 (Fib4) score.
Methods
This was a cross-sectional study of 8.363 postmenopausal women, retrieved from a University Menopause Clinic. Details of the personal and medical history were retrieved from the departmental database, including osteoprotective drug intake. Participants underwent a fasting blood test, in the context of their routine assessment in the Department, for estimation of biochemical and hormonal parameters. Moreover, we performed a bone density scan (DEXA) of either the lumbar spine (LS) or the femoral neck (FN) for evaluation of possible underlying osteoporosis.
Results
Mean age of our women was 56.7 ± 7.5 years, with a mean menopausal age of 8.87 ± 6.9 years and BMI 26.9 ± 4.7 kg/m^2. Correlation analysis between Fib4 values and bone parameters was as follows: LS-BMD, r = –0.083; LS-Tscore = –0.099; FN-BMD, r = –0.085; FN-Tscore r = –0.093,

P-value < 0.001 in all cases. The presence of osteoporosis in the lumbar spine only was associated with higher values of Fib4 score (1.14 ± 0.35 vs 1.08 ± 0.49, *F* = 5.509, *P*-value = 0.019, ANCOVA adjusted for age, menopausal age, BMI, smoking, alcohol, intake of calcium/bisphosphonates, type 2 diabetes, thyroid-stimulating hormone levels). Fib4 values > 1.45 vs lower levels were associated with 2.147 times higher risk for LS-osteoporosis (*P*-value = 0.001) in combination with the effect of age, calcium/bisphosphonates intake, BMI and HDL cholesterol. No associations were observed between FN-osteoporosis and values of Fib4 score either in dichotomous or continuous manner.
Discussion
These results are indicative of lower BMD in patients with higher values of Fib4 score, affecting particularly the LS-region. These findings are compatible with data available on patients with established cirrhosis. Differences between the lumbar and femoral skeletal region with regards to the amount of trabecular bone might be an explanation of the differing associations observed in this study. Further case-control studies are needed to confirm these findings.

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AEP91

Primary hyperparathyroidism: Differences in presentation between older and younger patients

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Introduction
The incidence of primary hyperparathyroidism (PHPT) increases with age; however, the clinical presentation might change with aging. We aimed to compare the clinical presentation of older and younger patients with PHPT.
Methods
We retrospectively analyzed the biochemical status, renal involvement, and bone mineral density (BMD) of patients who were diagnosed with PHPT at our endocrine clinic from 2004 to 2016. Patients over 65 years of age were compared to younger patients.
Results
We included 426 adult patients (339 women and 87 men) with PHPT. There were 231 patients over 65 years with a mean age of 73.4 (SD 5.3) years and 195 younger patients with a mean age of 52.2 (10.0) years. Gender distribution was similar with 49 (21.2%) males in older group and 38 (19.5%) males in younger group (*P* = 0.66). Older patients had biochemically less florid disease at presentation with a lower mean serum calcium: 2.72 (0.25) mmol/l vs. 2.79 (0.29) mmol/l; *P* = 0.01, lower urinary calcium: 5.18 (4.0) mmol vs. 8.39 (4.6) mmol; *P* < 0.01 and higher phosphate: 0.84 (0.15) mmol/l vs.0.8 (0.18) mmol/l; *P* = 0.02, but also higher creatinine: 83.56 (31.92) µmol/l vs. 72.23 (26.32) µmol/l; *P* < 0.01, lower estimated glomerular filtration rate: 68.4 (18.1) ml/min vs. 79.4 (14.5) ml/min; *P* < 0.01 and lower 25-OH vitamin D levels: 39.63 (22.41) nmol/l vs. 43.92 (21.53) nmol/l; *P* = 0.02. PTH and alkaline phosphatase levels did not differ between groups. Fewer older patients had nephrolithiasis and/or nephrocalcinosis than younger patients (56 out of 231 or 24.2% vs. 78 out of 195 or 40%; *P* < 0.01). BMD was significantly lower in older patients than in younger patients at the total hip (0.786 (0.157) g/cm^2 vs. 0.876 (0.150) g/cm^2; *P* < 0.01), femoral neck (0.640 (0.113) g/cm^2 vs. 0.717 (0.125) g/cm^2; *P* < 0.01) and at one-third distal radius (0.564 (0.108) g/cm^2 vs. 0.625 (0.100) g/cm^2; *P* < 0.01). There were no differences in BMD at the lumbar spine. Finally, 139 out of 231 older patients (60.2%) were diagnosed with osteoporosis, which was found in only 71 out of 195 younger patients (36.4%; *P* < 0.01).
Conclusion
Based on our study, patients with PHPT who are older than 65 years present with biochemically less florid disease and less nephrolithiasis/nephrocalcinosis, but with more severe bone impairment than younger patients.

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AEP92

Primary hyperparathyroidism – a contemporary picture based on 100 patients from the last decade

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Primary hyperparathyroidism (PHPT) is being more and more frequently diagnosed.
Objective
to describe the clinical presentation and the main laboratory and imaging findings in a group of patients with PHPT diagnosed during the last 10 years. Materials and Methods: This was a retrospective cross-sectional study with data review from the last 10 years. Secondary causes for elevated PTH were excluded. The symptoms and signs of hypercalcemia/HPT were reviewed. Serum calcium (total, albumin-corrected and ionized; sCa, corrCa, iCa +), phosphates (P), magnesium, creatinine, alkaline phosphatase, beta-crosslinks were measured. The intact parathyroid hormone (iPTH) and 25(OH)-vitamin D were determined by electro-hemi-luminescence (Elecsys, Roche Diagnostics). Neck ultrasound (US) was used as first localization study. Half of the participants underwent fine-needle aspiration biopsy (FNAB) with cytology and needle-washouts for iPTH. One fourth was assessed by Single-Photon Emission Tomography (SPECT-CT). Data on bone density (from DXA), fractures and renal stones (from renal US) were collected.
Results
100 patients met the study criteria – 95 were women. Most of them were in their 5th and 6th decades. The median corrected sCa was 2.73 mmol/l, iCa+ – 1.39 mmol/l, P – 0.88 mmol/l, iPTH – 14.5 pmol/l and 25(OH)D – 54.0 nmol/l. Normal sCa was registered in 20 participants (20%), while normal sP – in 67.0%. The neck US located single lesions (parathyroid adenoma) in 81% - behind or below the left inferior pole of the thyroid gland in 33 cases (33%) and contra-laterally in another 33%. FNAB of the suspicious lesion had been performed in 51% of the study subjects. The cytology confirmed the presence of parathyroid cells in 22 cases (43.1%), Bethesda II thyroid nodules in 21 cases (41.2%), Bethesda III nodules in 2 cases (3.9%) and insufficient samples (Bethesda I) in 5 cases (9.8%). SPECT-CT from 27 patients identified a suspicious left parathyroid in 11 cases, as well as three ectopic locations. Reduced eGFR and low bone mass were more prevalent than in the general population. Fractures however were not more frequent. Data from renal ultrasound were available in 77% and revealed chronic pyelonephritis without stones in 8 patients (10.4%) and renal stone disease – in 37 patients (48.0%).
Conclusion
Mild to moderate hypercalcemia is frequently the first clue to the diagnosis of PHPT. SPECT-CT seems to be replaced by US-guided FNAB with needle washout measurements of iPTH. Altogether the picture of PHPT is shifting towards milder and asymptomatic (and probably earlier) forms of the disease.

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AEP93

Quantifying the real-world clinical and economic burden of chronic hypoparathyroidism on secondary care in England: A multi-arm, retrospective cohort study

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Background
Chronic hypoparathyroidism (hypoPT) predisposes patients to comorbidities such as cardiovascular/cerebrovascular disease, infection, mental illness, and renal impairment often associated with an increased burden to healthcare systems. Suboptimal disease control is common with standard therapy. The objective of this study was to quantify and assess differences in the clinical and economic burden on secondary care among patients with post-surgical and non-surgical chronic hypoPT in England.

Methods
This multi-arm, retrospective cohort study was conducted using secondary care data collected between April 2014 and March 2019 by the Hospital Episode Statistics (HES) database records of patients with chronic hypoPT. Diagnosis of hypoPT was defined as the presence of ≥ 2 hypoPT ICD-10 codes reported ≥ 180 days apart. Patients with hypoPT must have had ≥ 1 HES interaction ≥ 360 days from the index date (inpatient, outpatient, or accident and emergency) to be included in this analysis. Data of patients with post-surgical and non-surgical chronic hypoPT were compared with those of patients with hypothyroidism and those who underwent thyroid surgery, respectively, for better understanding of clinical/economic burden against a broader patient population.
Results
The universal hypoPT cohort (n = 4.087) included data from post-surgical (n = 993) and non-surgical (n = 2.959) hypoPT patients and others (n = 135, defined as ICD-10 codes indicating both post-surgical and non-surgical hypoPT diagnoses). The prevalence of hypoPT and 1, 2 or 3 + comorbidities was consistently higher in non-surgical vs post-surgical hypoPT patients. Most comorbidities were significantly more frequent in non-surgical and post-surgical groups vs their respective comparators. The most common comorbidities included neuropsychiatric conditions (55.0% vs 55.1%; 55.2% vs 29.1%, P < 0001), renal insufficiencies (22.6% vs 12.9%; 35.4% vs 4.5%, P < 0.0001 both) and infections (25.3% vs 19.1%; 31.2% vs 7.4%, P < 0.0001 both). Healthcare resource utilization (HCRU) was higher in non-surgical and post-surgical hypoPT patients vs their respective comparator group (12.9 vs 6.5; 20.2 vs 2.4) in terms of longer mean spells per patient during inpatient visits and a lower proportion of outpatient appointments referred by a GP (17.8% vs 28.4%; 18.9% vs 41.6%). In the universal, post-surgical, and non-surgical cohorts, 0.2%, 0.5% and 0.1%, respectively, accrued annual inpatient and outpatient costs of > £60.000 per patient, mainly driven by renal comorbidities.
Conclusion
This study highlights the burden of disease, prevalence of comorbidities, and unmet medical needs in patients with hypoPT, as well as a high economic burden on the healthcare system in England by chronic hypoPT patients with a primary cost driver being renal complications across all cohorts.

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AEP94

'Primary hyperparathyroidism: Relationship between localisation of adenoma and calcium level'

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Aim
To assess relationship between serum calcium level and localization studies and management outcome.
Methodology
Retrospective analysis of data for patients referred by primary care for hypercalcemia from 1/3/2019 to 1/3/2020 to the Endocrinology department at Royal Berkshire Hospital. The sample size was 63 which excluded normo-calcemic hyperparathyroidism as well as MEN1/2 patients.
Results
The average age of cohort was 68.6 years with female preponderance (80.5%). The average referral adjusted calcium was 2.8 mmol/l and PTH was 12.5 mmol/l. End organ damage in the form of osteopenia and osteoporosis was highly prevalent at 60.3%. The sensitivity for USS was 47.6% and MIBI was 50.8%. The concordance between the two modalities was 71.4%. The lower limit of adjusted serum calcium level cut off for positive USS was 2.65 mmol/l and for positive MIBI was 2.62 mmol/l with p value of 0.00025. In terms of management outcome, 57.1% of cohort were referred to ENT team for surgery and the rest were conservatively managed.
Discussion
Hypercalcemia forms a significant proportion of referrals to endocrinology service. Primary hyperparathyroidism is the most common cause of hypercalcaemia, with an estimated prevalence of about 1–7 cases per 1000 adults.[1] This study reiterated the established expected demographics of patients with primary hyperparathyroidism i.e., female preponderance with increasing prevalence in older adults [2]. Half of the referrals were asymptomatic. About two third of the cohort had osteopenia and osteoporosis, a criterion that enables eligibility for surgical intervention if appropriate. The pick-up rate of parathyroid USS and scintigraphy were comparable at around 50%, with a discordance of 28.6% between them. The lower limit for adjusted calcium above which both the USS and SestaMIBI provided positive finding was 2.62 mmol/l which is reassuringly just above the lower limit cut off for NICE diagnostic criteria for hypercalcemia. It is important to note though that normo-calcemic hypercalcemia were not included in this study. With respect to management outcome, a significant 57.1% of cohort were referred to ENT team for targeted (63.9%) or exploration surgery (36.1%) depending on image findings. The rest were conservatively managed with either cinacalcet (34.6%) or wait and watch approach (65.4%). It is interesting to note that 80% of patients with adenoma on USS translated to a surgical outcome. This held true even in the event of discordance with MIBI scan, revealing this modality being favoured by ENT team.

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AEP95

High dose short term glucocorticoid (gc) treatment seems to have no long term negative effect on bone mineral density (bmd) of newly diagnosed multiple sclerosis (ms) patients

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Objectives
High-Dose-Intravenous-Steroid-Treatment-(HDIST) represents the first choice of treatment for MS relapses. Although chronic oral GC-administration is associated with bone loss there are still conflicting data regarding HDIST.
Methods
25 newly-diagnosed MS-patients (10-women) were prospectively enrolled meeting the following eligibility criteria: age 18–45 yrs, fully ambulatory, women with normal menstruation. Exclusion criteria: history of any chronic disease, previous GC-treatment in any dosage regimen. Patients received 1000 mg-Methylprednisolone intravenously daily for 5 consecutive days. 7/25pts were excluded due to mobility impairment, 8/25 were lost to follow-up. In the remaining 10pts (6-men) serum levels of: Calcium, Phosphorus, Albumin, Magnesium, Creatinine, 25-OH-D, Parathyroid-Hormone-(PTH), Thyroid-Hormones-(TH), Bone-fraction-Alkaline-Phosphatase-(BALP), N-terminal-propeptide-procollagen-type-1-(P1NP), C-terminal-peptide-type-of-collagen-(CTx), Receptor-Activator-of-Nuclear-Factor-Kappa-β-Ligand-(RANK-L), Osteoprotegerin, Sclerostin, Dickkopf-1-(DKK-1), Periostin, Interleukins-(IL)-1ή6.17 were determined prior to GC-administration and consecutively the days: 2–4–6-90 and months: 6–12–18–24. BMD of both hips and lumbar spine as well as whole-body measurement of adipose/lean tissue were assessed with Dual-X-ray-Absorptiometry-(DXA)-scan, prior to GC-administration and consecutively every six months.
Results
Bone formation markers, P1NP and BALP, showed an initial non-significant fall (P1NP day 6:–0.414 ± 0.128 ng/ml, BALP day 4:–0.864 ± 0.334 μg/l) followed by a significant increase in day 90 (P1NP: + 0.567 ± 0.13 ng/ml, P < 0.05, BALP: + 1.838 ± 0.464 μg/l, P < 0.05). No other significant changes were observed. A transient non-significant fall of BMD was observed at all sites 6-months after GC-administration, which subsequently appeared to be restored while in the lumbar spine this trend for reduction continued up to 24-months. The percentage changes of Periostin levels from baseline to 24-months correlated positively with the changes in total-left-hip-BMD and left-trochanter-BMD (r =+ 0.709, P = 0.022 and r =+ 0.77, P = 0.009, respectively) and negatively with CTx (r = 0.806, P = 0.005). The changes in CTx levels negatively correlated with the changes in left-trochanter-BMD (r =–0.782, P = 0.008). A positive correlation of the changes in left-femoral-neck-BMD with the changes in Body-Mass-Index-(BMI) was observed (r = +0.661, P = 0.038). The percentage changes of 25-OH-D levels form baseline to 24-months negatively correlated with the changes of IL-1β from baseline to 3 and 6 months (r = −0.806, P = 0.005 and r = −0.867, P = 0.002, respectively).

Conclusions
In spite of the small sample this is the first-to our knowledge-prospective study aiming to elucidate the impact of HDIST on BMD and simultaneously on biochemical parameters of bone metabolism in newly-diagnosed MS-patients; high dose short term GC administration seems to have no long term negative effect on BMD in this group of patients. The observed transient increase in bone formation markers -90 days after GC administration-probably indicates a high bone turnover phase as a 'response' to the transient adverse effects of GC on bone-metabolism. More prospective studies with larger sample size on similarly selected patients should be performed.

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AEP96

Normocalcemic primary hyperparathyroidism – an early stage of hypercalcemic hyperparathyroidism?

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Introduction
Primary hyperparathyroidism (PHPT) is a common endocrine disorder and classically associated with hypercalcemia (HHPT). There is a newest variant of PHPT, defined by normal albumin-corrected calcium levels - normocalcemic PHPT (NHPT) – which may represent an early stage of HHPT. Nevertheless, there is limited data on how this variant presents clinically and biochemically.
Aim
To evaluate the demographic, biochemical and clinical profile of NHPT, comparing with HHPT.
Methods
Retrospective single center study that included subjects with a confirmed diagnosis of PHPT followed at our hospital from November 2019 to November 2020. We excluded patients with malignancies and under treatment with glucocorticoids, cinacalcet, bisphosphonates and denosumab. Patients were categorized in two groups – HHPT and NHPT – whether they had hypercalcemia or not, respectively. Nephrolithiasis was documented by kidney ultrasound. Bone mineral density (BMD) at lumbar spine, femoral neck and one-third distal radius was documented by Dual-energy X-ray absorptiometry (DXA).
Results
We included 30 patients with HHPT and 28 with NHPT. The mean age was 59 ± 15 and 61 ± 15 years in NHPT and HHPT, respectively. There were predominantly females (80% NHPT and 78.6% HHPT). The group of NHPT presented with lower levels of PTH (122 pg/ml [101–142] vs 309 pg/ml [216–389], $P < 0.001$), albumin-corrected serum calcium (9.7 mg/dl [9.1–10.0] vs 11.4 mg/dl [11.1–12.2], $P < 0.001$), and higher phosphate concentration (3.6 mg/dl [2.7–4.3] vs 2.8 mg/dl [2.3–4.1], $P = 0.028$). There were no differences between groups in nephrolithiasis (40% NHPT vs 53.6% HHPT, $P = 0.300$), in femoral neck T score (−1.05 [−2.25; −0.63] vs −1.35 [−2.10; −1.20], $P = 0.159$) and lumbar spine T score (−1.45 [−2.70; −0.58] vs −2.35 [−3.20; −1.28], $P = 0.093$). Patients in the NHPT group showed a higher one-third distal radius T score compared to HHPT (−1.05 [−2.93; −0.08] vs −2.50 [−2.75; −1.70], $P = 0.028$). The prevalence of osteoporosis was 25% in NHPT and 41.7% in HHPT ($P = 0.246$). The prevalence of osteopenia at femoral neck and distal radius was lower in the NHPT group (40% vs 70.8%, $P = 0.040$).
Conclusion
Considering biochemical and clinical features, NHPT appears to represent an early stage of HHPT. However, it presents with high rates of nephrolithiasis and osteoporosis, reinforcing the need to recognize and treat this entity according to defined criteria. BMD at distal radius was more preserved in NHPT, corroborating the association with cortical, but not trabecular, bone loss. Therefore, one-third distal radius BMD should be assessed in all patients with PHTP.

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AEP97

Osteoporosis and prevalent vertebral fractures are associated with insulin resistance in non-diabetic postmenopausal women

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Introduction
Recent evidence suggests a possible link between prediabetes and lower density in postmenopausal populations. Moreover, earlier data suggest a link between diagnosis of diabetes and lower levels of bone density in women after the menopausal transition. We aimed to evaluate the possible association between insulin resistance and a diagnosis of lumbar or hip osteoporosis and/or prevalent fractures of the lumbar spine.
Methods
This cross-sectional study included 322 postmenopausal women, retrieved from the Menopause Clinic of Aretaieio Hospital. Women with insulin resistance (homeostasis model assessment, HOMA-IR > 5) clinically overt cardiovascular disease, diabetes mellitus, untreated thyroid dysfunction, gynecological malignancy or endometrial thickness of more than 5 mm were excluded. Blood samples were obtained to perform biochemical and hormonal assessment including markers of bone turnover. Bone density at the lumbar spine (LS) and femoral neck (FN) was estimated using DXA. Lumbar spine plain radiographs were performed to assess for the prevalence of vertebral fractures (VFs).
Results
The prevalence of VFs was 7.5% (24/322), while LS-osteoporosis was identified in 8.8% (19/216) and FN-osteoporosis was identified in 14.8% (31/209) women. Bone density measures correlated with HOMA-IR (LS, T-score r-coefficient = 0.149, P-value = 0.028; FN, BMD r-coefficient = 0.143, P-value = 0.040; FN, T-score r-coefficient = 0.147, P-value = 0.033), age, menopausal age. Markers of bone turnover did not associate with HOMA-IR, glucose or insulin levels. Osteoporosis vs normal bone density/osteopenia was related with lower levels of HOMA-IR, especially at the lumbar spine (LS: 1.2 ± 0.4 vs 1.7 ± 0.9, P-value = 0.018; FN: 1.3 ± 0.6 vs 1.6 ± 0.9, P-value = 0.091), as well as with higher age and follicular stimulating hormone levels. Logistic regression analysis showed that the prevalence of VFs associated inversely with HOMA-IR levels (1st vs 4th quartile, 2.5% vs 7.5%, P-value 0.018 after bootstrapping for 1000 samples), adjusted for age, BMI, FSH, E2. Presence of LS-osteoporosis associated inversely with HOMA-IR levels (1st vs 4th quartile, 13.7% vs 1.8%, P-value = 0.030 after bootstrapping for 1000 samples) as well as menopausal age, adjusted for the same variables. Presence of FN-osteoporosis associated inversely with HOMA-IR levels (1st vs 4th quartile, 16.9% vs 4.5%, P-value = 0.040 after bootstrapping for 1000 samples), adjusted for the same variables.
Conclusion
The development of VFs, LS- as well as FN-osteoporosis is inversely associated with insulin resistance, as estimated by levels of HOMA-IR, in a non-diabetic postmenopausal population.

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AEP98

The bone impact of body composition, adipokines and FGF23-Klotho axis in active acromegaly

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Introduction
Body composition (BC), adipokines and the fibroblast growth factor-23 (FGF23) - Klotho axis interfere with bone metabolism and also suffer important modifications in acromegaly. We aimed to investigate their influence upon bone in active acromegaly, compared to controls.
Methods
We performed a cross sectional study, investigating the adipokines (leptin, adiponectin, resistin) secretion pattern, BC parameters and FGF23-α-Klotho axis and their impact upon bone mineral density (BMD) and turnover, respectively, in 35 patients with active acromegaly (Acro), compared to sex, age and body mass index (BMI) - matched healthy controls (Ctl).

Results
Acro had higher lumbar and femoral neck Z-scores ($P < 0.05$), respectively, and a lower trunk-to-leg fat ratio compared to Ctl. Serum adipokines, but not FGF23, differed significantly in the two groups, with lower leptin ($P < 0.001$) and elevated adiponectin ($P < 0.001$) and resistin ($P = 0.001$) concentrations in the Acro group. Resistin was also higher in non-diabetic Acro compared to Ctl (15.9 ± 4.26 ng/ml vs 6.59 ± 0.66 ng/ml, $P = 0.048$). Age (negative), lean mass and trunk-to-leg fat ratio (positive) were the main independent BMD predictors in regression analysis in both Acro and Ctl. Adiponectin and resistin negatively correlated with BMD at various sites ($P < 0.05$) and α-Klotho was positively correlated with osteocalcin ($r = 0.52$, $P = 0.003$) in the Acro, but they lost significance after adjusting for age and BC.
Conclusions
Acromegalic patients display important BC, adipokines and bone changes. Age and BC were the main independent BMD predictors in active acromegaly, similar to the general population. Although serum adipokines showed an altered profile, related to the metabolic changes seen in acromegaly, they were not found to have independent bone actions.

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AEP99

Recurrent primary hyperparathyroidism due to ectopic retropharygeal adenoma

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Introduction
The ectopic parathyroid adenoma (EPTA) is the most common cause of failed parathyroid surgery. Most often localisations are intra-thymic and intra-mediastinal adenomas. We report a rare presentation of a symptomatic parathyroid adenoma located in ectopic retropharyngeal position diagnosed after surgical treatment of primary hyperparathyroidism (PHPT).
Obsevation
A 42-year-old female was referred to internal medecine department with fortuitous discovery of hypercalcemia. She had no medical history and there was no family history of multiple endocrine neoplasia syndrome or parathyroid disorder. On physical examination, her blood pressure was 100/65 mmHg. There was no palpable neck mass. Electrocardiogram was normal. Laboratory investigations revealed an elevated serum calcium level at 3.04 mmol/l [2.2- 2.6 mmol/l], hypophoshatemia of 0.52 mmol/l [0.81–1.62 mmol/l]. Serum parathyroid hormone level was markedly increased 287.7 pg/ml [15–65 pg/ml]. Urinary calcium rate was elevated. Her thyroid function test was normal. Diagnosis of hypercalcemic crisis resulting from PHPTwas retained and surgical treatment was indicated. Preoperative Neck US showed left mediolober thyroid nodule TIRADS4 and parathyroid scintigraphy showed lower cervical fixation and left upper plolarhypofixation corresponding to parathyroid adenoma. The patient underwent a lower right paratyroidectomy with an upper left loboisthmectomy. Histological examination showed left lobe adenoma and right lower parathyroid hyperplasia. The postoperative course was favorable. Three months later, she presented recurrent hypercalcemia, hypophosphatemia and increased PTH level at three times normal rate. Neck US and scintigraphy were negative for PTA or thyroïd disease. Cervical CT showed an ectopic retropharyngealparathyroid adenoma which previously had been dismissed as a nonpathological lymph node. The patient was referred again for revesion surgery.
Discussion
PHPT is commonly the result of parathyroid adenoma, less frequent the result of hyperplasia or multiple adenomas. Excision of adenoma is currently curative for primary PHPT but surgery failure and recurrent hypercalcemia are usually due to ectopic adenoma. Retropharygeal space is rarely reported as an area for EPTA.It is thought to be due to the common embryologic origin of the superior parathyroid gland and the apex of the piriform sinus from the fourth branchial pouch.The goal of preoperative imaging in PHPT is not only to identify solitary PTA or multigland disease but also to detect ectopic adenoma.
Conclusion
This case highlights the retropharyngeal space as an important and rare ectopic site for parathyroid adenoma that must be researched carefully before surgery to avoid surgical revision. We insist on using multiple imaging technics to increase the chance for detection of ectopic adenomas.

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AEP100

Denosumab rebound effect associated with breast cancer recurrence – a coincidence? Case report

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Denosumab discontinuation leads to loss of bone mineral density (BMD) achieved with treatment and in some patients to multiple vertebral fractures (VFx). Beyond bone, antiresorptive agents such as denosumab may affect breast cancer biology. We report a 69-year-old woman treated with the aromatase inhibitor anastrazole for breast cancer who suffered from five spontaneous vertebral fractures after denosumab cessation. Initially, she received four years of ibandronate followed by three years of denosumab (6 injections) as antiosteoporotic treatment. On denosumab her BMD significantly improved (increase of 12% in lumbar spine and 4.8% in hip BMD); after attaining nonosteoporotic BMD the treatment was withdrawn. Six months after the last injection of denosumab peroral ibandronate was administered. Despite ibandronate treatment, 13 months after stopping denosumab, C-terminal collagen cross links (CTX) increased 14-fold in comparison with their values on denosumab, demonstrating accelerated bone resorption, and hip BMD fell by 7.5%. Furthermore, VFx occurred 11 and 13 months after stopping denosumab. At the same time local breast cancer recurrence was diagnosed after six years of remission. The patient underwent left mastectomy followed by trastuzumab treatment. Bone scintigraphy and spine magnetic resonance imaging ruled out bone metastasis and confirmed osteoporosis- related fragility vertebral compressions. Denosumab was resumed and after three injections BMD significantly increased (increase of 17.5% in lumbar spine and 7.4% in hip BMD). The patient postponed one injection to avoid the risk of osteonecrosis of the jaw linked to dental treatment. CTX increased and BMD dropped again significantly (decrease of 21% in lumbar spine and 8.5% in hip BMD). Denosumab was reinitiated for the third time and has been continued. This case illustrates a rebound effect after denosumab cessation in a postmenopausal woman treated for breast cancer. Neither pretreatment nor subsequent postdenosumab treatment with ibandronate prevented high bone turnover, bone loss, and VFx. Denosumab decreases the risk of fractures and, moreover, may provide an adjuvant survival benefit in breast cancer patients. Denosumab discontinuation is, however, associated with a rapid reversal of its effect in bones. Whether this rebound effect has also negative clinical implications for breast cancer recurrence remains to be elucidated. Supported by MZČR - RVO (Institute of Endocrinology - EU, 00023761).

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AEP101

Association of preoperative factors and postoperative hypocalcemia after parathyroidectomy for primary hyperparathyroidism

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Background
Parathyroidectomy (PTE) is the basic treatment for symptomatic primary hyperparathyroidism (PHPT). It is also recommended for some asymptomatic patients. However, PTE can be followed by some complications such as postoperative hypocalcemia.
Aim
To evaluate association of demographic, clinical, laboratory factors, preoperative cholecalciferol supplementation and hypocalcemia after PTE in patients with PHPT.
Methods
478 patients with PHPT were included in retrospective study, 256 of them had postoperative hypocalcemia (group 1) and 222 hadn't (group 2). The data were obtained from the PHPT registry and the qMS medical information system. The demographic, clinical and laboratory features were compared between groups using Mann-Whitney and Chi-square tests. Cut-off for serum 25(OH) vitamin D (25(OH)D) was determined by ROC-analysis. Bonferroni correction was used for multiple comparisons.

Results
Hypocalcemia was identified in 54% cases (95% CI 49%–58%). Median and quartiles of age were 57 [47; 64] in group 1 and 59 [47; 64] in group 2. Median levels of serum parathyroid hormone (PTH), total calcium, albumin-corrected and ionized serum calcium, alkaline phosphatase (AP) and osteocalcin were significantly higher in group 1 (223.3 vs 165.7 pg/ml, 2.90 vs 2.81 mmol/l, 2.85 vs 2.72 mmol/l, 1.36 vs 1.32 mmol/l, 142 vs 111 IU/l, 64 vs 48.6 ng/ml, respectively, $P < 0.001$ for all), and phosphorus and serum 25(OH)D were lower in group 1 (0.81 vs 0.89 mmol/l, 15.9 vs 19.1 ng/ml, $P = 0.002$). Severe osteoporosis was more frequent in group 1 (14% vs 7%, $P = 0.003$). Taking cholecalciferol before PTE is associated with a lower incidence of postoperative hypocalcemia (27% vs 59%, $P < 0.001$, OR = 0.254, 95% CI 0.147–0.440). Cut-off for serum 25(OH)D as a predictor of postoperative hypocalcemia is 21.6 ng/ml with PPV = 61%, 95% CI 57%–64%, and NPV = 64%, 95% CI 56%–72%.
Conclusion
PTH, laboratory factors of calcium and bone metabolism, as well as severity of osteoporosis are associated with hypocalcemia in patients with PHPT after PTE. Taking cholecalciferol before PTE reduces the odds of postoperative hypocalcemia by 2–6 times.

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AEP102

Which patients with primary hyperparathyroidism were not referred for surgery? A single-center experience

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Although primary hyperparathyroidism (PHPT) can be successfully cured by parathyroidectomy (PTX) and indications for surgery are well defined, a considerable number of patients do not get operated on. By evaluating referrals for PTX in our academic hospital, we might improve our approach to the care of these patients. We retrospectively reviewed patients' hospital records with newly diagnosed PHPT between 2014 and 2020. Biochemical and clinical parameters along with results of diagnostic tests were collected. Among 123 retrieved patients, 26 were not sent for surgery by a referring clinician (nonsurgical group) and they were compared with 66 patients that underwent PTX. The remaining 31 patients were unwilling to undergo surgery, lost from follow up or their workup and surgery were postponed. The statistical analysis was performed by χ^2 test, parametric tests, and multivariate logistic regression. The comparison between the nonsurgical group and the PTX group found that the age of non-operated patients was higher, but they had no more comorbidities. Non-operated patients had lower serum calcium at first presentation, lower PTH and calciuria, but higher serum phosphate. There were also more normocalcemic PHPT patients in the nonsurgical group. The presence of PHPT complications (osteoporosis, fractures, and urolithiasis) was similar between groups and so was the presence of at least one indication for surgery. The sonographic size of enlarged parathyroid glands did not differ between groups. The nonsurgical group had significantly fewer positive findings on ultrasound, FNA cytology, PTH washout, and sestamibi scan. At least two concordant imaging tests (ultrasound, sestamibi scan, or 4DCT) were significantly less frequent among non-operated patients. In a logistic regression model, the absence of concordant imaging tests was the only independent predictor for the nonsurgical approach (OR 14, 95% CI 3.9–50.2, $P < 0.001$). Parathyroid disease localization should not be a criterion for surgery, but these results emphasized a tendency to obtain concordant imaging prior to the referral for PTX. This impression also emerged in our multidisciplinary team meetings and similar real-life data were already encountered in different settings. In practice, this means opting for focused minimally invasive surgery and potentially a lower risk of persistent and recurrent disease, especially in rare multigland disease. The asymptomatic nature and the option for pharmacological intervention in the control of the PHPT complications also seem to discourage surgery. Further improvements in imaging methods and genetic testing to exclude multigland hereditary hyperparathyroidism might contribute to overcoming barriers to PTX.

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AEP103

F18-choline PET/CT for primary hyperparathyroidism localization

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Objective
Surgery is the only curative treatment for primary hyperparathyroidism. Minimally invasive parathyroidectomy is superior in terms of cure and complication rates and is less costly than inpatient bilateral cervical exploration. Preoperative localization of parathyroid adenoma by imaging is a requirement for outpatient minimally invasive surgery. One of the most frequently used imaging techniques for parathyroid adenoma localization is Tc99m-sestaMIBI SPECT/CT plus cervical echography. However, one-fourth to one-third of patients have non-localizing disease with usual techniques, needing to undergo bilateral cervical exploration. Some factors associated with negative MIBI-SPECT/CT results are presence of thyroid nodules, lower PTH and calcium levels, parathyroid gland of 12 mm or less and previous cervical surgeries. Recent studies suggest the superiority of F18-choline PET/CT for parathyroid adenoma localization, with a reported sensitivity of 80–90% in patients with negative or inconclusive MIBI SPECT/TC. It also showed a superior accuracy for the detection and correct localization of small adenomas. The aim of this study is to evaluate the efficacy of F18-choline PET/CT in patients with negative or inconclusive MIBI SPECT/TC/echography.
Methods
A retrospective observational study was designed in 15 patients with PHPT, studied between 2018 and 2020, with a negative or inconclusive result in echography + MIBI SPECT/TC and a F18-choline performed afterwards. We analysed the efficacy of this imaging technique and described our patient's characteristics associated with non-localized adenoma with usual techniques.
Results
15 patients (13 women) were included. Mean age was 63 years old. 4 of them had underwent previous cervical surgeries (2 had previous parathyroidectomy, the other 2 had underwent hemithyroidectomy for thyroid nodules). Mean PTH was 138 pg/dl and mean adjusted calcium was 10.45 mg/dl Mean urine calcium excretion in 24 h and the Ca/Cr index were, respectively, 270 mg/24 h and 0.37 mg/mg. 66% (10/15) had T-score < –2.5. 20% (3/15) had nephrolithiasis. All of them had normal kidney function. 54% of patients had concurrent thyroid nodules. 18-choline PET/CT localized hyperfunctioning parathyroid adenomas in 80% of patients with non-localized adenoma with usual image techniques. Mean adenoma size in PET/TC was 7 mm.
Conclusions
F18-choline PET/CT is a valuable tool in localizing parathiroid adenomas not localized with usual techniques (Tc99m-sestaMIBI and echography), specially for those cases with lower calcium and PTH leves and smaller gland size. This will lead to a greater number of patients who are candidates for minimally invasive parathyroidectomy, resulting in more cured patients and less number of complication rates.

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AEP104

Evaluation of bone quality by dxa-based bone strain index in primary hyperparathyroidism

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Backgroud
Primary hyperparathyroidism (PHPT) is associated with impaired bone quality and increased fracture risk. Reliable tools for the evaluation of bone quality parameters are not yet clinically available. Bone Strain Index (BSI) is a new metric for bone strength based on Finite Element Analysis from lumbar spine and femoral neck dual X-ray absorptiometry images.

Aim
To assess the lumbar spine (LS), femoral neck (FN), and total hip (TH) BSI in PHPT compared to controls.
Design
Cross-sectional study. Outpatient clinic
Patients
44 PHPT and 39 age- and sex-matched control subjects.
Main outcome measures
LS-BSI, FN-BSI, TH-BSI.
Results
TH bone mineral density (BMD) and 1/3 distal radius BMD were lower in the PHPT group than in controls (TH 0.802 ± 0.13 vs 0.872 ± 0.09, $P < 0.05$; radius 0.565 ± 0.07 vs 0.620 ± 0.06, $P < 0.001$). There were no differences between groups in trabecular bone score (TBS) and T-score adjusted for TBS. BSI was significantly higher at LS (2.20 ± 0.58 vs 1.94 ± 0.48, $P = 0.003$), FN (1.66 ± 0.39 vs 1.40 ± 0.36, $P = 0.003$) and TH (1.46 ± 0.3 vs 1.24 ± 0.25, $P = 0.001$) in PHPT. LS-BSI showed moderate accuracy for detecting vertebral fractures [(area under the ROC curve 0.68 (CI:0.52–0.848)]. The best cut-off was set at 2.12 (sensibility 72%, specificity 64%, accuracy 67.4%).
Conclusion
BSI, a DXA-derived bone quality index, is impaired in PHPT and may help to identify PHPT subjects at high risk of fractures.

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AEP105

Ectopic parathyroid hormone as a rare aetiology of hypercalcemia with rhabdomyosarcoma: A new treatment strategy with Zoledronic Acid and Denosumab

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Introduction
Paraneoplastic hypercalcemia is extremely rare in the pediatric population, requiring urgent treatment. Pediatric malignancy-related hypercalcemia (PMRH) has been associated with rhabdomyosarcoma (RMS). Hypercalcemia with elevated parathyroid hormone (PTH), ectopic PTH secretion, is rarer (< 1% of cases). Reports of the use of Zoledronic Acid (ZA) as a second line bisphosphonate are limited. The monoclonal antibody, Denosumab, which inhibits RANKL-mediated osteoclast activity may be effective when bisphosphonates are not. The aim of presenting this case of PMRH secondary to ectopic PTH secretion was to highlight the benefits of ZA as a first choice bisphosphonate and Denosumab as an alternative therapy.
Case
The patient was diagnosed at 12.5 years with alveolar RMS. He had three subsequent relapses. Multiple bone metastases first appeared at 15.5 years but he remained normocalcemic until 17.5 years when serum calcium (Ca) was 14.9 mg/dl, ionized-Ca 2.36 mmol/l, phosphate 3.27 mg/dl, alkaline phosphatase 154 U/l, PTH 249 pg/ml, and 25-OHD 15 ng/ml; urinary Ca/Cr ratio 0.77. The patient was dehydrated and debilitated. Nephrocalcinosis and primary hyperparathyroidism were excluded by ultrasonography. Aggressive hydration and furosemide didn't reduce hypercalcemia. ZA was given immediately (see Table 1). Although a good response was obtained following the first ZA cycle, there was a decrease in response to successive cycles. A single dose of Denosumab was given after the third ZA infusion, resulting in normocalcemia 72 hours later. There were no further hypercalcemic episodes while PTH remained elevated (755 pg/ml). Hypophosphatemia occurred, requiring treatment.

Table 1. Response to treatment modalities

Time after presentation	Treatment	Ca (mg/dl)	Phosphate (mg/dl)	PTH (pg/ml)	Ca (mg/dl) 48-hours after treatment
Presentation	ZA cycle 1	14.6	2.64	249	11
4 weeks	ZA cycle 2	18.2	2.41	1231	11.9
5 weeks		13.7	1.65	831	
6 weeks	ZA cycle 3	19.1	3.79		15.8
6 weeks and 3 days	Denosumab	15	2.98		12.1

Discussion and conclusion
RMS is a non-parathyroid tumor but may cause hypercalcemia through ectopic PTH secretion. PTH mRNA has been identified in RMS cells, implying activation of the gene and direct secretion of PTH. There is *in vitro* evidence that ZA directly sensitizes RMS cells to γδ T-cell cytotoxicity. Thus, for treatment of RMS with hypercalcemia there may be a two-fold benefit in using ZA. PMRH was likely due to ectopic PTH production. We believe ZA should be the bisphosphonate of choice in hypercalcemia with RMS while Denosumab is a new option in ZA-refractory cases; both are safe and effective.

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AEP106

Mineral and bone disorders in patients after combined kidney-pancreas or kidney transplantation

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Background
The kidney or kidney-pancreas transplantation corrects many of the metabolic or biochemical abnormalities associated with chronic kidney disease (CKD); however, mineral bone disease (MBD) and cardiovascular pathology remain frequent in transplant recipients. This happens especially in patients who have long history of secondary hyperparathyroidism (SHPT), as well immunosuppressive therapy plays an important role in the progression of MBD.
Aim
To evaluate the main biochemical parameters and manifestations of MBD in patients after combined kidney-pancreas or kidney transplantation.
Methods
We divided all patients in two groups: #1 ($n = 36$) – after combined kidney-pancreas transplantation (cKPT), #2 ($n = 22$) – after isolated kidney transplantation (iKT). The duration of follow-up varies from 1 month to 2 years. Data analysis was performed with the Statistica 13 (StatSoft, USA). Quantitative data were assessed for normal distribution using the Shapiro-Wilk's W-test. Bonferroni correction was used for multiple comparisons (p0). A prognostically significant model was considered at $P < 0.05$.
Results
We did not find any significant differences in the parameters of phosphorus-calcium metabolism between two groups: albumin-adjusted calcium (AAC) 2.3 mmol/l [2.2; 2.5] vs 2.3 mmol/l [2.3; 2.4]; PTH 80 pg/ml [80.2; 149] vs 95.8 pg/ml [83.9; 241.5], phosphorus 1.1 mmol/l [0.9; 1.2] vs 1.2 [0.9; 1.4], $P > 0.05$ for all. The prevalence decreased BMD on DEXA was 77.8% in group #1 and 50% in group #2 (Tbs 1.4 [1.3; 1.4] vs 1.5 [1.4; 1.6], $P > 0.05$). Vascular calcification was detected in 42% after cKPT and in 27% after iKT. We assessed the levels of FGF23 and Fetuin A: 0.7 pmol/l [0.4;2.1] vs 4.8 pmol/l [0.7;4.0] and 32 5240.0 ng/ml [27 2590.0; 38 2030.0] vs 29 4507.3 ng/ml [24 0010.0; 35 0830.0] respectively, $P > 0.05$ for all. However, osteoprotegerin was significantly higher in patients after iKT (90.6 pg/ml [59.1; 136.1] vs 61.5 pg/ml [48.8; 98.7], $P = 0.04$). We didn't find any association between the presence of calcification in our patients according to the instrumental examination and the levels of FGF23, Fetuin-A and osteoprotegerin.
Conclusion
Our research detected the high prevalence of bone disorder and vascular calcification in patients after cKPT and iKT. These disturbances are associated with increased morbidity and mortality, therefore, regular follow-up is required to establish the optimal therapeutic strategies. Further research is much needed.
Keywords
Mineral and bone disorders, hyperparathyroidism, kidney transplantation, combined kidney and pancreas transplantation, osteoporosis, extraskeletal calcification.

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AEP107

New variant of the casr gene (c.2459c > t) associated with primary hypoparathyrodism – a case report

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Background
Autosomal dominant hypocalcaemia, caused by either inherited or de novo mutations in calcium-sensing receptor gene (CASR), is biochemically characterized by the presence of hypocalcaemia, hypercalciuria and inappropriately low levels of PTH. Receptor-activating mutations induce an increase sensitivity to calcium by parathyroid and renal cells, leading to suppression of PTH synthesis and consequently hypocalcaemia. Clinical manifestations are variable: from asymptomatic individuals to severe disease forms with neonatal seizures. Some of the associated comorbidities include intellectual disability, neuropsychiatric symptoms, basal ganglia calcification, and nephrolithiasis.
Case report
Female child, referred to medical consultation at 11 years old due to poor growth (< p3). History of a 36 weeks delivery due to intrauterine growth restriction, and birth weight of 2050g (< p5). Past medical history of congenital kidney hydronephrosis submitted to surgery at 2 years old; double J-stent placement and lithotripsy due to renal pelvic stones at 13 years old. Followed by paediatric nephrology since age 10 due to bilateral renal lithiasis and recurrent UTIs. Deficient neurodevelopment due to intellectual disability. Bilateral pallidal, anterior frontal subcortical and cerebellar calcifications were also found, even though without specific associated neurological complaints. No family disease was found. Initial evaluation showed Tanner stage I, bone age of 10 years and absence of dysmorphisms. Analytical study revealed: Ca^{2+} 1.8 mmol/l (2.19–2.66), phosphate 2.02 mmol/l (0.95–1.75), hypomagnesemia and an inappropriately low PTH level of 13.1 pg/ml (16–87 pg/ml). A diagnosis of primary hypoparathyroidism was set. Supplementation with calcium carbonate/lactogluconate (875 mg + 1132 mg/day) and calcitriol 1µg/day was started. To perform an etiological study, a karyotype and a search for mutations in critical regions of 22q11 chromosome were made, but no changes were identified. At the age of 18, the patient started the follow up in a tertiary adulthood hospital centre. An additional molecular study revealed the presence of a possible pathogenic variant c.2459C > T(Ser820Phe) in the *CASR* gene, in heterozygosity. Currently, the patient remains under the same therapeutic regimen, without worsening of the hypocalcaemia.
Discussion and conclusion
Poor height progression was the basis for this patient's study, allowing the diagnosis of hypocalcaemia and related complications. The identification of a c.2459C > T(Ser820Phe) CASR gene variant found in heterozygosity has been previously described in patients with hypocalcaemia and hypoparathyroidism, being classified as a probable pathogenic variant. Its more recent detection explained the clinical features showed, as well as provided an adequate genetic counselling for the patient and family.

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AEP108

PET/CT with 11C-methionine in the diagnosis of primary hyperparathyroidism

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Background
Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder mainly caused by a single parathyroid adenoma. The localization of the parathyroid adenoma is useful for increasing the recovery rate of PHPT, and reducing the complication rate. Conventional localization techniques include neck ultrasound, Tc99m-MIBI-SPECT and CT. However, each one of those has its limitations; particularly in cases of ectopic, or multiple parathyroid adenomas. 11C-methionine PET/CT may be a useful tool for patients who test negative/inconclusive with other techniques.
Aims
To compare sensitivity, specificity of 11C-methionine PET/CT in comparison to conventional imaging techniques.
Materials and methods
We analyzed the data of 59 patients diagnosed with PHPT from 2016 to 2020. All of them underwent ultrasound and a second confirmation test (mainly Tc99m-MIBI-SPECT). In case the result was negative or inconclusive, a third test was administered (mainly CT). In 2019–2020 11C-methionine PET/CT was used as last-line localization technique in 13 patients. All patients underwent parathyroidectomy and pathological findings were used in order to evaluate the characteristics of imaging modalities.
Results
We conducted a single-centre study at the Almazov National Medical Research Centre in order to evaluate the utility of 11C-methionine PET/CT. Sensitivity of PET/CT was 100 %, CT and Tc99m-MIBI-SPECT showed a bit lower sensitivity, at 91% and 84% respectively. The least sensitivity, 71% was ultrasound. The estimated specificities of PET/CT, CT, Tc99m-MIBI-SPECT and ultrasound were 86%, 73%, 79%, 70% respectively. Relatively low specificities of CT and Tc99m-MIBI-SPECT may explain why 37/59 patients required three techniques (ultrasound, CT, Tc99m-MIBI-SPECT). Though 11C-methionine PET/CT was performed in 9/59 as a third-line, and in 4/59 as a forth-line technique, this method showed the highest sensitivity and specificity.
Conclusion
11C-methionine PET/CT demonstrated the highest sensitivity and specificity and may be a valid alternative to conventional imaging in order to elude negative/inconclusive results. In patients with ectopic or multiple lesions, it can help avoiding bilateral cervical exploration, and persistent hyperparathyroidism.

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AEP109

Frequency of metabolic syndrome in Paget's disease of bone

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Objective
Scanty data about glucose metabolism, hypertension and metabolic syndrome (MS) have been reported in Paget's disease of bone (PDB) to be related with increased cardiovascular mortality. We aimed to determine prevalence of metabolic syndrome in PDB and to determine the relationship between metabolic syndrome and bone-specific alkaline phosphatase levels.
Patients and methods
Twenty three patients with PDB and 23 age, sex and body mass index (BMI) matched controls were recruited to the study from the outpatient clinics of Endocrinology. All participants were evaluated using the International Diabetes Federation (IDF)-2006 metabolic syndrome criteria. Parameters of bone and mineral metabolism were assessed.
Results
Seventeen of 23 (%73) patients had MS while 8 of 29 (% 27) controls had metabolic syndrome. Difference between groups was statistically significant. Compared with controls, patients group had higher prevalance of anti-hypertensive medication usage and impaired glucose tolerance. While ALP level was statistically higher in patients group, calcium, phosphate, albumin and HDL levels were lower in patients ($P < 0.05$). There was a significant correlation between ALP level and hypertension medication ($P = 0.0045$, $r = 0.27$).
Conclusion
To the best of our knowlegde, this is the first study evaluating the prevalance of MS in patients with PDB. The result of this study indicate that individuals with PDB may also exhibit metabolic disturbances associated with cardiovascular risk. Therefore, these patients should also be regularly monitored for metabolic syndrome.

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AEP110

Is necessary long-term follow-up of all patients with primary sporadic hyperparathyroidism undergoing parathyroidectomy?

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Introduction
Post parathyroidectomy cure in primary hyperparathyroidism (PHPT) is defined as normocalcemia six months after surgery. The frequency of persistent or recurrent post-surgical disease according to lengthy follow-up studies varies between 1% and 14%.

Objective
To determine if there is a subset of patients with cure criteria 6–12 months after parathyroidectomy that would not require long-term follow-up.
Methods
The medical records of 156 patients with PHPT who underwent initial parathyroidectomy in our hospital between 2005 and 2017, were retrospectively reviewed. Patients with a history of multiple endocrine neoplasia syndrome, and secondary or tertiary hyperparathyroidism were excluded. Cure was defined as a normal level of serum calcium and parathyroid hormone (PTH) 6–12 months after surgery. Disease-free survival was calculated by the Kaplan-Meier method.
Results
The mean age was 56.4 years (± 12.7), with 80.3% being women. Mean follow-up time was 71.2 months (1–180). 141 patients met cure criteria (91.6% cure rate). There was no significant difference in age between cured and not cured (56.7 vs 56.4 years, $P = 0.9$). Three patients had recurrent disease. The mean time to recurrence was 80 months (range 60–120). Disease-free survival was 90.2% and 88% at 2 and 10 years respectively. 75% of the cured patients had preoperative imaging that was concordant to intraoperative findings and a decrease in intraoperative PTH (IOPTH) > 50%, compared to 50% of the not cured patients ($P = 0.17$). Disease free survival was 91% at 5 years in patients met these two criteria. The absence of abnormal parathyroid tissue in the histological study was more frequent in not cured patients (25% vs 2.9%) ($P < 0.01$).
Conclusions
Patients operated on for sporadic PHPT and cured at 6–12 months who present preoperative imaging concordant with surgical findings, a decrease in IOPHT > 50% and abnormal parathyroid tissue in the histological study, probably would not require routine long-term follow-up.

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AEP111

The challenge of genetic workup in hypercalcaemia suspected hyperparathyroidism

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The commonest cause of hypercalcaemia is primary hyperparathyroidism (PHPTH). The diagnostic work up includes paired blood samples for serum corrected calcium, parathyroid hormone (PTH) and vitamin D levels. But in young patients, rare genetic conditions could be contributing towards hypercalcaemia and hence could produce a diagnostic challenge. We report hypercalcaemia work up in two young females where genetic tests were required.
Case 1
A 19yr girl presented with fatigue and osmotic symptoms. She is noted to have mild hypercalcaemia (2.61–2.77 mmol/l) since the age of 13 yrs. Her PTH was persistently high (7.8–14.4 pmol/l) with normal vitamin D (71–83 nmol/l) supporting a diagnosis of primary hyperparathyroidism. Her urinary calcium excretion suggested possibility of familial hypocalciuric hypercalcaemia (FHH). Her parathyroid imaging showed bilateral parathyroid adenomas and she was also noted to have raised prolactin along with a pituitary incidentaloma. Her case was discussed in MDT. Since she was a teenager with PHPTH with multiple gland involvement, it was decided to exclude multiple endocrine neoplasia (MEN). Due to her low urinary calcium excretion, it was also advised to exclude FHH. Genetic tests were sent for both conditions and were reported as normal. Her parathyroid imaging (4D CT scan, SESTAMIBI and Ultrasound) was reviewed in MDT again it was decided to proceed with right superior parathyroidectomy. This resolved hypercalcemia (corrected calcium = 2.39 mmol/l, PTH = 2.8 pmol/l). Histology confirmed parathyroid adenoma.
Case 2
A 42 yr lady presented with incidental hypercalcaemia (2.7–3.05 mmol/l) with normal PTH on routine blood tests. She had mild symptoms of constipation, fatigue, lower back pain. There was no osteoporosis or nephrocalcinosis on DEXA and US scans, respectively. Parathyroid imaging (4D CT scan, SESTAMIBI and Ultrasound) failed to identify any adenoma. Her urinary calcium excretion was low which suggested possibility of familial hypocalciuric hypercalcaemia (FHH). The genetic tests for FHH were organised which confirmed heterozygous mutation for CASR supporting the diagnosis of FHH type 1. The patient was reassured with no further treatment of her hypercalcaemia however, genetic work up was offered for her family to avoid unnecessary work up in incidental hypercalcaemia. Both these cases highlight important message of genetic workup in cases of hypercalcaemia with suspected hyperparathyroidism. In teenage patients with multi-gland disease and those with imaging negative primary hyperparathyroidism one should consider doing genetic tests for MEN and FHH. This avoids unnecessary interventions and also prevents missing serious conditions associated with MEN.

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AEP112

4D-CT – is it useful in Hyperparathyroidism?

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Introduction
Primary Hyperparathyroidism (PHPT) results from one or more parathyroid glands hyperfunction. It is recommended that the preoperative location of the parathyroid lesion be performed with cervical ultrasonography and sestamibi-scintigraphy. Recently 4-Dimensional Computed Tomography (4D-CT) has revealed anatomic, morphologic and functional precision for detecting those lesions, either for typical or ectopic location. This study evaluates the diagnostic value of 4D-CT in the preoperative location and whether the severity of PHPT interferes with the success of this location.
Methods
Retrospective study with 34 patients attending with diagnosis of PHPT that performed 4D-CT for parathyroid lesion location. Variables such as age, gender, calcium (Ca), phosphorus (Ph), parathormone (PTH), cervical sonography, sestamibi-scintigraphy and 4D-CT were analysed. In patients who underwent surgical treatment we also analysed surgical criteria, histology and Ca, Ph and PTH postoperative values.
Results
34 patients were evaluated, with mean age of 67 years, 55.9% female. 73.5% had PHPT diagnosis and 26.5% had normocalcemic HPT. At diagnosis, patients had mean values of Ca, Ph and PTH of 10.7 mg/dl, 2.8 mg/dl and 161.2 pg/dl respectively. All patients performed cervical sonography, sestamibi-scintigraphy and 4D-CT. Positive location occurred in 70.6% (29.4% sonography; 38.2% scintigraphy and 55.9% 4D-CT). From those with identified lesion, 83.3% had one lesion and 16.7% multi-glandular lesions. There was a statistically significant positive correlation between the increase measure of Ca, Ph and PTH and the success of identifying the lesion, either in the 4D-CT or in any of the imaging tests ($P < 0.01$ in all). 9 patients underwent surgical treatment and all of them had image exams identifying a lesion (mean dimension of 16.3 mm). From those, 30% were evident on sonography, 60% on scintigraphy and 100% on 4D-CT. All patients were cured after surgery. After histological analysis of the respective lesions, there was a sensitivity of 100% for 4D-CT, 50% for scintigraphy and 40% for ultrasound.
Conclusion
4D-CT revealed to be a useful and reliable exam in the preoperative location of patients with PHPT. In patients that underwent surgical treatment, this image exam has shown a sensibility of 100%, result overlapping the literature (> 90%). Calcium, phosphorus and parathormone values seems to influence the success of lesion location.

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AEP113

The effect of food supplement with calcium and vitamin D3 administration on calcium homeostasis and falls incidence in patients with high fracture risk undergoing medical rehabilitation

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Background
Vitamin D and calcium deficiencies is of particular importance in older patients undergoing medical rehabilitation and having a high risk of fractures. Preventing falls and fractures, including during the course of rehabilitation, is an important challenge that can be addressed in these patients, in particular through improved nutrition and vitamin D and calcium supplementation.
Objectives
To evaluate the effect of long-term calcium and vitamin D3 intake on calcium homeostasis and fall's rate in patients with high fracture risk starting rehabilitation course.

Methods
The study enrolled 119 men and women aged 50–80 y.o. with high absolute fracture probability by FRAX who started medical rehabilitation. 41 patients have been receiving antiresorptive therapy already comprised group 1, other patients were randomized into groups 2 (n = 39) and 3 (control, n = 39). In groups 1 and 2, a food supplement containing calcium citrate 1000 mg and vitamin D3 600 IU was prescribed for 12 months. All patients undergo laboratory examination, food calcium intake and fall assessment at baseline, in 6 and 12 months
Results
Daily calcium intake in the study sample (n = 119) was 782.9 ± 243.4 mg. Vitamin D deficiency was detected in 38.4% of the examined. An increase in 25(OH)D level was noted in groups 1 and 2 after 6 and 12 months (P < 0.01). Patients in group 1 showed an increase in serum osteocalcin and calcium levels after 6 and 12 months (P < 0.05). In group 3, there was an increase of immunoreactive parathyroid hormone levels after 6 (P < 0.05) and 12 months (P < 0.01), C-terminal telopeptide of type I collagen level and alkaline phosphatase activity after 12 months (P < 0.05). In group 1, there was also a decrease in proportion of patients who fell after 6 months (χ^2 = 4.97, P = 0.026) and a decrease in the total number of falls after 12 months (χ^2 = 4.89, P = 0.027). Group 2 showed a decrease in the number of patients who fell after 6 and 12 months (χ^2 = 48.58, P = 0.0034 at both stages of the study) and the number of falls in general after 6 months (χ^2 = 6.02, P = 0.0142).
Conclusion
The obtained data allow us to recommend prescription of dietary supplements containing calcium and vitamin D3 as a part of complex rehabilitation of patients with high fracture risk.

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AEP114

Vitamin D deficiency is a key element in COVID-19 hypocalcemia

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Hypocalcemia has been recently identified as a major biochemical distinctive feature of COVID-19, predicting poor clinical outcomes. Besides the calcium-dependent viral mechanisms of action and the enhanced cellular permeability to calcium ions, we previously hypothesized that hypovitaminosis-D could be a predisposing factor to hypocalcemia. Actually, high prevalence of vitamin D (VD) deficiency in COVID-19 patients (pts) was reported by several studies, but, to date, only few tried to investigate the role of hypovitaminosis-D on calcium and parathyroid hormone (PTH) levels. We aimed at evaluating the relationship between calcium, PTH and VD in COVID-19 pts. Patients admitted to San Raffaele University Hospital for COVID-19 from February 2020 were enrolled in this study. We excluded pts with comorbidities and therapies influencing calcium and VD metabolism. Ionized and total calcium, 25OH-Vitamin D and PTH levels were evaluated at admission in hospital. VD insufficiency and deficiency were defined as VD level below 30 ng/ml and 20 ng/ml, respectively. We defined hypocalcemia for ionized calcium (Ca^{2+}) level below 1.18 mmol/l and total calcium (tCa) level below 2.1 mmol/l. Hyperparathyroidism was defined as PTH above 65 pg/ml. A total of 88pts were included in the study. Median (IQR) tCa and Ca^{2+} levels were 2.15 (2.05–2.22) mmol/l and 1.14 (1.11–1.18) mmol/l, respectively. Low total and ionized calcium levels were found in 36.5% and in 72.9% of pts, respectively. Median (IQR) VD levels were 16.3 (11.2–23.9) ng/ml. VD insufficiency and deficiency were observed in 88.6% and in 68.2% of pts, respectively. Median (IQR) PTH levels were 46.2 (37.4–64.5) pg/ml and hyperparathyroidism was detected only in 23.9% of pts. No significant differences were found in serum PTH levels between patients with VD insufficiency vs. sufficiency (46.5 (38.2–65.3) vs. 41 (27.5–63.4) pg/ml) and between hypocalcemic vs. normocalcemic pts (Ca^{2+} 49.5 [37.7–65.7] pg/ml vs. 48.5 [37.2–56.6] pg/ml; P = 0.15). Linear regression analyses showed a positive correlation between VD and tCa (P = 0.017; r = 0.26). A borderline significant negative correlation between VD and PTH (P = 0.049; r =–0.21) was also detected. Finally, PTH negatively correlated with Ca^{2+} levels (P < 0.001; r =–0.35). In conclusion, we confirmed a high prevalence of hypocalcemia in COVID-19 pts and showed for the first time that it occurred largely in the context of marked hypovitaminosis-D not adequately compensated by secondary hyperparathyroidism, the reasons of which need to be explored. Since hypocalcemia may be marker and cause of severe clinical consequences in COVID-19, we can hypothesize that VD supplementation may play a relevant role in COVID-19, also possibly preventing hypocalcemia.

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AEP115

Transient hypocalcaemia and definitive hypoparathyroidism after total thyroidectomy in Graves' disease

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Introduction
Hypocalcaemia is a complication of total thyroidectomy (TT) and may be more frequent in patients with Graves' disease. The reason for this increased risk is unclear and its occurrence has been associated with: ophthalmopathy severity, preoperative calcaemia and reimplantation of parathyroid glands.
Objectives
To evaluate the risk factors for transient hypocalcaemia (TH) and definitive hypoparathyroidism (DH) in patients undergoing total thyroidectomy for Graves' disease.
Methods
Retrospective study of patients with Graves' disease, who underwent TT between January/2016 and January/2020. Patients with histological diagnosis of malignant thyroid neoplasm or concomitant hyperparathyroidism were excluded. Clinical and laboratory data were collected from clinical files. In the statistical analysis, SPSS software (version 25.0) was used. The variables are expressed as mean and standard deviation, calculating the relative risk (RR) and considering a 95% confidence interval.
Results
49 patients (out of 71 operated) were selected according to the inclusion/exclusion criteria, 73.5% were men. Prevalence of TH was 49.0% and of DH 8.2%. There were no statistically significant differences between patients without (WPH) or with (PH) postoperative hypocalcaemia according to age, interval between diagnosis and surgery, gland weight, serum TSH, FT4, FT3, TRAB levels at diagnosis, or preoperative calcaemia. In the PH group, postoperative PTH levels were significantly lower (58.6 ± 5.9 vs. 23.9 ± 5.5 pg/ml; P < 0.01) and the length of hospital stay was significantly higher (4.3 ± 0.5 vs. 2.8 ± 0.1 days; P = 0.02). There was a statistically significant correlation between preoperative TRAB and postoperative PTH (r =–0.14; P < 0.05). For the 5 patients who underwent reimplantation of at least 1 parathyroid gland, all had hypocalcaemia: definitive hypoparathyroidism – 3; transient hypocalcaemia – 2. Thyroid orbitopathy was present in 30 patients (61%); these patients did not have a higher RR for occurrence of hypocalcaemia (RR = 0.77 [0.5–1.23]), transient hypocalcaemia (RR = 0.8 [0.47–1.39]) or definitive hypoparathyroidism (RR = 0.63 [0.1–4.12])
Conclusion
In this study, we found a high prevalence of postoperative hypocalcaemia and a correlation between postoperative PTH levels and TRAB levels at diagnosis. The reimplantation of at least 1 parathyroid gland predicts high risk for occurrence of hypocalcaemia, since in this sample all patients subjected to this intervention presented transient or definitive hypoparathyroidism. On the other hand, it was not found an association between orbitopathy and calcium-related postoperative complications.

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AEP116

European Registries for Rare Endocrine Conditions (EuRRECa): The use of an e-reporting tool for registering calcium and phosphate conditions

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Introduction
The European Registries for Rare Endocrine Conditions (EuRRECa) project was launched in February 2018 and aims to support the needs of the endocrine and bone community by facilitating the collaboration between patients, health care professionals and researchers across Europe and beyond. It is closely linked to the European Reference Networks on Rare Endocrine Conditions (Endo-ERN) and Rare Bone Diseases (ERN BOND) with its registry EuRR-Bone. EuRRECa is open to all professionals involved in endocrine care, providing two different tools: a core registry that includes new and existing cases and an electronic reporting tool (e-Reporting of Rare Conditions) for newly encountered cases.
Objective
To describe the user community characteristics and the generated data on the Calcium and Phosphate condition group via the electronic reporting tool, e-REC (e-Reporting of Rare Conditions) in the period July 2018 to December 2020.
Methods
Clinicians willing to participate are provided with access to e-Rec and receive invitations to complete a monthly return to report new cases of conditions that are included in Endo-ERN and ERN BOND. e-REC does not collect personally identifiable information and when a case is reported a unique ID is generated and provided to the user to be stored locally at reporting centres.
Results
Between July 2018 and December 2020 a total of 38 centres from 18 different countries reported cases in this condition group. Of these, 26 are Endo-ERN and 11 are ERN BOND members and 16 participate in both. A total of 163 adults and 144 children were newly diagnosed with a Calcium and Phosphate condition. Amongst adults, the most frequently reported conditions were hypoparathyroidism (n = 66), hyperparathyroidism including parathyroid cancer (n = 47) and X-linked hypophosphataemia (n = 13). In children pseudohypoparathyroidism (n = 44), hypoparathyroidism (n = 23) and X-linked hypophosphataemia (n = 27) were the most reported.
Conclusion
The number of centres joining the project and reporting cases continues to grow. e-REC is a promising tool enabling clinical networks to objectively map conditions and related activity. This highlights that genetic disorders are the most frequent cause of calcium and phosphate disturbances in children and provides a better understanding of the occurrence of the rare endocrine and bone conditions. Wide dissemination of the use of the platform is essential.

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AEP117

Skeletal and bone defects in Turner syndrome

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Introduction
Turner syndrome is one of the most common chromosomal disorders, with a reported prevalence of 1/2500 live females. It is characterized by short stature, ovarian failure, malformative, autoimmune, skeletal and bone abnormalities. The objective of our work is to study the prevalence of skeletal and bone malformations in our Turnerian patients.
Material and method
This is a retrospective descriptive study realized in 17 patients followed for a Turner syndrome at the Endocrinology-Diabetology and Nutrition Department of the Mohammed VI University Hospital Center of Oujda. The data collected were analyzed using SPSS 25 software.
Résultats
The mean age of diagnosis was 16.4 ± 12.4 years. Shorte stature was the most frequent reason for consultation in 47% of cases, followed by amenorrhea in 35.3%. Statural retardation was present in all patients, with short legs in 47.1%. Kyphosis was reported in 5.8% of cases with erosions on the anterior surfaces of the vertebrae and layered cervical vertebral compression on MRI, scoliosis in 11.7% and bradymetacarpia in 5.8% of cases. Vitamin D deficiency was objectively diagnosed in all patients with a mean of 18.9 ± 7.2 ng/ml. Osteoporosis (spine and femurs) was observed in 17.6% of cases in patients diagnosed in adulthood with primary amenorrhea not substituted on the hormonal level.
Discussion-conclusion
Skeletal and bone deformities are common during turner syndrome. Osteoporosis is still a real problem with its high fracture risk, hence the importance of early hormonal replacement, adequate intake of calcium products and correction of vitamin D deficiency.

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AEP118

A retrospective review of the management of skeletal effects following thyroid stimulating hormone suppression therapy (tshst) in patients treated for differentiated thyroid carcinoma (dtc)

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Background
Thyrotropin Stimulating Hormone Suppression Therapy (TSHST) in Differentiated Thyroid cancer (DTC) patients can result in reduced bone mineral density (BMD) which is a potential serious problem [1]. Studies on the effects of TSHST on BMD have demonstrated conflicting results [2–5]. There is insufficient guidance regarding the degree and duration of TSHST in the context of skeletal effects despite multiple existing guidelines.
Aim
To conduct a retrospective review of the current management of the skeletal effects of DTC patients against current guidelines.
Methods
Data was collected on patients with DTC on TSHST from the Liverpool University Hospital database in the last 15 years.
Results
73% (45/62) of patients with DTC aged between 21 to 85 years were included in the study. 42% (19/45) including 5 men, 4 pre-menopausal women and 10 postmenopausal women had at least one DEXA scan whereas 58% (26/45) had no DEXA. Only 31.6% (6/19) had two or more DEXA scans. Average time from starting TSHST to first DEXA was 4.5 years (SD 4.5). 60% (6/10) of patients within 12 months of surgery and radioiodine treatment had a recorded TSH level with only 50% (3/6) having a TSH level < 0.1 mu/l as recommended by the British Thyroid Association(BTA)[6]. All pre-menopausal women had a single normal DEXA with 75% (3/4) on vitamin D. All men had osteopenia with 66.7% (2/3) showing optimal vitamin D levels on replacement and 1/3 with inadequate levels. 40% of post-menopausal women with osteopenia were on vitamin D and 10% with osteoporosis on bisphosphonates. 50% (5/10) of post-menopausal women had TSH levels of < 0.05 for > 5 years (average 12.8 years, SD 1.1) but no documented FRAX as recommended by BTA[6]. A retrospective risk stratification using the Sheffield Fracture Risk Assessment (FRAX) tool [7] showed the average risk of a major and hip fracture in post-menopausal women was higher at 10.6% and 2.4% respectively compared to 5.1% and 1.5% in men. 22.2% (2/9) of post-menopausal women met the treatment threshold.
Conclusion
This study highlights important factors in the surveillance and management of skeletal effects. Achieving optimal TSH suppression and monitoring long-term skeletal effects of TSHST would be more effectively achieved by establishing local protocols specifying frequency of blood tests (thyroid function test, vitamin D levels), individual target TSH ranges and introducing the FRAX tool. This would identify at risk patients, determine timing of DEXA scans and guide treatment in the appropriate age group.

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AEP119

Interest of the 'single photon emission tomography computed tomography' in an atypical location of a parathyroid adenoma

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Objective
Illustrate the interest of imaging: Single photo emission tomography or Computed tomography in the topographic diagnosis of parathyroid adenomas.
Observation
A 67-year-old man, with renal lithiasis presenting a clinical-biological picture of primary hyperparathyroidism with renal bone and colic pain. PTH was 463.2 pg/ml, calcemia 3.4 mmol/l. Cervical ultrasound objectified a lesion suspected of parathyroid adenoma. A first scan objectified a hyperfixative focus that projects against the lower pole of the thyroid.The patient had surgery. No post-operative problem were referred. We noted a persistence of elevated serum PTH and calcemia values. Pathology examination found a benign thyroid nodule. A SPECT/CT was then performed objecting a hyperfixative focal spot whose scanno-scintigraphic configuration corresponds to a very posterior nodular formation of 20 mm right lateral-esophageal and prevalent at D2. The diagnosis of atypical parathyroid localization was retained. The patient had a surgical revision with a right lower parathyroid adenoma of 30 * 20 mm near the pre-vertebral plan. Post-operative outcomes were simple with clinical improvement and normalization of biological numbers.
Conclusion
The SPECT/CT plays a decisive role in the management of patients with persistent or recurrent hyperparathyroidism. It is most often used to visualize atypical parathyroid adenomas and to guide the surgeon.

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AEP120

An unusual case of primary hyperparathyroidism due to hyperplasia resembling tertiary hyperparathyroidism

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Primary hyperparathyroidism is a common endocrine condition; 80% due to a parathyroid adenoma. We present an unusual case of a 69-year old white European female, who presented first in 2012 with mild hypercalcaemia (< 2.8 mmol/l), osteoporosis, hypertension and type 2 diabetes. Pharmacotherapy included Bendroflumethiazide, but no phosphate supplements. Investigations revealed primary hyperparathyroidism and dual-modality scanning showed no evidence of an adenoma, although hyperplasia was suggested on ultrasound. Molecular analysis showed no CASR mutation, making familial hypocalciuric hypercalcaemia unlikely. She was discharged to follow-up in primary care with advice to refer if the plasma adjusted calcium was above 2.9 mmol/l consistently, which was the practice prior to UK NICE 2019 guidance. There had been no other change to her health; she had normal vitamin D level without supplementation and no renal disease. She presented 8 years later with severe hypercalcaemia (peak plasma adjusted calcium 3.5 mmol/l), but with few symptoms. Plasma PTH was 30 pmol/l and the concern was of malignant transformation. Treatment included IV 0.9% sodium chloride, sc calcitonin, IV pamidronate and then PO cinacalcet; the thiazide was stopped. The hypercalcaemia was fairly resistant to cinacalcet, which she found difficult to tolerate. Dual modality imaging showed similar findings for the Sestamibi scan to the previous scan: no tracer retention to suggest an adenoma. The ultrasound scan showed evidence of thyroiditis on the right and possible right inferior parathyroid adenoma. She underwent four-gland exploration which was complicated by a severe nodular thyroiditis but demonstrated significant enlargement of the left superior (2 g) and right inferior (1 g) parathyroids (both excised) and a normal left inferior parathyroid. Histological features were more consistent with hyperplasia than adenoma and with features seen in tertiary hyperparathyroidism. The patient's biochemistry normalised postoperatively. This case illustrates an unusual progression of primary hyperparathyroidism hyperplasia progressing to more autonomous parathyroid hormone production. The histopathology would be seen usually in tertiary hyperparathyroidism associated with severe nephropathy, but this patient had normal renal function. This progress can also be seen in secondary hyperparathyroidism due to chronic hypovitaminosis D, but our patient was vitamin D replete. Thiazide-associated hypercalcaemia tends to be seen in older females and persists after drug withdrawal. We may speculate whether the lack of response to cinacalcet points to thiazide-associated renal PTH resistance, leading to increased PTH and promotion of hyperplasia; but the association of thiazides with hyperparathyroidism is inconsistent, some studies showing no effect on PTH levels.

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AEP121

The endocrine effects of lithium treatment. Report of a case

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Lithium is considered a mainstay treatment option for the management of bipolar affective disorder. However, lithium administration is characterized by endocrine effects. The aim was to present the case of a patient who was on treatment with lithium for many years for the management of bipolar affective disorder and presented with a large parathyroid adenoma causing clinical hyperparathyroidism with severe hypercalcemia who was successfully treated by surgical excision of the adenoma and hypothyroidism. A patient, aged 68 years, presented with severe hypercalcemia, calcium levels on admission 13 mg/dl and difficulty in walking due to osteoporosis. PTH levels on admission were 300 pg/ml. After rehydration and diuretic treatment for the management of hypercalcemia, cinacalcet was administered at a dose of 30 mg twice daily for the management of hypercalcemia. Diagnostic evaluation revealed the presence of a large parathyroid adenoma situated inferiorly to the left thyroid lobe. Surgical treatment was undertaken and the parathyroid adenoma was successfully excised. Histology revealed a large cystic parathyroid adenoma. During follow up calcium levels normalised and the patient improved clinically. During follow up a TSH level of 6.7 mIU/l was noted. Thyroxine was administered. Lithium administration for the management of bipolar affective disorder is used successfully for many years. However, it may cause many endocrine effects. It may cause hypothyroidism and hypercalcemia due to hyperparathyroidism. Hypothyroidism is easily managed by thyroxine administration. However, hyperparathyroidism is usually due to one or more parathyroid adenomas or parathyroid hyperplasia. The optimum management of parathyroid adenomas in the case of long-term lithium treatment is surgical and usually controls hyperparathyroidism. In other reports most cases of hyperparathyroidism in the context of lithium treatment were due to one or more parathyroid adenomas. In conclusion, the case of a patient presenting with endocrine disease, namely primary hyperparathyroidism and hypothyroidism due to long term lithium administration is described. The disease was successfully treated with surgical excision of the parathyroid adenoma and thyroxine administration.

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AEP122

Ectopic parathyroid adenomas: where to find them?

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Hypercalcaemia due to primary hyperparathyroidism (PHPTH) is fully curable by parathyroidectomy. Occasionally recurrent hypercalcemia presents as a results of either residual adenoma, recurrent disease or an ectopic parathyroid gland. The most challenging cases are those with ectopic glands which are not identified on usual surgical neck exploration. We present a similar case that went through multiple surgeries for recurrent hypercalcemia. A 79-year-old lady initially was diagnosed as primary hyperparathyroidism (in 2009) with symptomatic hypercalcaemia (2.84–3.0 mmol/l) and raised PTH (8.8–11 pmol/l). Multiple parathyroid imaging modalities (CT scan neck, SESTAMIBI and Ultrasound) failed to identify any adenoma. She underwent first surgical exploration in 2010 and three parathyroid glands were removed (both right glands and left superior gland). One gland was suspected to be adenoma. Histology confirmed hyperplastic parathyroid glands. Postoperative biochemistry didn't normalise and she continued to have persistent primary hyperparathyroidism (Corrected calcium = 2.79 mmol/l, PTH = 10.3 pmol/l). She had osteoporotic wrist fracture. Further imaging to identify parathyroid adenoma was done (CT scan neck and chest with contrast) in 2012. No adenoma was identified again and the plan was to proceed with another surgical neck exploration in 2012. The residual hyperplastic parathyroid left inferior parathyroid gland could not be located and PHPTH was not resolved postoperatively (Corrected calcium = 2.66 mmol/l, PTH = 8pmol/l, Vitamin D of 20 nmol/l). Due to low vitamin D levels, it was thought to be mild secondary hyperparathyroidism.

Low dose Cholecalciferol was advised to prevent further growth of the remaining hyperplastic gland and subsequent end organ damage. Vitamin D repletion failed to correct the Calcium (2.6–2.8 mmol/l) and PTH levels (9–10 pmol/l). In view of symptomatic hypercalcaemia with ongoing end organ damage it was decided to reimage her with newer modalities and explore for ectopic mediastinal parathyroid adenoma. 4D CT scan identified an ectopic parathyroid adenoma in the left trachea-oesophageal groove posterior and inferior to the lower pole of the left lobe of thyroid gland. A 3rd neck exploration in 2020 successfully excised the ectopic parathyroid tissue which was confirmed to be adenoma on histology. The biochemistry was normalised (Ca 2.24 mmol/l, PTH 2.8 pmol/l) and her symptoms settled. The ectopic parathyroid adenomas (3–4% of all parathyroid adenomas) occur as a result of embryonic migration during foetal development. The actual prevalence of mediastinal parathyroid adenomas is unrecognized but it ranges from 6–30%. Surgical neck exploration can be facilitated by use of modern imaging techniques like 4D CT scan (sensitivity = 96.7%, specificity = 95.7%) to identify ectopic parathyroid glands.

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AEP123

Prevalence, characteristics, and associated factors of Fahr's syndrome in permanent hypoparathyroidism

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Introduction
Fahr's syndrome (FS) is a rare neurodegenerative disorder. It's characterized by abnormal calcifications in basal ganglia and cerebral cortex inducing neuropsychiatric disorders and cognitive impairment. The aim of our study was to assess the prevalence of FS, its characteristics, and its associated factors in patients with permanent hypoparathyroidism.
Methods
We conducted a cross-sectional study including 38 patients with chronic hypoparathyroidism. A brain computed tomography scan was performed to all participants. Clinical and biological data were collected. The adherence to treatment was evaluated using Girerd adherence scale.
Results
There were 30 (82%) women and 8 (20%) men with a mean age of 53 ± 15.9 years. Neck surgery was the most frequent etiology of chronic hypoparathyroidism (66%). FS was diagnosed in 40% of cases (n = 15) with a sex-ratio of 2.75. Clinical manifestations included amnestic disorders, depressive mood, psychotic symptoms, tetany crisis and seizures in 80, 47, 27, 27, and 20% of cases, respectively. Brain CT-scan showed bilateral intracerebral calcifications located in the central gray nuclei (67%) or diffuse symmetric calcifications (33%). The prevalence of FS increased with the duration of hypoparathyroidism (P = 0.048) and decreased with the patient age at the diagnosis (P = 0.028). Amnestic disorders (Odds Ratio = 5.143, P = 0.043), poor adherence to treatment (Odds Ratio = 6, $P < 10^{-3}$), and hypomagnesemia (Odds Ratio = 98, $P < 10^{-3}$) were positively associated with FS. However, calcium level, PTH level, and coexisting vitamin D deficiency were not associated with FS.
Conclusion
Patients with chronic hypoparathyroidism are most likely to develop intracranial calcifications because of phosphocalcic metabolism disorders and blood-brain barrier alteration, leading to various neuropsychiatric manifestations. This study highlights the importance of adequate treatment and medication adherence to prevent Fahr's syndrome.

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AEP124

The natural history of hypoparathyroidism according to the database of endocrinology research centre

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Background
Hypoparathyroidism is a rare disorder characterized by hypocalcemia and hyperphosphatemia due to absent or inadequate parathyroid hormone secretion. Data on effective treatment strategies and predictors of long-term complications have only recently began to emerge. The epidemiological information regarding chronic hypoparathyroidism in Russia is strictly limited that prompted this research.
Aims
To estimate the clinical course, demographic features and treatment regimes in patients with chronic postsurgical and nonsurgical hypoparathyroidism.
Materials and methods
The database of patients with chronic postsurgical and nonsurgical hypoparathyroidism from Endocrinology Research Centre was used for retrospective analysis. The study included 357 patients from 61 regions of the Russian Federation. The descriptive statistics are presented by medians (Me) and the first and third quartiles (Q1; Q3) and by absolute and relative frequencies.
Results
Hypoparathyroidism was most frequent in women (85.4%) at the age of 43 [32; 52] years. The prevalence of chronic postsurgical hypoparathyroidism was 86%, most often it occurs after thyroid surgery, especially because of thyroid carcinoma and multinodular goiter. In a subanalysis of patients who underwent thyroid surgery hemi- and thyroidectomy were noted in 7% and 93% respectively. Nonsurgical hypoparathyroidism was registered in 14% of patients (n = 50: idiopathic (28), autoimmune (13) and other genetic form of disease (9) with. Less than a half of the study group had target indicators of serum calcium and phosphate levels (32% and 47%, respectively) despite ongoing treatment. Among the disease complications, kidney disorders were detected in 38%, visual disturbance in 14%, brain calcification in 6%, arrhythmias in 7% and neuropsychiatric symptoms in 8%. Conventional therapy with calcium supplements and activated vitamin D analogues was noted in 71% of patients. The mean dose of calcium supplements was 1837 mg/day (per elemental calcium) and 1.74 mg/day for alfacalcidol.
Conclusions
This study represents one of the first large-scale epidemiological assessments of chronic postsurgical and nonsurgical hypoparathyroidism in Russian Federation. Longitudinal prospective studies are necessary to permit a better understanding of the clinical manifestations, short- and long-term complications, and therapeutic approaches of disease. Being aware of our current management of this rare disease is the first step to improving our clinical approach in the future.

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AEP125

Summer sunshine exposure and vitamin d status in young and middle age poles: is 30 ng/ml Vitamin D cut-off really suitable for the polish population?

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Background
There is no universal consensus regarding vitamin sufficiency status with values either above 20 ng/ml, or 30 ng/ml being quoted as denoting 'sufficient' status. We have endeavoured to assess the effects of summer sunshine exposure on vitamin D status from a single GP practice in central Poland.
Subjects and methods
We measured concentrations of vitamin D, parathyroid hormone (PTH), creatinine and total calcium in 132 subjects (56 males), age 29.36 ± 13.57 years (range 6–50 years), BMI 25.32 ± 6.33 kg/m^2 in spring and subsequently in autumn (n = 125).
Results
There was an overall increase in vitamin D concentrations from 18.1 ± 7.39 ng/ml to 24.58 ± 7.72 ng/ml, $P < 0.001$, accompanied by a decrease in PTH from 44.4 ± 17.76 pg/ml to 36.6 ± 14.84 pg/ml, $P < 0.001$, without significant change in calcium concentrations (P = 0.65). Vitamin D concentrations were lower in spring in males (16.5 ± 6.82 ng/ml vs 19.38 ± 7.62 ng/ml, P = 0.02, for males & females, respectively), but these sex differences became insignificant in autumn (23.8 ± 7.11 ng/ml vs 25.36 ± 8.1 ng/ml, P = 0.24). In spring only 5.3% were vitamin D

sufficient for a 30 ng/ml cut-off, with an increase to 23.2% in autumn, $P < 0.001$. In contrast, where a 20 ng/ml cut-off was employed, then vitamin D sufficiency was found in 34.1% in spring and in 66.4% individuals in autumn, respectively, $P < 0.001$. Correspondingly, vitamin D deficiency was noted in 62.1% and 29.6%, $P < 0.001$ (spring vs autumn), for a 20 ng/ml cut-off, but only in 17.4% (spring) and 2.4% (autumn), $P < 0.001$ for a 12 ng/ml vitamin D cut-off. In multivariate analysis neither BMI, nor age were important determinants of summer vitamin D increase, if at least two week period of holiday leave was taken into account ($P < 0.001$).
Conclusions
Holiday leave for at least two weeks is the strongest determinant of an increase in vitamin D concentrations. If the majority of healthy individuals fail to reach a 30 ng/ml vitamin D cut-off after summer sunshine exposure, then this raises the question, whether such cut-off is too high, and a 20 ng/ml vitamin D sufficiency cut-off should be universally employed.

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AEP126

How frequent is vitamin D toxicity? Data from the national survey of endocrinologists in Russia

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Introduction
Clinical guidelines for the prevention and treatment of vitamin D deficiency in adults were formulated and implemented into clinical practice by the Russian association of endocrinologists in 2014. While having multiple health benefits, in some cases, prescribing vitamin D supplements may be accompanied by its toxicity, which has various manifestations and exert potentially dangerous health consequences.
Aim
To study the frequency and key features of vitamin D toxicity in 'real-life' clinical practice settings.
Materials and methods
710 healthcare professionals took part in an online survey in January 2021. Endocrinologists accounted for 79% of respondents while 21% of survey participants were doctors of other specialties, 94% were women, all age groups from 20 to 65 + years old were presented nearly equally.
Results
16.2% of interviewed doctors had met with a toxicity of vitamin D: once – 42%, twice – 25.2%, three times – 21% and 11.8% reported 4 or more cases over the course of their clinical practice. The most common reasons for toxicity of vitamin D were the intake of an increased doses of colecalciferol initiated by the patient (58.3%) or by the doctor (36%), as well as the intake of active metabolites of vitamin D (24%). Somewhat less often, doctors observed an overdose due to an inaccuracy in the drug concentration indicated by the manufacturer (the actual was higher than stated) – in 22.3%. Least often, doctors met with an overdose due to a genetic defect of CYP24ñ1 (11.4%), granulomatous (sarcoidosis, histiocytosis, tuberculosis, etc.) (8%) or lymphoproliferative diseases (4.6%). About 70% of doctors always refer for a blood calcium evaluation along with 25(OH)D, 77.2% also check parathyroid hormone levels and 24% – calcium levels in 24 h urine.
Conclusions
Endocrinologists are often faced with an overdose of vitamin D. Particular care should be taken when prescribing high doses of colecalciferol or active metabolites/analogues of vitamin D without regular monitoring of the parameters of calcium-phosphorus metabolism, as well as when patients take them on their own.

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AEP127

Large parathyroid adenomas: unusual clinical characteristics

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Introduction
The differential diagnosis between benign and malignant parathyroid neoplasms may be challenging and should always be based on clinical and histological criteria. We are presenting a case series of three patients with clinical, biochemical and imaging findings supporting the presence of a malignant neoplasm but histological findings confirming the diagnosis of a parathyroid adenoma.
Case 1
A 24-year-old man presented with acute pyelonephritis in the presence of obstructive urinary tract calculi of the right kidney. Laboratory examination was indicative of primary hyperparathyroidism (PHPT) (Total Ca = 17mg/dl, PTH = 1000 pg/ml). Parathyroid ultrasound imaging demonstrated a 3 cm tumor under the left lobe of the thyroid gland. Plain radiographs revealed the presence of multiple osteolytic lesions in the humeri, femurs and pelvic bones, as well as subperiosteal bone resorption of the finger phalanges of the hand.
Case 2
A 32-year-old woman was admitted in the ICU due to acute pyelonephritis and sepsis in the presence of obstructive urolithiasis of the right kidney. Laboratory examination was indicative of PHPT (Total Ca = 13.5mg/dl, PTH = 1500 pg/ml). Parathyroid ultrasound imaging demonstrated a 6.5 cm tumor under the right lobe of the thyroid gland. Plain radiographs revealed the presence of pepper pot appearance of the skull, subperiosteal resorption in the middle phalanges of the second finger of the hands as well as the appearance of floating tooth syndrome.
Case 3
A 52-year-old woman presented with bilateral urolithiasis and laboratory results indicative of PHPT (Total Ca = 13mg/dl, PTH = 504 pg/ml). She had a history of parathyroidectomy of 2.5 hyperplastic parathyroid adenomas and was receiving treatment with cinacalcet due to persistent hypocalcaemia. CT imaging revealed the presence of a 5 cm tumor in the mediastinum originating from the right inferior parathyroid gland. Plain radiographs revealed the presence of brown tumors in the right femur and ilium. All three patients underwent surgical removal of the parathyroid tumors and histopathological examination confirmed the presence of parathyroid adenomas. In all cases, postsurgical PTH concentrations returned to normal range, while the patients developed hungry bone syndrome and were offered calcium and alfacalcidol supplementation.
Conclusion
Large parathyroid adenomas may present with severe clinical manifestations such as osteitis fibrosa cystica, severe urolithiasis, as well as extremely high PTH and calcium concentrations, even in young-aged patients. Since the biological behavior of such adenomas is not definite, long-term surveillance is essential.

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AEP128

COVID-19 and impaired calcium metabolism upon admission to the hospital

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Introduction
There is evidence of the interaction between the main parameters of calcium-phosphorus metabolism, vitamin D and the course of a new coronavirus infection. Moreover, hypocalcemia is one of the most frequent biochemical disorders and is associated with severity of the disease, increased likelihood of hospitalization, need for mechanical ventilation, and poor prognosis in COVID-19.
Objective
To estimate the main parameters of calcium-phosphorus metabolism in patients with COVID-19 upon admission to our hospital.
Material and methods
A single-center study was carried out at the Endocrinology Research Centre, Moscow. We included 60 patients (aged ≥ 18 years) with acute respiratory infectious diseases related to COVID-19 (CoV). Baseline biochemical investigations, including serum calcium, phosphate, albumin, 25-hydroxyvitamin D, parathormone, as well as instrumental assessment of the COVID-19 severity were performed before any specific immunotherapy. Statistical analysis was conducted with Statistica 13 (<<StatSoft>>, USA). A p-value of < 0.05 was considered statistically significant.
Results
The prevalence of hypocalcemia (for albumin-adjusted calcium (Ca_{adj}) < 2.15 mmol/l) and vitamin D deficiency (< 20 ng/ml) was 36.7 and

86.7%, respectively. Lower saturation (SpO2) was observed in patients with the lowest Ca_{adj} (P = 0.002) and 25(OH) D levels (P = 0.001). Moreover, lower Ca_{adj} was related to lower values of SpO2 (OR 12 725.213, 95% CI 2.661–60 863.931.6) and vice versa Ca_{adj} > 2.17 mmol/l was associated with SpO2 > 93% with a probability of 71–92%. In addition, there were no associations between total and albumin-adjusted calcium levels and 25(OH) vitamin D (p1 = 0.061 and p2 = 0.339, respectively). Patients with severe COVID-19 pneumonia (computer tomography (CT) scan grade 3–4) compared with those with less grades (CT 1—2) had significantly lower total Ca and albumin (P < 0.001 for all). In 11.6% of cases, the level of 25(OH)vitamin D was less than 5 ng/ml. Decreased vitamin D levels were associated with higher CRP values (OR 0.892, 95% CI 0.8—0.995) and lower SpO2 (OR 1.227, 95% CI 1.028—1.465). Patients with normal and increased (10 pg/ml or more) IL-6 levels have significant differences in total calcium (2.25 [2.18; 2.38] mmol/l vs 2.15 [2.07; 2.23] mmol/l; P < 0.001) and albumin (44.5 [42; 47] g/l vs 39, 5 [36; 42] g/l; P < 0.001) concentrations.
Conclusion
The hypocalcemia and vitamin D deficiency are highly prevalent in patients with severe course of COVID-19 with the need for hospitalization. Further research is required to determine the impact of impaired calcium-phosphorus metabolism on COVID-19 to develop the optimal therapeutic strategies.

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AEP129

CDC73 associated primary hyperparathyroidism and essential tremor

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Objective
Primary hyperparathyroidism (PHPT) is a common endocrine disorder affecting 2% of the population aged 55 years or older. Primary hyperparathyroidism is due to parathyroid adenoma in about 85% of cases, parathyroid hyperplasia in about 15% of cases, and parathyroid carcinoma in less than 1% of cases. Familial parathyroid disorders are responsible for 10% of the PHPT cases and include among other disorders caused by parafibromin malfunction. Parafibromin is a tumour-suppressor protein that regulates apoptosis, cell-cycle transition, grow factor gene expression and tumour-associated wingless-type (Wnt) pathway. The loss of parafibromin tumour-suppressor function is associated with parathyroid tumours. Parafibromin is coded by gene CDC73 (cell division cycle 73, previously HRPT2). Immunohistochemical assay of parafibromin has limited validity, therefore it is recommended molecular-genetic analysis of the gene CDC73. The spectrum of disorders associated with mutations of the gene CDC73 includes such phenotypes: HPT-JT syndrome (hyperparathyroidism-jaw tumor syndrome), isolated familial hyperparathyroidism and parathyroid carcinomas. Here, we are presenting a case of a family with primary hyperparathyroidism, which was manifested by adenomas of the parathyroid gland for most members of the family. Associated comorbidity in 4 members of the family was an essential tremor.
Methods
Molecular-genetic analysis of 17 genes from DNA obtained from peripheral blood leukocytes (Parathyroid NGS panel, Endocrinological institute): AIP; AIRE; AP2S1; CASR; CDC73; CDKN1A; CDKN1B; CDKN2B; CDKN2C; GATA3; GCM1; GCM2; GNA11; MEN1; PTH; RET; STX16 and then examination of segregation of causal mutation in 14 family members (3 generations).
Results
Causal mutation of the gene CDC73 was detected. It is a deletion of 4 nucleotides NM_02 4529.4:c.520_523delTCTG; p.(Ser174LysfsTer27) in 7th exon, which causes premature stop of parafibromin synthesis in 200th amino acid.
Conclusion
Disorders associated with CDC73 are autosomal dominant inherited. The mutation is inherited from the affected parent with a 50% probability or arises de novo. Patients with CDC73 associated disease should be observed by an endocrinologist in regular terms. It includes an annual examination of PTH and calcium levels, dental examination and periodic ultrasound of the pelvis and kidneys.

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AEP130

The benign course of MEN I disease. Implications for treatment

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MEN (multiple endocrine neoplasia) I disease represents a compilation of multiple endocrine neoplasms affecting a patient in the course of a life-time. It thus represents a phenotype which has survived over many years. Pituitary neoplasms, lipomas and parathyroid hyperplasia are observed in the disease. The aim was to describe a patient with MEN I disease who presented with lipomas and acromegaly in his early adulthood and developed primary hyperparathyroidism in his senior years. A patient presented with lipomas at the age of 35 years. At the age of 36 years acromegaly was diagnosed as the patient had increased perspiration, weight gain, increased growth of his hands and feet and headaches. A diagnostic evaluation revealed the presence of acromegaly due to a pituitary tumor in the left side of the pituitary gland. The pituitary tumor was excised transsphenoidally. Following the surgical removal of the pituitary adenoma the patient improved dramatically and lost 10 kg of weight within a few weeks. Thirty-six years later a thyroid ultrasound was performed which showed a nodule inferior to the left thyroid lobe. A diagnostic evaluation revealed increased PTH levels 76 pg/ml, mildly elevated blood calcium levels 10.1 mg/dl and normal 24 h urinary calcium levels. Bone mineral density was normal. An abdominal ultrasound was performed which did not reveal the presence of kidney stones. The diagnosis of mild hyperparathyroidism was made. Conservative management was decided. MEN I disease is a genetic disease which has been transmitted in families allowing the survival of the patients and the genotype and corresponding phenotype. Moreover, primary hyperparathyroidism in the case of MEN I is due to parathyroid hyperplasia. Additionally, some of the tumors present in MEN I patients may be completely silent for many years. It is therefore proposed that the management of hyperparathyroidism should preferably be conservative as it is due to parathyroid hyperplasia and may be mild. Hence, surgical removal, if decided should lead to the excision of more than one parathyroid glands. Additionally, complete removal of the parathyroid glands leads to hypoparathyroidism, a disease known for its notoriously difficult management. Thus, in the management of tumors diagnosed in the course of MEN I conservative management should be considered, if clinical findings are mild and the tumor does not cause obstructive or other size related manifestations.

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AEP131

Hypercalciuria and associated mineral metabolism disorders in osteopenic/osteoporotic patients: effects of treatment with thiazide diuretics

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Hypercalciuria may represent a challenge during the workup for osteoporosis management. The present study aimed: 1) to describe the phenotype associated with hypercalciuria in vitamin D-repleted (serum 25OHD > 20 ng/ml) osteopenic/osteoporotic patients, focusing on kidney, bone and mineral metabolic features; 2) to analyze the effects of thiazides and anti-resorptive drugs on urine calcium excretion (UCa) and mineral metabolism markers. Seventy patients (67 postmenopausal females; mean ± SD age 63.5 ± 7.8 years)

with hypercalciuria (UCa > 4.0 mg/kg body weight/24 h on two determinations) were retrospectively enrolled in a real-world setting. Median (interquartile range) UCa was 5.25 (4.60–6.50) mg/kg/24 h. Kidney stones occurred anamnestically/by imaging in 28% of patients, whose UCa was similar to that of patients without kidney stones [5.2 (4.4, 6.7) vs 5.2 (4.6, 6.5) mg/kg/24 h]. By means of bone densitometry scan (n = 66), osteoporosis was diagnosed in 65% of patients at lumbar site and in 45% at femour site; 50% of patients experienced at least one fragility fracture. Clustering analysis considering the 3 correlated variables serum calcium, phosphate and PTH, identified 3 clusters of hypercalciuric patients: cluster 1 (n = 27) included patients with normal mineral profile, cluster 2 (n = 33) included patients with relatively elevated PTH, normocalcemia and normophosphatemia, resembling normocalcemic hyperparathyroidism, while cluster 3 (n = 10) included patients with a primary hyperparathyroidism-like profile, suggesting a certain degree of autonomous PTH secretion from parathyroid glands. After a follow up of 2.2 ± 1.3 years, 56 patients were reevaluated; 40 patients were treated with thiazides (13 with hydrochlorothiazide, 27 with indapamide). Concomitant therapies were: bisphophonates (n = 12), denosumab (n = 14), calcium salts (n = 15). Thiazides induced a mean 41% reduction in UCa and 64% of patients obtained UCa < 4.0 mg/kg/24 h. Hydrochlorothiazide and indapamide reduced UCa at a similar extent (–2.3 ± 0.9 vs –2.6 ± 1.2 mg/kg/24 h). Multiple logistic regression analysis showed that: 1) thiazides induced a consistent UCa reduction (r^2 = 0.330), though the effect did not reach significance (P = 0.08), while bisphosphonates and denosumab did not affect UCa; 2) increases in PTH levels were induced by bisphosphonates (P = 0.02) and denosumab (P = 0.02), but not by hypercalciuria, but the effects were limited (r^2 = 0.059); 3) similarly, reduction in calcium levels were induced by bisphosphonates (P = 0.02) and denosumab (P = 0.01), but not by hyperecalciuria, with clinically inconsistent effects (r^2 = 0.04 and r^2 = 0.08, respectively). In conclusion, in elder osteoporotic patients, hypercalciuria is associated with kidney stones in about one fourth of patients and with a wide range of impaired PTH secretion. Thiazides normalized urine calcium excretion in about 2/3 of patients.

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AEP132

Bone mineral density evolution after Denosumab withdrawal

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Introduction
Denosumab (Dab) withdrawal is associated with a quick loss in bone mineral density (BMD) and a high risk of multiple vertebral fractures. It is still not stablished which strategy best prevents BMD loss after Dab discontinuation.
Aim
Compare the use of bisphosphonates for one year after Dab withdrawal versus a tapering Dab regimen in terms of BMD and fracture occurrence.
Methods
Descriptive retrospective study including 20 patients with osteoporosis treated with Dab, whose treatment was retired after achieving their BMD target (T-score ≥ –2 SD). One group received weekly alendronic acid and the other group followed a tapering regimen (two doses every 9 months and then two annual doses). Bone turnover markers and BMD were measured before starting Dab, before withdrawing it and one year after withdrawal.
Results
20 patients. 90% (18) women. Mean age: 62.65 years. Mean treatment time of 51.85 (20.11) months. 2 patients with history of osteoporotic fractures. In 9 patients (45%) Dab was tapered and 11 patients (55%) received alendronic acid weekly. There are no differences as long as age, initial BMD or history of osteoporotic fractures between groups. There is a statistically significative reduction in BMD (1.043 ± 0.084 to 0.091 ± 0.093; P = 0.011) and T-score (–1.03 ± 0.43 to –1.63 ± 0.75; P = 0.012) in lumbar spine one year after in the group where Dab was tapered. There are not differences in the evolution of lumbar spine BMD either in the group who received bisphosphonate or in the whole sample. There are neither statistically significative differences in hip BMD in any of the groups, neither globally nor individually. Between groups there are not statistically significative differences in BMD, T-score or percentage of BMD modification one year after Dab withdrawal.
Conclusions
After Dab withdrawal using a bisphosphonate is a safe strategy and it is not associated with BMD loss in our series. In neither of the groups where fractures one year after Dab discontinuation.

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AEP133

Serum and urinary calcium level in Latvian patients with sarcoidosis at the time of diagnosis – 2013–2018 data

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Keywords
Sarcoidosis, serum, 24 h urine, calcium.
Introduction
Sarcoidosis is a systemic disease of unknown etiology that is defined by the formation of granulomas in different organ systems. Due to these pathologies, there may be an increase in serum and 24 h urine calcium that can have a clinical impact on the course of the disease.
Aim
The goal of this study was to assess the changes in total serum calcium and 24 h urine at the time of diagnosis in new cases of sarcoidosis from 2013 till 2018, as well as to calculate an annual disease incidence rate.
Materials and methods
In a retrospective study, medical records of all patients who were screened due to suspected sarcoidosis (n = 1271) in the Riga Eastern University Hospital's 'Clinic of Tuberculosis and Lung Diseases' between the 1st of January 2013 and 31st of December 2018 were analyzed. For further analysis, only patients with first-time histologically and/or clinically confirmed diagnosis of sarcoidosis (n = 956; 507 men and 449 women) were selected, and only the data from the first episode was evaluated. The information was obtained from patients' case files and medical records in the centralized hospital information system.
Results
On average, there were 159 (ranging from 140 to 182) new sarcoidosis cases (approximately 46.96% women and 53.04% men) per year, with an annual incidence rate calculated between 6.92 (2013) and 9.16 cases (2015) per 100.000 population in Latvia. Patients' age ranged from 16 to 84 years with mean age of 39 ± 13.4 years. The highest number of newly diagnosed sarcoidosis was in the age group of 30–39 years (n = 315 or 33%; 114 women (25.39%) and 201 men (29.64%)). Serum calcium level was evaluated in 664 patients (69.46%), hypercalcaemia was detected in 9.2% cases (n = 61), there was no significant association found between elevated serum calcium and gender. 24 h urine calcium level was evaluated in 716 patients (74.89%), hypercalciuria was detected in 17.6% cases (n = 126). 24-h urine calcium was significantly higher in men, regardless of units used (mg (P < 0.001); mmol (P < 0.011)). Pearson Chi-Square test showed that men had a tendency to hypercalciuria (3.5), but women – to hypocalciuria (2.4).
Conclusions
Many patients lack serum and/or 24 h urine calcium levels evaluated at the time of the diagnosis of sarcoidosis. Hypercalcaemia was observed in 9.2% cases, but hypercalciuria – in 17.6%. No significant association was found between serum calcium level and gender, but 24 h urine calcium level was significantly higher in men.

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AEP134

FGF23 secreting mesenchymal tumor of the foot: Localizing pitfalls

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Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome of chronic hypophosphatemia caused by the production of FGF23 in a typically small, benign, mesenchymal tumor. The diagnosis is often delayed and finding the tumor is sometimes challenging. We present a case of a 50 yrs old woman with TIO, referred to our clinic for progressive muscle weakness, diffuse bone pain and fractures, extensively investigated for 3 years. 2 years before admission she had a vertebroplasty for severe L5 vertebral fracture and in the last 12 months she suffered multiple moderate thoracic and lumbar vertebral fractures. At presentation she was unable to stand or walk without help. Laboratory findings: hypophosphatemia 1.1 mg/dl, phosphate renal wasting (phosphaturia 0.56 g/l; TmP/GFR = 0.36 mg/dl/l), Alkaline Phosphatase 462 U/l (40–150), normal serum Calcium, 25OHD 20 ng/ml, PTH 58 pg/ml, high bone turnover – CTX 0.640 ng/ml (0.162–0.436), P1NP 152 ng/ml (15–74), osteocalcin 26 ng/ml (11–43); no proteinuria/aminoaciduria/glucosuria, normal urinary electrolytes. The very high FGF23 level (5495 pg/ml, normal range 26–110) in this context suggested the diagnosis of TIO and

the patient was referred for 68Ga PET-CT. Despite specific recommendation for whole body scanning, both feet were excluded from imaging exam and no tumor was found. Oral phosphates and alfacalcidol were started, with clinical improvement and modest increase in phosphate levels. At follow-up a plantar tumor was found by palpation in the soft tissue beneath the first left metatarsal, confirmed by ultrasonography and subsequently by MRI. Tumor resection completely resolved the symptoms and rapidly normalized the biochemistries. The biopsy revealed a mesenchymal tumor, with giant osteoclast-like cells, mitoses, areas of osseous metaplasia.
Conclusion
A thorough head-to-toe physical examination and functional imaging are essential for tumor localization.

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AEP135

Osteoporosis treatment following osteoporotic fractures- data from a single medical center

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Background
Most post-osteoporotic fracture patients do not receive osteoporosis treatment, although it reduces risks for additional fractures. This retrospective, observational study reviewed osteoporosis evaluation and treatment following typical osteoporotic fractures.
Methods
We identified patients with hip, vertebral, humerus or radius fractures, examined in Meir Medical Center, January-December 2017. Exclusion criteria were: not a Clalit Health Services member, high energy or pathologic fracture, or 30-day post-operative mortality. Primary endpoint was osteoporosis drugs issued within 12-months of fracture. Secondary endpoints were bone density testing and mortality.
Results
Of 928 patients diagnosed, 346 (37%) were excluded. 582 (78.6 ± 11.1 years-of-age, 75.8% women) were included: 321 (55.5%) hip, 84 (14.1%) humerus, 33 (5.6%) vertebra, 144 (24.7%) radius. Hip fracture patients were older, with more previous fractures. Osteoporosis drugs were issued to 26.5%; humerus fracture received the least (21.4%) and vertebral fracture, the most (30.3%), $P = 0.51$. Treatment related to age, gender or previous fracture, was similar. Bone density testing was done in 23.2% of patients, with vertebra (39.4%) and radius (34%) the most. One-year mortality after hip fracture was 12.1%, with humerus (3.6%), vertebral (3%) and radius (1.4%) ($P = 0.0$). Logistic regression demonstrated that previous treatment (OR = 7.4, 95% CI 3.6–15.2), bone density testing (OR = 4.4, 95% CI 2.6–7.4) and endocrinology visit (OR = 2.6, 95% CI = 1.4–4.6) were the most significant discriminating factors associated with osteoporosis treatment.
Conclusions
Fewer than one-third of patients received pharmacotherapy within a year post-fracture. Since pharmacotherapy reduces future fractures and mortality, we encourage medical staff, including orthopedic surgeons, rehabilitation team and general practitioners to increase awareness of their importance.

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AEP136

Relationship between muscle function and trabecular bone score (TBS) in Type 2 diabetes mellitus

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Context
The incidence of Type 2 diabetes mellitus (T2DM) is increasing and muscle strength and function are reported to be decreased in patients with T2DM compared to healthy controls.However, the relation between bone and muscle remain unclear.
Objective
Our aims was to examine bone health parameters [by Dual energy X-ray absorptiometry (DXA) and trabecular bone score (TBS)] and muscle strength (by hand grip) in T2DM patients.
Design
Cross-sectional observational study
Setting
Tertiary care hospital
Patients
60 T2DM patients (60% males and 40% postmenopausal women) aged 49–85 years.
Measures
Anthropometric and metabolic parameters were determined. Bone mineral density (BMD) of the lumbar spine(LS), femoral neck(FN) and total hip(TH) and TBS were assessed using DXA and TBS iNsight Software. Hand grip strength (kg/cm^2) was measured with a jamar hydraulic hand dynamometer (5030j1; jackson, MI).Handgrip strength < 30 kg (male) or < 20 kg (female) was defined as low muscle strength. Data were analysed using SPSS 25.0.
Results
60 patients with T2DM were studied. Mean age of T2DM patients was 66.3 ± 8.31 years. Mean HbA1C was 7.7 ± 1.1%. 73.3% had poorly glycemic control (HbA1c > 7.5%).95.8% of female and 91.7% of male had low muscle strength.Hand-grip strength was positively correlated with TBS ($R = 0.321$, $P < 0.01$) and with TH- BMD ($R = 0.268$, $P < 0.05$).
Conclusions
Our study show that the reduction of muscle strength was significantly associated with decreased bone mass and deteriorated bone microarchitecture in T2DM patients.

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AEP137

Predictive factors for postoperative hypoparathyroidism after total thyroidectomy

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Introduction
Hypoparathyroidism (hypoPT) is one of the most complications after thyroid surgery, usually as transient hypocalcemia. Permanent hypoPT due to permanent parathyoid lesion, despite being less frequent, is associated to long term consequences for both objective and subjective well-being and should be prevented. Identifying predictive factors associated with post-thyroidectomy hypoPT is thereby crucial.
Aim
To investigate predictive factors for permanent hypoPT after total thyroidectomy(TT).
Materials and methods
This retrospective study enrolled patients submitted to total thyroidectomy in Centro Hospitalar e Universitário do Porto from January 2017 to June 2019. Patients without post-operative follow up were excluded. Postoperative hypoPT was defined by iPTH < 15 pg/ml, calcium levels < 2.15 mmol/l or patients' requirement on daily vitamine D and calcium suplementation to avoid symptoms of hypocalcaemia. It was classified as permanent if parathyroid gland function has not recovered within six months after surgery. We investigated possible predictive factors for permanent postoperative hypoPT such as gender,age, thyroid specimen weight, histologic diagnosis of the specimen, presence of substernal goiter or autoimune thyroid disease, postoperative PTH and calcium levels.
Results
From a 357 total thyroidectomy procedures performed during the study's period, two-hundred and fifty two patients were included for the analysis, with a higher predominance of the female gender (84.1%) and a mean age at thyroid surgery of 54.2 ± 13.6 years. Twenty patients patients with permanent hypoPT were identified (5.6% from all TT performed). A lower postoperative PTH level (median 28.0 vs 49.0 pg/ml, $P < 0.001$), lower postoperative (median 2.24 vs 2.38 mmol/l, $P = 0.026$) and 3-months postoperative calcium levels (median 2.28 vs 2.36 mmol/l, $P < 0.001$) were associated with permanent hypoPT. Substernal goiter (16.1% vs 5.3%, $P = 0.006$) was also associated with permanent postoperative hypoPT. We did not found any statistically significant difference regarding risk for permanent hypoPT according to age ($P = 0.61$), gender ($P = 0.60$), thyroid specimen weight (0.12), autoimune thyroid disease ($P = 0.38$) or diagnosis of malignancy ($P = 0.78$).

Conclusions
In our current study, low postoperative PTH and calcium levels, and presence of substernal goiter were associated to permanent hypoPT. Understanding the factors associated with permanent HypoPT can assist in adequately monitoring these patients in the postoperative period and preventing hypocalcaemic events

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AEP138

Continuous rhPTH(1–34) Treatment in Chronic Hypoparathyroidism

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Introduction
Hypoparathyroidism still remains the only hormone-deficiency related disorder whose standard treatment is not based on replacing the missing hormone. In the last few years, there has been growing evidence on the use of recombinant human PTH, mostly with subcutaneous injections of rhPTH(1–34). More recently, some clinicians have tried to administer teriparatide through a continuous delivery system using insulin pumps.
Case report
A 31-year-old woman was referred to our Department for further evaluation of chronic severe hypocalcemia due to iatrogenic postsurgical hypoparathyroidism. She was chronically medicated with high doses of calcium, cholecalciferol, calcitriol, magnesium, indapamide and subcutaneous teriparatide injections. However, she still reported hypocalcemia symptoms on a daily basis and she frequently needed treatment with intravenous calcium perfusions due to episodes of severe hypocalcemia. During hospitalization, oral supplementation doses were progressively titrated up to 5g/day of elemental calcium and 4µg/day of alphacalcidol, with supervised treatment to rule out noncompliance. Despite these measures, six episodes of symptomatic severe hypocalcemia were documented, requiring treatment with intravenous calcium infusions. Our team then decided to implement a continuous subcutaneous perfusion of rhPTH(1–34) through an insulin pump. We slowly titrated the infusion rate up to 0.5 IU/h (30 mg/day). After that, no more severe hypocalcemia episodes occurred and we were able to reduce the oral supplementation doses. The treatment was monitored daily by clinical evaluation, dosing of serum ionized calcium and calculation of the urinary calcium:creatinine ratio. 4 months after hospital discharge, the patient remained with a rhPTH(1–34) infusion rate of 0.5 IU/h but it had been possible to fully suspend oral supplementation therapy. Her serum calcium level consistently remained within normal range and no other episodes of hypocalcemia occurred.
Discussion
The only way to effectively restore long-term calcium homeostasis in our patient was to start a continuous subcutaneous infusion of rhPTH(1–34). With this regimen, there was no need to maintain calcium or vitamin D supplementation. To our knowledge, this case represents the first report of successful treatment of hypoparathyroidism with a continuous perfusion of a PTH analogue in Portugal. We now have to closely monitor the incidence of potential adverse effects.

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AEP139

Metabolic disorders in patients with primary hyperparathyroidism

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Background
The nonclassical complications of primary hyperparathyroidism (PHPT) can include metabolic syndrome associated with cardiovascular diseases. According to clinical studies, an increased incidence of diabetes mellitus, insulin resistance, obesity, dyslipidemia and other disorders are observed in patients with PHPT regardless of the severity of the disease. The aim of this study is to estimate metabolic parameters in patients with PHPT compared to healthy volunteers.
Material and methods
19 patients with PHPT (15 women, 4 men; median age 36years [30; 40]) underwent biochemical and hormone evaluation, standard oral glucose tolerance test with 82.5g glucose monohydrate, euglycemic hyperinsulinemic clamp and bioelectrical impedance analysis of the body composition before surgery. The exclusion criteria were the GFR < 60 ml/min/1.73 m^2, severe comorbid illnesses, body mass index (BMI) ≥ 32 kg/m^2, diabetes mellitus, using drugs affected glucose and calcium balance. Control group (n = 19) was sex-, age- and BMI-matched without pathology of parathyroid glands (median serum albumin-adjusted calcium (Ca_{adj}) 2.25 mmol/l [2.19; 2.29], PTH 38.3 pg/ml [29.6; 43.5]).
Results
All patients had symptomatic PHPT (median Ca_{adj} 2.8 mmol/l [2.61; 2.96], PTH 137.8 pg/ml [106.1; 209.5]) and 18 had normal glucose metabolism according to standard tests (in 1 man glucose intolerance) – median fasting plasma glucose 5.06 mmol/l [4.77; 5.24], 2-hour postload plasma glucose 5.51 mmol/l [4.56; 6.88], HbA1c (NGSP) 5.3% [5.0; 5.5]. 10 patients (52.6%) had normal weight, 8 (42.1%) – overweight and 1 person (5.26%) – obesity I, besides 36.8% patients had features of visceral obesity. PHPT patients had higher serum triglycerides and lower 25(OH)D_3 level comparing to control group (1.19 [0.93; 1.32] vs 0.8 [0.66;1.0] mmol/l, P = 0.001 and 18.6 [12.8;21.9] vs 24.5 [19.5;42.2] pg/ml, P = 0.018 respectively). However the clamp showed a significant lower M-index in PHPT group (5.48 [4.3; 7.47] vs 7.5 [6.45; 10.99], P = 0.005), insulin resistance was detected in 52.6% patients. We found significant correlations between PTH and triglycerides (r = 0.43) and total cholesterol levels (r = –0.44), P < 0.05 as well as Ca_{adj} and fasting plasma glucose (r = 0.36) and triglycerides (r = 0.60), P < 0.05 in general group. M-index correlated with serum phosphorous level (r = 0.46), triglycerides (r = –0.53), BMI (r = –0.43), %-total fat mass (r = –0.4) and visceral fat area (r = –0.45) in general group, P < 0.05 for all. But these data were not confirmed in the PHPT group except a correlation of M-index with triglycerides level (r = –0.59, P < 0.05).
Conclusion
Our results demonstrated the potential effect of PHPT on metabolic parameters, but further studies are required to clarify these links.

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AEP140

Parathyroid crisis – a conspicuous case of hypercalcemia

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Introduction
Parathyroid crisis (PC) is a very rare yet fatal clinical condition which mandates urgent intervention. We present a case of parathyroid crisis with severe symptomatic hypercalcemia and multi-organ involvement.
Case description
A 63-year-old male presented with three days of generalized fatigue, abdominal pain and vomiting. Review of systems revealed constipation and symptoms suggestive of depression over the past 6 months. Vital signs were notable for tachycardia with a heart rate of 120 beats/minute. On physical examination, the patient was in mild distress and looked dehydrated. Laboratory investigations revealed hypercalcemia with a total calcium of 19.9 mg/dl, ionized calcium of 1.83 mmol/l, phosphorus of 3.2 mg/dl, creatinine of 2.7 mg/dl. Hypercalcemia workup revealed a PTH level of 2472 pg/ml and a normal urine calcium, vitamin D level and serum protein electrophoresis. Acute kidney injury, depression and gastrointestinal symptoms were explained by severe hypercalcemia. He was promptly treated with aggression fluid resuscitation, pamidronate and calcitonin. A Technetium 99m sestamibi scan demonstrated two large bilateral parathyroid masses which correlated with the findings on the ultrasound. The patient underwent bilateral parathyroidectomy and left thyroid lobectomy as the left sided mass was adherent to the thyroid gland. Parathyroid carcinoma was ruled out on biopsy and was consistent with hyperplastic parathyroid tissue. The PTH level decreased to 125 pg/ml intraoperatively and subsequently normalized. Post-operatively the patient developed hungry bone syndrome requiring IV calcium therapy and large-dose vitamin D supplementation.
Discussion
PC is a rare phenomenon where PHPT manifests as a hypercalcemic crisis (serum calcium > 14 mg/dl and multi-organ involvement) requiring urgent therapeutic intervention to prevent life-threatening complications from severely elevated calcium levels. PHPT can be due to parathyroid hyperplasia, adenoma or carcinoma. It is difficult to distinguish the etiology of PHPT clinically but when PTH levels are greater than 5 times the upper limit of

normal, it usually suggests parathyroid carcinoma. However, in our case, the inordinate levels of PTH were due to parathyroid hyperplasia. Imaging modalities are helpful in localizing the disease but cannot assess malignancy potential and fine needle aspiration cytology (FNAC) is contraindicated due to the risk of seeding. Hence, early surgery is the ultimate diagnostic and curative modality.

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AEP141

Aggressive hypercalcaemia with recurrent giant parathyroid adenoma following three parathyroidectomies

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The incidence of recurrent primary hyperparathyroidism (PHPTH) (> 6 months from initial exploration) has been reported to be between 1–10%. Repeated neck explorations could be challenging for surgeons and ensuring normalised biochemistry is vital for peri-operative safety. Recurrent parathyroid adenomas can present with aggressive hypercalcaemia which can be challenging to control prior to surgery. We report a similar case below. A 72 year old lady had her first presentation of PHPTH in 2008 (Corrected Calcium = 3.23 mmol/l, PTH = 29.3 pmol/l). Parathyroid imaging showed a right inferior adenoma (1.5 × 0.6 cm^3) reflecting a possible right parathyroid adenoma. The first surgery for parathyroidectomy needed to be abandoned in view of severe bradyarrhythmia (heart rate 37 due to complete heart block requiring pacemaker insertion). The second surgery was successful with removal of 3 parathyroid glands which confirmed two parathyroid adenomas and one hyperplastic parathyroid gland. Post-operative biochemistry normalised (Corrected Calcium = 2.51 mmol/l, PTH = 8.9 pmol/l). 10 years later the patient was referred to the endocrine team for symptomatic severe hypercalcaemia of 3.5 mmol/l. it was biochemically confirmed recurrent PHPTH with very high PTH levels (PTH = 65 pmol/l). Parathyroid imaging showed a left inferior giant parathyroid mass (4 × 2 × 2.7 cm) with mediastinal extension with displacement of oesophagus and possible infiltration into it. Given the high PTH levels, the size of the mass and refractory hypercalcaemia, it was discussed in MDT with suspicion of parathyroid carcinoma. Patient had significant cardiac history and hence normalization of calcium levels was mandatory for peri-operative safety. Despite repeated admissions for IV hydration and bisphosphonate infusions her calcium remained in range of 3–3.5 mmol/l. due to refractory hypercalcemia unresponsive to hydration and bisphosphonates, she was admitted to hospital 10 days prior to surgery. Her calcium was normalised by use of calcitonin subcutaneous injections along with conventional treatment. During surgery a large mass about 8 cm in size (7.8 × 2.6 × 0.6 cm^3) was removed which was confirmed to be parathyroid adenoma with no evidence of malignancy. This case highlights the aggressive nature of recurrent parathyroid adenomas. Perioperative refractory hypercalcaemia can be effectively controlled by use of calcitonin. Patients with multi-gland disease should also be screened for genetic causes of primary hyperparathyroidism like multiple endocrine neoplasia (MEN).

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AEP142

Height loss is almost 3 times more correlated with trabecular bone score than with bone mineral density

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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 # 50 0074. Vertebral microarchitecture was investigated by Trabecular Bone Score (TBS). TBS software: TBS iNsight, version 3.0.2.0. B. Patients. 784 patients, 737 (94%) women, 47 men. Only 38 under 50 years. Age average: 66.04 years. Women: 65.8 years, men 69.89 years. C. Height measurement. At the time of DEXA analysis, each patient's height was measured (centimeters). Patients were asked to appreciate the difference in height compared to a previous age to which they can relate. D. Statistical analysis. Student t́test 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 in only 28.2% of patients. TBS T scores suggested the diagnosis of osteoporosis in 71.56% of patients (Table).

		BMD-T score			
		Normal	Osteopenia	Osteopo-rosis	Total
TBS-T score	Normal	33	11	5	49
		4.2%	1.4%	0.6%	6.3%
	Partial degraded -1 – 2.5 (osteopenia)	63	81	30	174
		8.0%	10.3%	3.8%	22.2%
	Degraded <-2.5 (osteoporosis)	121	254	186	561
		15.43%	32.40%	23.72%	71.56%
	Total	217	346	221	784
		27.7%	44.1%	28.2%	100.0%

The concordant diagnosis of osteoporosis by the intersection of BMD and TBS scores occurred in only 23.72% of patients. 2. Decreasing height. a. Average: 3.49 cm. Women loss height = 3.49 cm, Men loss height = 3.404 cm. Maximum average loss was recorded at over 85 years = 7.4 cm. The minimum mean loss was found at < 45 years = 0.8 cm. b. Correlations between height decrease and DEXA values. The correlation of the decrease in height with the T score of the BMD was $r = 0.1409$. The correlation of height decrease with TBS was 'r' = 0.4019. Both correlations generate $P < 0.001$. However, the value 'r' for the correlation with TBS was 2.85 times higher.
Conclusions
1. Vertebral compression is correlated with age, higher in women than in men. 2. Patients lose up to 7.4 cm in the 8th decade of life. 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 and the correlation between height decrease and BMD is almost 3 times higher.

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AEP143

Postsurgical hungry bone syndrome in unrecognized severe primary hyperparathyroidism: A case report

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Parathyroidectomy for hyperparathyroidism can be complicated with development of Hungry Bone Syndrome (HBS), a constellation of profound hypocalcemia with hypomagnesemia and hypophosphatemia. The severity of this potential life-threatening condition is related to the extent of the parathyroid-mediated high-turnover bone disease. We present a case of a 59-year-old woman developing post-surgical HBS as a result of longstanding severe unrecognized primary hyperparathyroidism (PHPT) and improper perioperative management. Our patient had a six-year history of upper gastrointestinal pain, progressive weight loss, recurrent bilateral nephrolithiasis with advanced chronic kidney disease (CKD) and chronic normocytic anemia. Due to fall related subtrochanteric fracture the patient was admitted in the local surgical hospital. Computed tomography evaluation revealed multiple osteolytic lesions in the axial and appendicular skeleton. The finding of elevated parathyroid hormone (PTH) (1355 pg/ml), hypercalcemia (3.54 mmol/l) and elevated alkaline phosphatase (ALP) led to the diagnosis of PHPT with brown tumours. 99mTc-sestamibi scan confirmed presence of left parathyroid adenoma

and notable tracer uptake in the affected bones. The patient was scheduled for parathyroidectomy. Comprehensive preoperative and postoperative care was not performed, and the occurrence of HBS was not considered. Early postoperative laboratory assessment showed normocalcemia and the patient was discharged. Two months later the patient presented to our clinic with laryngeal stridor, paraesthesia of the hands, muscle weakness and confusion. Laboratory assessment revealed severe hypocalcemia (0.65 mmol/l), hypomagnesemia (0.49 mmol/l), hypophosphatemia (0.94 mmol/l), elevated PTH (406 pg/ml) and profound vitamin D deficiency (7.39 ng/ml). Diagnosis of HBS was supported by the presence of parameters reflecting diminished osteoclast activity as demonstrated by the normalisation of ALP and significant osteoblast activity denoted by 5 times normal value of osteocalcin. Moreover, preoperative risk factors for HBS were also present such as brown tumours, depleted Vitamin D and most notably, missed opportunity for preoperative prevention of HBS. Our case shows that CKD associated secondary hyperparathyroidism does not protect from HBS in longstanding and neglected PHPT with extensive bone disease. Duration of HBS is determined by the time needed for skeleton remineralization, normalisation of markers of bone turnover, withdrawal of radiological features of brown tumors and significant gain in bone mass after initiation of calcium, magnesium and calcitriol supplementation. As COVID pandemic situation ensued, our patient refused radiological assessment for bone lesion remineralization, but the presence of clinical improvement, correction of anemia and normalization of bone markers turnover allowed us to conclude that resolution of HBS occurred.

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AEP144

Quality of life changes in patients with primary hyperparathyroidism after parathyroidectomy: The usefulness of PHPQoL questionnaire in clinical practice

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Primary hyperparathyroidism (PHPT) is a complex endoctinopathy that involves parathyroid glands which secreting too much parathyroid hormone and due to causes hypercalcemia effecting different organs and leading to significant quality of life (QoL) impairment. QoL assessment before and after surgery in patients with PHTP may be useful for comprehensive evaluation of the treatment effect, as well as for monitoring of the patient' condition after surgery, including in real clinical practice. The aim of the study was to evaluate changes in QoL of PHPT patients after parathyroidectomy (PTX) and to test applicability of the disease-specific QoL questionnaire – PHPQoL for its further implementing in clinical practice and research in this patients group. The PHPQoL includes 16 items; the total PHPQoL score is standardized from 0 (worst QoL) to 100 (best QoL). The linguistic and cultural adaptation of the PHPQoL questionnaire was carried out in accordance with international guidelines. Adult patients with PHPT who were referred to PTX filled out the PHPQoL twice: before and 3 mos after PTX. Psychometric properties of PHPQoL were tested – its reliability, validity and sensitivity. Statistical analysis of QoL data included assessment of Spearman correlations and Student's paired test. In the whole, 65 patients with PHPT were involved into the study (mean age – 52.3 ± 10.5 years, 97% – women): 67.7% patients were symptomatic, 35.4% patients had moderate or severe hypercalcemia. Satisfactory external and content validity of the PHPQoL were demonstrated; the tool was easy to understand and informative to capture specific concerns of PHPT patients. Reliability of PHPQoL was confirmed by the high Cronbach's alpha coefficient ($\alpha = 0.87$). Clinical validity of PHPQoL was shown: symptomatic patients had worse QoL than asymptomatic (PHPQoL total score 47.4 vs 64.7, $P = 0.01$); the more symptoms of PHPT the worse QoL ($r = –0.46$; $P < 0.001$). The positive effect of the surgery on QoL in PHPT patients was demonstrated: PHPQoL total score before PTX 46.7 vs 55.7 after PTX ($P < 0.05$), these results may testify sensitivity of the tool. Clinically meaningful QoL increase (MID for PHPQoL total score ≥ 9 points) was demonstrated in 44% patients after PTX; PHPQoL total score range 51–100 was revealed in 76% patients after surgery. PTX leads to noticeable QoL improvement in PHPT patients. PHPQoL is a feasible and practical PHPT specific tool with satisfactory reliability, validity and sensitivity for QoL assessment in PHPT patients undergoing surgery.

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AEP145

Adjuvant endocrine therapy impact on bone health in premenopausal women with hormone receptor-positive breast cancer: Results of a case series

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Introduction
Adjuvant endocrine therapy has an important role in the management of hormone receptor-positive (expressing oestrogen/progesterone receptors) early-stage breast cancer, reducing the risk of recurrence and improving associated mortality. The estradiol depletion produced by hormone therapy has detrimental effects on skeletal health, which can lead to low bone mineral density (BMD), altered bone microarchitecture and increased risk of fracture.
Methods
7 premenopausal patients with histologically proven hormone receptor-positive breast cancer, treated with luteinising hormone releasing hormone (LHRH) analogue goserelin were evaluated in our clinic. 6 of them were treated also with selective oestrogen receptor modulator tamoxifen and one patient was receiving aromatase inhibitor letrozole. All of the patients received adjuvant chemotherapy and all had secondary amenorrhea. Lumbar spine, total hip and femoral neck BMD and Z-scores along with lumbar spine trabecular bone score (TBS) were measured using dual energy x-ray absorptiometry (DXA GE Lunar). Bone turnover was assessed by measuring C-terminal telopeptide of type I collagen (CTx), osteocalcin (OC) and N-terminal propeptide of type I procollagen (P1NP).
Results
The mean age was 43.8 ± 3.5 years old and the mean duration of endocrine therapy was 2.3 ± 1.6 years. The mean lumbar spine and femoral neck BMD were 1.025 ± 0.13 g/cm^2 and 0.895 ± 0.15 g/cm^2, respectively. The mean Z-scores were –1.08 ± 5 SD at lumbar spine and –0.51 ± 0.4 SD at femoral neck region. 2 patients had a Z-score at lumbar spine below –2 SD and one of the patients was diagnosed with a vertebral fragility fracture using radiography. Therefore, the treatment with bisphosphonates, calcium and vitamin D was initiated. All other patients also received calcium and vitamin D supplementation. The mean TBS was 1.324 ± 0.08, 4 patients having a TBS < 1.350, suggesting a degraded bone microarchitecture. The mean P1NP, OC and CTx were 65.7 ± 28.4 ng/ml, 19.54 ± 5.95 ng/ml and 0.49 ± 0.25 ng/ml, respectively, indicating an increased bone turnover, demonstrated by the elevated serum CTx and P1NP levels (mean values). There was no significant difference regarding BMD and bone biomarkers in letrozole-treated patient compared to tamoxifen group.
Conclusion
This study emphasizes the importance of assessing bone health and regular follow-up in women undergoing hormone therapy for breast cancer, as it can lead to bone loss and degraded bone microarchitecture. Furthermore, prevention of fragility fractures can be obtained by calcium and vitamin D supplementation or antiresorptive therapy, whenever it's necessary.

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AEP146

Parathyroid elastography—elastography evaluation algorithm

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Introduction
Primary hyperparathyroidism is a common disorder of the parathyroid glands and the third most frequent endocrinopathy, especially among elderly women. Secondary hyperparathyroidism is a common complication of chronic kidney disease, associated with high cardiovascular morbidity and mortality. In both

primary and secondary hyperparathyroidism, the need to correctly identify the parathyroid glands is mandatory for a better outcome. Elastography can be an effective tool in the diagnosis of parathyroid lesions, by differentiating possible parathyroid lesions from thyroid disease, cervical lymph nodes, and other anatomical structures. There are currently no guidelines or recommendations and no established values on the elasticity of parathyroid lesions.
Materials and Methods
We have evaluated using shear wave elastography (SWE), both primary and secondary hyperparathyroidism, determining that parathyroid glands have a higher elasticity index than both thyroid tissue and muscle tissue. We evaluated two parathyroid lots, the first lot of patients diagnosed with primary hyperparathyroidism, clinically, biochemically and confirmed by pathological evaluation of parathyroid glands and the second lot of renal secondary hyperparathyroidism, confirmed clinically, biochemically and either by scintigraphy or MRI.
Results
For primary hyperparathyroidism, we have determined, using 2D-SWE, the parathyroid adenoma tissue (mean elasticity index (EI) measured by SWE 4.74 ± 2.74 kPa) with the thyroid tissue (11.718 ± 4.206 kPa) and with the surrounding muscle tissue (16.362 ± 3.829 kPa). For secondary hyperparathyroidism, by SWE elastographic evaluation, we have found that the mean EI in the parathyroid gland was 7.83 kPa, a median value in the thyroid parenchyma of 13.76 kPa, and a mean muscle EI value at 15.78 kPa.
Conclusion
Elastography can be a useful tool in localizing parathyroid disease, whether primary or secondary, by correctly identifying the parathyroid tissue. We have determined that an EI below 7 kPa in SWE elastography correctly identifies parathyroid tissue in primary hyperparathyroidism, and that a cut-off value of 9.98 kPa can be used in 2D-SWE to accurately diagnose parathyroid disease in secondary hyperparathyroidism.

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AEP147

Topographic diagnosis of primary hyperparathyroidism

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Introduction
The diagnosis of primary hyperparathyroidism (PHP) is essentially biological. Current imaging techniques (ultrasound and scintigraphy) make it possible to locate an adenoma in the majority of cases. The objective of this study is to clarify the place of imaging in the topographic diagnosis of hyperparathyroidism.
Patients and methods
This is a retrospective study including 40 patients with PHP who have undergone cervical ultrasound and parathyroid scintigraphy, CT scan and MRI are performed as a second line when the latter are negative.
Results
40 patients are identified with a sex ratio of 4/1, the average age was 51 years (range from 18 to 70 years). HPP has been confirmed biologically in all patients. Cervical ultrasound revealed a single adenoma in 30 patients and hyperplasia in 2 cases. Parathyroid scintigraphy was performed in 37 patients, it demonstrated an adenoma in 59.5% of cases. The CT and MRI were negative.
Discussion
Imaging for parathyroid localization should be performed only after the diagnosis of PHP has been confirmed and the decision has been made to proceed with surgery. Localization is not to be used for diagnosis and should not be used to decide if a patient should proceed with surgery.
Conclusion
Through this study, cervical ultrasound appears to be more sensitive than parathyroid scintigraphy in the topographic diagnosis of PHP. Additional CT or MRI is indicated in the event of discordance or ectopic locations.

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AEP148

Paraplegia: a serious consequence of treatment delay in hyperparathyroidism During the COVID-19 pandemic

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Background
Currently, serious complications of secondary hyperparathyroidism (sHPT) are rare due to early diagnosis and more effective treatments. These complications include osteitis fibrosa cystica, which is characterized by bone resorption and brown tumors. Depending on the location, they can cause pain or compressive symptoms.
Case report
We report a case of a 41-year-old black woman with a past medical history of arterial hypertension diagnosed at 25 years-old and chronic kidney disease (CKD) diagnosed at 35 years old, undergoing hemodialysis treatment. sHPT was present since the diagnosis of CKD, with PTH values consistently > 1000 pg/ml despite the use of cinacalcet and paricalcitol thrice-weekly during hemodialysis. In March 2020, during a visit to relatives in Angola, the patient had an intense and sudden dorsal pain. She developed progressive paraparesis and hypoesthesia of the lower limbs and fecal and urinary incontinence. Due to limited health care assistance and a travel ban due to the COVID-19 pandemic, medical evaluation was only possible six months later in Portugal. At hospital admission in September 2020, she presented with paraplegia and hypoesthesia of the lower limbs and fecal and urinary incontinence. CT-scan revealed bone lesions in three ribs, ischiopubic ramus, left acetabulum, and D7 and D11 vertebral bodies, with spinal canal invasion. A pathologic fracture in D11 and multiple millimetric lesions in some vertebral bodies and iliac bones were also detected. The lesions presented with a dominant blastic component. Serum levels of PTH were 1310 pg/ml (18.5–88.0 pg/ml) with normal total corrected calcium, vitamin D and phosphate levels. Bone biopsy was performed in one of the affected ribs, reporting histological abnormalities consistent with brown tumors. The 99m Tc-sestamibi scintigraphy detected increased metabolic activity in the inferior left lobe of the thyroid gland and in the bone lesion of the first costal arch. A subtotal parathyroidectomy was performed. On the first day post-surgery, PTH levels normalized (56.73 pg/ml). The histopathology report confirmed hyperplasia of the parathyroid glands. Currently, the patient is under motor rehabilitation and medicated with calcium, cholecalciferol, and alfacalcidol.
Conclusion
Despite being rare and benign, brown tumors can cause severe morbidity and should be considered in the differential diagnosis of bone lesions. Persistent sHPT unresponsive to medical therapy with calcimimetics and vitamin D derivates is a significant risk factor and should prompt a timely referral to parathyroidectomy. Unfortunately, the COVID-19 pandemic caused delays in consultations and surgeries reducing the possibility of early interventions.

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AEP149

Brown tumours resulting of secondary hyperparathyroidism in patients with chronic renal insufficiency

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Objectif
Brown tumour is a rare focal bone lesion encountered in patients with uncontrolled hyperparathyroidism (HPT). This disease affects only 1.5% of patients with secondary HPT. This bone lesion can affect any part of the skeleton. The treatment is mainly medical based on reducing the rates of parathyroid hormone (PTH). Surgery is reserved for severe form of brown tumour or in case of uncontrolled level of PTH. The aim of our work is to illustrate the clinical and therapeutic features of these rare tumour.
Patients and methods
This is a retrospective study of 5 chronic hemodialysis patients who developed a brown tumour due to secondary hyperparathyroidism. This study was carried out over a period of 10 years from 2008 to 2018.
Results
The average age of our patients was 38 years old with a sex ratio of 1.5. The average time to diagnosis brown tumours was 5 years. These tumours were located in the mandible in two cases, sternum bone in 1 case and femora in 2cases. The Mean serum calcium level was 1.90 mmol/l, the mean phosphoremia level was 2.20 mmol/l and 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 tumour. The outcome was favorable in all patients with clinical and radiological stabilization of bone lesions in 2 cases and spontaneous regression after parathyroidectomy in 3 patients without any recurrence.

Conclusion
Patients with chronic renal insufficiency may develop brown tumours 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 parathyroidectomy. The patient's prognosis is favourable, but the possibility of kidney transplantation to prevent relapse and the development of further brown tumours will have to be considered.

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AEP150

Symptomatic mastoidian brown tumor in a dialysed child

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Brown tumors (BT) consist of focal bone lesions, caused by increased osteoclastic activity and fibroblastic proliferation. They appear in chronic kidney disease (CKD) as a result of renal osteodystrophy with high bone turnover, due to secondary hyperparathyroidism. BT are composed of mononuclear stromal cells mixed with multinucleated giant cells and hemosiderin deposits, which give the characteristic brown colour. We present the case of a 13-year-old girl, with end-stage CKD on peritoneal dialysis for 3 years, who accused important retroauricular pain with right hemifacial oedema and right retroauricular tumefaction. The cranio-cerebral CT shows a 3.6/2.4/1.6cm polylobate mastoidian tumor. The cervical US shows two homogenous hypoechoic nodules at the lower poles of the thyroid gland. Biologically there was severe vitamin D deficiency 4.7 ng/ml, mildly elevated parathormone levels 180 pg/ml, hypercalcemia and hyperphosphoremia, sugesstive of tertiary hyperparathyroidism. Total parathyroidectomy with subsequent parathyroid tissue transplantation in the left sternocleidomastoidian muscle was performed. Two months following surgery, a significant reduction in tumor volume was observed, the retroauricular region having a quasi-normal normal appearance. Clinically significant brown tumors in the pediatric population are uncommon and may mimic malignant lesions of the bone. Choosing between medical and surgical management may be challenging, due to the rarity of the tumor and lack of existing data. The effective control of hyperparathyroidism will often lead to tumor regression and calcification.

Keywords: brown tumor, chronic kidney disease, hyperparathyroidism

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AEP151

Phosphaturic mesenchymal tumour – diagnostic and therapeutic challenges

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Introduction
Tumour-induced osteomalacia (TIO) is a rare paraneoplastic syndrome caused mainly by a phosphaturic mesenchymal tumour (PMT) as a consequence of fibroblast growth factor 23 (FGF23) overproduction. The manifestation of TIO is mostly musculoskeletal. Locating the PMT is usually challenging and a successful surgical resection of the tumour leads to complete recovery.
Case presentation
A 42-year-old, Caucasian male patient, moving with the help of crutches, was admitted to our Clinic in August 2018, for exacerbating muscle and joint pain, and waddling gait. The pain of the lumbar spine and both feet was noticed for the first time in May 2014. The neurological treatment with pregabalin, venlafaxine, methylprednisolone, physiotherapy, and high doses of antibiotics due to suspicion of borrelia infection were not helpful in pain relief. Laboratory results revealed hypophosphatemia, hyperphosphaturia, and a high level of alkaline phosphatase. A chest CT showed multiple fractures of spinous processes both sides of the rib cage. Based on the clinical manifestation and the additional examinations, including 68GaDOTA-TATE PET/CT performed in March 2018, PMT of the right femur was suspected. In May 2018, the tumour resection was performed and the histopathological examination of the lesion confirmed the diagnosis. However, the patient's condition and post-surgical laboratory parameters had not improved. A second 68GaDOTA-TATE PET/CT scan revealed two lesions: in previously operated femoral bone and in jaw. After a systemic venous sampling of FGF23, performed to decide which foci should be treated, we focused on the right thigh. In January 2019, we carried out transarterial embolization (TAE) of the vessels supplying blood to the PMT to facilitate subsequent radiofrequency ablation (RFA) of the tumour remnants. After TAE and RFA, a profound improvement of the patient's condition was observed and he was able to walk without the aid of crutches, and the waddling gait withdrew. However, despite FGF-23 normalization, he presented with severe hypophosphatemia, and a year after the RFA a fatigue fracture of the left tibia occurred. A third 68GaDOTA-TATE PET/CT, performed in July 2020, showed an increased expression of somatostatin receptors of the tumour remnants. Treatment with somatostatin analogs turned out to be ineffective. In December 2020, a successful surgical resection of the PMT combined with prophylactic intramedullary nailing of the femur resulted in phosphates normalization and complete recovery.
Conclusion
By presenting this case we would like to encourage clinicians to persist in locating PMT and therefore resection, which may require innovative diagnostic tools and treatment.

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AEP152

The relevance of the problem of osteoporosis for medical professionals working in the field of physical and rehabilitation medicine

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Background
There is a high prevalence of osteoporosis (OP) among patients of the older age undergoing rehabilitation. Therefore, it is obvious that physicians working in the field of physical and rehabilitative medicine should be well oriented in this medical problem.
Objectives
to study the relevance of the problem of osteoporosis (OP) for physicians working in the field of physical and rehabilitation medicine, their awareness of the main methods of diagnosis, treatment and prevention of this disease, as well as the frequency of their use in daily clinical activitie.
Methods
A cross-type study was carried out using a questionnaire survey. The study included 157 doctors (M-34, F-123) of 8 medical specialties working in 27 specialized medical institutions on the profile of 'medical rehabilitation. The questionnaire for doctors consisted of 21 items of special questions.
Results
90.45% of the surveyed doctors believed that the problem of OP is relevant for their clinical activities, 100% of the respondents indicated that the presence of OP significantly affects the rehabilitation prognosis and 95.54% – on the degree of effectiveness of medical rehabilitation. According to the respondents, patients with OP make up on average 30.0% [20.0; 50.0] (0–90) of the total flow of patients. 92.36% (145/157) of doctors indicated that they know the risk factors for OP, 98.73% (155/157) – methods for diagnosing OP, 68.79% (108/157) – methods for treating OP, 80.25% (126/157) – methods of preventing OP, 47.13% (74/157) – what is FRAX. However, 35.01% (55/157) of the respondents considered their level of awareness of the problem sufficient for managing patients with OP. Diagnostic procedures for OP are recommended by the all endocrinologists (100%) and the majority of traumatologists (72.73%), gynecologists (66.67) and cardiologists (64.28%), as well as on average half (50%) neurologists and therapists. Endocrinologists (100%), gynecologists (66.67%) and therapists (60%) are mainly involved in the treatment of OP. 32.48% (51/157) of physicians have ever referred their patients to a bone mineral density assessment.

Conclusion
The problem of OP is relevant for the clinical activities of specialists in physical and rehabilitation medicine, and there is the need for advanced training on the problem of OP among these specialists.

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AEP153

Unexpected association of severe hypercalcemia and hypophosphatemia in a patient with chronic hypoparathyroidism: A case report

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Clinical vignette
A 65-year-old woman was hospitalized due to severe hypercalcemia (albumin-corrected calcium 16.9 mg/dl) associated with severe renal failure (creatinine 3.48 mg/ml), normal phosphate levels (3.9 mg/dl) and PTH < 5 pg/ml. Her past medical history included total thyroidectomy complicated by chronic hypoparathyroidism, for which she was followed by her primary care physician. One year before hospital admission, renal function was normal. The patient was on L-thyroxine at 75 mg/day, calcitriol at 1 mg/day and calcium carbonate at 1 g/day and hydrochlorothiazide at 25 mg/day. Hydrochlorothiazide had recently been added to control her blood pressure. Calcium and calcitriol were promptly stopped, and hydration and intravenous furosemide were given. We noticed that her initial phosphate levels were normal and apparently not consistent with vitamin D intoxication or her history of hypoparathyroidism. Her lab tests were checked over the following days and we observed a progressive reduction of her calcium levels (15.0–12.0–10.7–8.6 mg/dl) and creatinine (3.55–3.43–3.21–2.37 mg/dl). Unexpectedly, at the same time, her phosphate levels dropped (3.9–2.3–1.9–1.7 mg/dl). 24 h-urinary calcium (475 mg/day, normal range 50–400 mg/day) and urinary proteins were increased (19 mg/dl, normal range < 15 mg/dl), urinary phosphate reduced (0.2 g/day) but inappropriately high for her hypophosphatemia; 25(OH) vitamin D (15 ng/ml) and 1.25(OH)2 vitamin D were low (14.3 ng/ml, measured once calcitriol was stopped), CTX and bone alkaline phosphatase were within normal limits. After six days, the patient was discharged with low doses of calcitriol (0.25 mg/day) and addressed to the outpatient clinic. After fourteen days, renal function improved (creatinine 1.61 mg/dl), her calcium and phosphate levels were normal (9.5 and 2.8 mg/dl, respectively).
Discussion
Since her biochemistries improved within days, the most likely diagnosis was an overdose of calcitriol and calcium. However, this hypothesis did not explain her low phosphate levels. We believe that her hypophosphatemia might have been caused by a massive increase in her FGF-23 levels driven by calcitriol intoxication and hypercalcemia-induced acute tubular necrosis. Hypophosphatemia was unmasked soon after calcitriol was stopped. Our hypothesis could also explain the lower-than-expected tubular phosphate reabsorption in a patient with hypoparathyroidism and progressive improvement of her labs within a short time.
Final diagnosis
Calcitriol-intoxication associated with acute tubular necrosis and renal phosphate loss in a patient with chronic hypoparathyroidism.

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AEP154

Male osteoporosis

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Introduction
Osteoporosis has generally been considered a female disease; this may explain why this pathology has focused less attention on men. While osteoporosis has been underestimated and poorly treated in female patients, the situation is even worse in male patients, despite the fact that up to one third of hip fractures are suffered by men.
Goal
To assess the characteristics and risk factors associated with male osteoporosis.
Patients and methods
This is a retrospective study conducted at the endocrinology department of EPH Bologhine, which included 100 patients referred for a measurement of bone mineral density. 23 patients had a Tscore<- 2.5.
Results
The mean age of the patients was 45.26 years with extremes of 20 to 82 years. A history of fracture was noted in 4 patients. Long-term corticosteroid therapy was found in 6 patients, 2 patients had cushing's disease. Hypogonadism is found in 4 patients, 2 patients were followed for digestive pathology (celiac disease and RCUH). Discussion Osteoporosis in men is a public health problem and puts you at risk of fractures. In fact, 15% of men over the age of 50 will have an osteoporotic fracture during their lifetime. One in two cases of male osteoporosis is a result of illness, treatment or exposure to a risk factor. There are multiple factors that influence the risk of fracture, beyond the simple decrease in bone mineral density and the risk of falls.
Conclusion
Male osteoporosis has a number of peculiarities that must be taken into account in diagnostic and therapeutic procedures.

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AEP155

8 cases of parathyroid cancer: One-center experience

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Introduction
Parathyroid carcinoma (PC) occurs in 0.5–5% of cases among patients with primary hyperparathyroidism (pHPT). The prognosis for patients with PC is variable and depends on the presence of local or distant metastases and the completeness of the initial surgery. About 50% of patients become recurrence of the disease and require palliative surgery and/or drug therapy aimed at correcting severe hypercalcemia.
Objective
To assess the experience of diagnosis and management of PC in the Republican clinical oncological dispensary (RCOD) of the Ministry of Health of the Republic of Tatarstan (Kazan, Russia) in the period from 2008 to 2020.
Subjects and methods
Medical records of 8 patients with PC treated in RCOD from 2008 to 2020 were analysed.
Results
2 men aged 35 and 50 years and 6 women aged 29–76 years included in this review. 6 patients had symptomatic HPT with bone and visceral involvement, 2 had a pre-diagnosis of a thyroid tumor with mass-effect symptoms. Parathyroid hormone (PTH) varied from 350 to 3227 pg/ml (15–65), serum calcium (Ca) – from 2.77 to 3.35 mmol/l (2.0–2.57). According to ultrasound imaging, MIBI-scintigraphy, neck and chest CT PC was located on the neck in 6 patients, retrosternal – in 1 patient, in the upper mediastinum – in 1 patient. All patients received surgical treatment: 5 patients underwent hemithyroidectomy with PC removal; 1 – thyroidectomy with PC removal and central lymph node dissection; 1 – cervicotomy, sternotomy, PC removal; 1 – videothoracoscopic PC removal. Histologically and immunohistochemically PC was verified in all cases. 7 of 8 patients are alive. Recurrences of PC manifested with an increase of PTH and Ca, occurred in 2 patients. Paratracheal lymph nodes metastases were detected in male patient 5 years after the initial surgery. Multiple bones and lung metastases were diagnosed in female patient 1.5 years after first surgery. Both patients underwent palliative surgery. The persisting severe hypercalcemia after surgery in the female patient was successfully corrected with cinacalcet and denosumab for 9 months. Female patient died 3 years after the initial surgery due to hypercalcemic crisis and multiple organ failure. The male patient is alive, has mild hypercalcemia and continues treatment with bisphosphonates and calcimimetics.
Conclusion
Diagnosis of PC and its recurrence is a difficult task for the practitioner. The main method of treatment remains surgical. Hypercalcemia, which develops during the dissemination of the process, requires long-term medical correction with antiresorptive drugs and calcimimetics.

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Diabetes, Obesity, Metabolism and Nutrition

AEP156

The association of vitamin D with peripheral neuropathy among prediabetic individuals and the effect of vitamin D supplementation

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Background
Vitamin D deficiency seems to be more prevalent among diabetic patients with distal symmetrical polyneuropathy. Besides, those patients have a lower pain threshold; there is a shortage of data concerning pre-diabetic individuals with peripheral neuropathy (PN).
Aim
First,to study the association of vitamin D deficiency with PN severity. Second, to determine the effect of vitamin D supplementation on PN in pre-diabetics.
Methods
178 pre-diabetic individuals aged18–60 years were recruited from outpatient department of the National Institute of Diabetes and Endocrinology, Cairo, Egypt; 89 patients with and 89 patients without PN (group A and group B, respectively).All patients werescreened for PN using 10 g monofilament, tuning fork, ankle reflex and pinprick test.In the first visit, baselineneuropathic total pain score and severity were assessed for group A, by Douleur Neuropathic 4 diagnostic questionnaire (DN4) and Short-form McGill Pain Questionnaire(SF-MPQ), respectively.In addition, serum 25- hydroxyvitamin D, ionized calcium, phosphorus, PTH, HbA1c, fasting blood glucose (FBG), 2hrs post 75 g glucose (2hr PPBG), creatinine, thyroid function test and lipid profile were measured for both groups. Prediabetic patients with PN were given vitamin D3 200.000IU IM monthly for 3 months. They were assessed clinically in 3 subsequent visits,one month apart. In the last visit all the laboratory measures, DN4 and (SF-MPQ) were repeated.
Results
None of the patients in both groups had sufficient vitamin D status.Vitamin D deficiency was highly prevalent among both groups, where 79.8% and 89.9% were deficient; 20.2% and 10.1% were insufficient among group A and group B respectively, *P* value 0.001.Nonetheless, there was insignificant difference in vitamin D levels between group A and group B (14 ± 6.4 and 14.6 ± 4, $P = 0.4$).Vitamin D level was negatively correlated with peripheral neuropathic total pain score and severity ($r = –0.65$, –0.47 respectively, $P < 0.001$) among group A. Moreover, vitamin D level was an independent predictor of neuropathic pain severity (odds ratio –0.18, 95% CI –0.33 –0.03, $P = 0.018$) after adjustment for age, BMI, FBG, 2hr PPBG, HbA1c, lipid profile, serum ionized calcium, phosphorus, PTH and TSH. Supplementation of vitamin D resulted in a highly significant improvement in FBG, 2hr PPBG, HbA1cand lipid profile, $P < 0.001$. Interestingly, total pain scoreand severity before vitamin D supplementation was (6.4 ± 1.6 and 28.3 ± 7.2, respectively) and after was(2.5 ± 0.9 and 17 ± 6.3, respectively, $P < 0.001$).
Conclusion
Vitamin D deficiency is prevalent among prediabetics and can be considered an independent risk factor for painful PN in those patients. Correction of vitamin D deficiency improves glycemic parameters and severity of peripheral neuropathy.

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AEP157

Lipid accumulation product can accurately rule out, but not rule in non-alcoholic fatty liver disease in type 1 diabetes

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Introduction
Lipid accumulation product (LAP), an index based on waist circumference (WC) and serum triglyceride levels, is associated with the presence and severity of non-alcoholic fatty liver disease (NAFLD). However, its potential as a risk marker of NAFLD in subjects with type 1 diabetes (T1D) has not been studied yet.
Aims
This study evaluated the ability of LAP to estimate the presence of NAFLD in adults with T1D.
Methods
Four hundred and seven adult T1D patients (age 18–88, 56.8% males) were included. Anthropometric, biochemical and imaging data were acquired during the screening visit. LAP was calculated as [WC (cm) – 58] × triglycerides (mmol/l) in females; [WC – 65] × triglycerides (mmol/l) in males. NAFLD was assessed using ultrasound, controlled attenuation parameter (CAP) and fatty liver index (FLI), ultrasound was set as the reference method.
Results
NAFLD prevalence according to ultrasound was 20.4%. LAP was positively correlated with FLI ($r = 0.728$, $P < 0.001$), CAP ($r = 0.433$, $P < 0.001$), the number of elements of the metabolic syndrome ($r = 0.659$, $P < 0.001$), age ($r = 0.115$, $P = 0.020$), insulin dose/kg ($r = 0.236$, $P < 0.001$), liver stiffness ($r = 0.110$, $P = 0.027$), HbA1c ($r = 0.188$, $P < 0.001$) and uric acid ($r = 0.324$, $P < 0.001$). LAP was negatively correlated with estimated glucose disposal as a measure of insulin sensitivity ($r = –0.478$, $P < 0.001$) and HDL-c ($r = –0.326$, $P < 0.001$). LAP values could be used to diagnose NAFLD in the total cohort (AUC = 0.767 [0.708–0.827], $P < 0.001$). The AUC to indicate NALFD was 0.790 [0.715–0.865] in males and 0.732 [0.635–0.828] in females ($P < 0.001$ for both), indicating a slight difference between genders. The ideal gender-specific cut-off value was 32.6, with a sensitivity and specificity of 70% vs . 78% for males, and 27.0 (72% vs . 75%) for females. Dichotomised based on the optimal cut-off, the prevalence of NAFLD according to LAP was 32.9%. This was significantly higher compared to ultrasound (χ^2, $P < 0.001$). True positive rate was 58/133 subjects (44%), false negative rate was 25/271 (9%), false positive rate was 56%, while true negative rate was 91%. LAP ≥ 32.6 (males) or ≥ 27 (females) was associated with ultrasound-based NAFLD (OR = 4.120 [1.954–8.690], $P < 0.001$) in a multivariate regression model including BMI (OR = 1.146 [1.043–1.260], $P = 0.005$), insulin dose/kg (OR = 4.838 [1.672–13.995], $P = 0.064$) and liver stiffness (OR = 1.410 [1.114–1.784], $P = 0.004$).
Conclusion
We are the first to demonstrate that LAP is an easily available risk marker of NAFLD in T1D, with high accuracy to rule out. If LAP is ≥ 32.6 (males) or ≥ 27 (females), NAFLD should be suspected but other tools are needed to confirm the diagnosis.

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AEP158

Assessment of serum adiponectin levels in patients with type 1 diabetes and chronic kidney disease

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Aims
Diabetic nephropathy (DN) is a leading cause of chronic kidney disease (CKD). Renal impairment may affect not only glycemic control, but also metabolism of biologically active cytokines such as adiponectin. Taking into account multiple effects of adiponectin the purpose of the study was to assess its changes in patients with type 1 diabetes (T1D) and comorbid CKD.
Materials and methods
We recruited 129 patients with T1D and 39 healthy controls. T1D patients were divided into 2 groups according to GFR. The group 1 comprised 67 patients with GFR > 60 ml/min, group 2–62 patients with GFR < 60 ml/min. Biochemical parameters, lipid profile, HbA1c, NGAL, serum adiponectin levels were measured. Nonparametric statistical methods were used. A P-value < 0.05 was considered significant.
Results
Comparison groups were matched by age, gender, BMI, duration of T1D, HbA1c levels. Comparative analysis of patients in the subgroups according to GFR revealed reliable differences in basal adiponectin levels. Mediana of adiponectin levels in patients with GFR > 60 ml/min (15.65 [9.34; 32.58]) were lower than those in GFR < 60 ml/min (28.21 [16.73; 45.34]), control group had 37.58 [27.38; 42.86]). Then we divided T1D patients according CKD stages. Adiponectin level was 15.65 [9.34; 32.58] in CKD 1–2 ($n = 67$), in CKD 3 ($n = 32$) was 25.36 [14.02; 39.40], in CKD 4 ($n = 14$) was 27.46 [12.83; 69.31], in CKD 5 ($n = 16$) was 32.76 [23.54; 57.34]. It was found that the values of the median adiponectin levels progressively increase with deterioration of renal function towards end-stage CKD ($P = 0.002$), which suggests the possibility of considering this parameter as an indirect marker of decreased renal function. In both comparison groups, correlations

of adiponectin levels with marker of renal damage NGAL were obtained (ρ^1 =–0.413 and ρ^2 =–0.427, resp.). Patients with T1D and GFR < 60 ml/min had relationship between adiponectin and serum creatinine (ρ = 0.302) and eGFR (ρ =–0.298), which indicates the sensitivity of this parameter to decrease in renal function. The increase in adiponectin levels is most likely due to the non-absolute content of adiponectin in the serum, but the relative increase in the amount due to the decrease in renal clearance. We didn't observed relationship of adiponectin and BMI, gender, HbA1c.
Conclusion
In patients with T1D and diabetic nephropathy decline of GFR is accompanied by an increase of serum adiponectin levels due to decrease in renal clearance. Correlation of adiponectin and renal impairment markers suggests the possibility of considering this parameter as an indirect marker of decreased renal function.

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AEP159

Pharmacogenetics of metformin in polycystic ovary syndrome and type 2 diabetes mellitus

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Background
Metformin is a widely used and effective agent in type 2 diabetes mellitus (T2DM) and polycystic ovary syndrome (PCOS). Yet, the mechanisms of action and the occurrence of side effects (e.g. abdominal bloating and pain), are still poorly understood. Since organic cation transporters (OCTs) are responsible for the hepatic and renal transport of metformin, we investigated a series of short nucleotide polymorphisms (SNPs) in the OCT genes in PCOS and in T2DM patient samples from either our PCOS patient registry or the Graz Diabetes Registry for Biomarker Research (GIRO).
Methods
After DNA isolation from plasma in 181 PCOS samples and 44 T2DM samples followed by a subsequent polymerase chain reaction (PCR) with a combined TaqMan assay, we compared 17 SNPs (rs456598, rs461473, rs3798174, rs7766568, rs316007, rs3798167, rs662301, rs2048327, rs376563, rs622591, rs9295125, rs3798172, rs2197296, rs12208357, rs34059508, rs628031 and rs3777392) from OCT1 and OCT3 transporters.
Results
Data of the study participants were analyzed according to the presence or absence of documented metformin-induced side effects. The distributions of different genotypes of the rs2197296 locus in the SLC22A1 gene, the rs376563 locus in the SLC22A2 gene and the rs3798167 locus in the SLC22A3 gene were statistically significant between the two groups. The effect was shown by a higher minor allele frequency in the group with documented metformin associated side effects ($\chi^{(2)}$ = 3.953, P = 0.047, $\chi^{(2)}$ = 7.342, P = 0.025 and $\chi^{(2)}$ = 12.251, P = 0.002 respectively).
Conclusion
In conclusion, we found three specific allelic variants in OCT candidate genes with distinct associations for side effects in metformin users either in PCOS or in T2DM. Therefore, those variants can be further investigated to better understand the metformin-associated side effects.

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AEP160

Could we use SGLT2 inhibitors without serious concern in the elderly?

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Background
Therapeutic experience with SGLT2i is limited in the elderly. Its initiation is not recommended in patients over 85 years based on volume depletion risk. The aim of this study is to analyze clinical efficacy and safety of SGLT2i in elder T2DM patients.
Methods
This observational retrospective study included 544 T2DM subjects who initiated SGLT2i as add-on treatment between February 2018–2019 and were monitored until February 2020. Two groups were performed: youngest-old = aged 60–74 years (N = 282) and old = 75 years and older (N = 111), patients < 60 were excluded. Clinical and biochemical outcomes were studied at baseline and at the end of monitoring.
Results
Mean age for the youngest-old was 62.3 and 79.7 for the old (maximum age 92 and N = 55 were ≥ 80). Most used SGLT2i was Empagliflozin (75.5% vs 79.28%, p 0.483). In 15.95% of the youngest SGLT2i adjustment was made facing 6.3% of the old (p 0.011). Both groups were fairly homogeneous in male percentage, renal function, HbA1c, stablished CVE, preexisting heart failure (HF) and use of loop diuretics (see table1). In the old group, patients had longer duration of T2DM, more concomitant insulin users and lower BMI.

Table 1.

	Youngest-old 60–75 (N = 282)	Old ≥75 (N = 111)	p
Male (N;%)	176 (62.4)	57 (51.3)	NS
BMI (kg/m² ± SD)	31.3 ± 6.27	29.57 ± 4.05	0.002
eGFR (ml/min ± SD)	83.3 ± 19.6	74.15 ± 17.90	NS
HbA1c (mean% ± SD)	7.85 ± 1.20	8.16 ± 1.27	NS
DM duration (years ± SD)	13.28 ± 7.46	16.97 ± 7.56	< 0.001
Insulin treatm ent (N;%)	83 (29.43)	49 (44.14)	0.005
Loop diuretic (N:%)	34 (12)	17 (15.31)	NS
Stablished CV disease (N;%)	77 (27.3)	33 (29.7)	NS
Pre-existing HF (N:%)	33 (11.7)	16(14.4)	NS
CVE follow-up (N:%)	12 (4.2)	6 (5.4)	NS
SGLT2i discontinuation (N;%)	45 (15.9)	27 (24.32)	NS
HF follow-up (N;%)	13 (4.6)	9 (8.10)	NS
Death	7 (2.4)	5 (4.5)	NS

Final %HBA1c was lower in the youngest: 6.9% (–0.88) vs 7.5% (–0.67), (p 0.136). CVE were infrequent: peripheral vascular disease was the main event in the youngest (6/12) whereas stroke prevailed in the elderly (4/6). There was a tendency to more SGLT2i discontinuation, HF in follow-up and death in the elderly although it was not statistically significant. The most frequent side effects in youngest and oldest were eGFR drops < 30, genital and urinary tract infection (31.8 vs 37%, 28.8% vs 22%; and 15.5% vs 25%). Oncological disease (6/7) was the main death cause in the youngest group while CVE and HF were in old group.
Conclusions
Initiation of SGLT2i seems to be safe and effective regardless of age.

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AEP161

An analysis of flash glucose monitoring (FGM) data on insulin-treated patients with diabetes: Effects of COVID-19 lockdown

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Introduction
Following the WHO declaration of COVID-19 as a pandemic and as many countries around the world, the United Arab Emirates government introduced gradual measures to stop the spread of the virus placing the country in a state of almost complete-lockdown. We report the impact of these restrictions on glucose control in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D) on insulin therapy.
Methods
Data were retrieved on 21 individuals who were monitoring their glucose levels using FreeStyle Libre flash glucose monitoring (FGM) and were remotely connected to the diabetes clinic at Imperial College London Diabetes Centre (ICLDC), Abu Dhabi, UAE. Fourteen (8 females and 6 males) individuals had viable data (> 3 scans per day; consecutive 3 days) using international consensus on use of continuous glucose monitoring guidelines (Danne, Nimri *et al*. 2017). Non-parametric analyses of the data were performed on average glucose, percentage time in range (3.9–10.0 mmol/l) and percentage time in hyperglycaemia (> 10.0 mmol/l) using the Wilcoxon signed-rank test in STATA 15.0. These variables were calculated for each of the following periods: 30 days before the announcement of lockdown (period 1); and 30 days into lockdown (period 2) using MATLAB.
Results
Overall glycaemic control improved during lockdown as compared to the weeks before the spread of SARS-CoV-2. The 24-hour glycemic patterns were divided into 3-hour time slots for review and analyses; thus, identifying precise spikes contributing to hyperglycaemia. The highest glycaemic peaks were observed between 2 pm-5 pm (period 1) and between 7 pm-9 pm (period 2). Average glucose median (IQR) declined significantly from 7.5 (6.1, 10.8; period 1) to 6.9 (6.2, 9.9; period 2; $P = 0.005$) mmol/l. There was a modest, but statistically significant improvement in percentage of time in range (TIR) (3.9–10.0 mmol/l) from 88.5% to 90.6% ($P = 0.07$); glucose management indicator (GMI) also improved modestly and in a similar way from 6.5 (5.9, 8.0) % in period 1 to 6.3 (6.0, 7.6) % in period 2 ($P = 0.041$).
Conclusion
Despite the limited possibility to exercise and the incumbent psychologic stress of the COVID-related lockdown period, our study indicates an improvement in FGM-derived markers of glycaemic control. This suggests that slowing down routine daily activities can have beneficial effects on diabetes management.
References
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AEP162

Effects of long-term testosterone therapy on anthropometric parameters in men with functional hypogonadism and obesity: 12-year observational data from a controlled registry study in a urological setting

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Background
While almost all studies consistently show reduction of waist circumference as a result of testosterone therapy (TTh), effects on body weight are inconsistent and may depend on treatment duration, route of administration, and adherence.
Material and methods
After excluding men with primary hypogonadism, 476 men with functional, symptomatic hypogonadism were obese. 281 men received testosterone undecanoate injections 1000 mg/12 weeks following an initial 6-week interval (T-group), 195 men opted against TTh and served as controls (CTRL). Anthropometric measurements were performed at every visit for approximately 4.367 patient-years. 12-year data are reported. Changes over time between groups were compared and adjusted for age, weight, waist circumference, fasting glucose, blood pressure, lipids and quality of life to account for baseline differences between the two groups.
Results
Mean baseline age (years): 59.9 ± 5.5 (T-group), 62.9 ± 5.0 (CTRL) ($P < 0.0001$). Mean (median) follow-up: 9.4 ± 3.0 (11) years (T-group), 8.9 ± 3.0 (10) years (CTRL). Anthropometric parameters at 12 years, mean ± SE: Waist circumference (cm) decreased by 13.7 ± 0.3 (T-group) and increased by 8.1 ± 0.4 (CTRL), estimated adjusted difference between groups: –21.8 [95% CI: –22.9; –20.7] ($P < 0.0001$ for all). Weight (kg) decreased by 23.7 ± 0.4 (T-group) and increased by 7.3 ± 0.5 (CTRL), between-group difference: 31.0 [95% CI: –32.5; –29.6] ($P < 0.0001$ for all). Weight loss was 20.9 ± 0.3% (T-group), weight gain 7.8 ± 0.4% (CTRL), between-group difference: –28.7% [95% CI: –29.8; –27.5] ($P < 0.0001$ for all). BMI (kg/m^2) decreased by 7.8 ± 0.2 (T-group) and increased by 2.5 ± 0.3 in CTRL, between-group difference: –10.2 [95% CI: –11.0; –9.5] ($P < 0.0001$ for all). Waist:height ratio decreased by 0.08 ± 0.00 (T-group) ($P < 0.0001$) and increased by 0.05 ± 0.00 (CTRL) ($P = 0.05$), between-group difference: –0.12 [95% CI: –0.13; –0.12] ($P < 0.0001$). The visceral adiposity index (VAI) decreased by 2.8 ± 0.1 (T-group) and increased by 3.8 ± 0.2 (CTRL), between-group difference: –6.6 [95% CI: –7.2; –6.1] ($P < 0.0001$). 25 patients (8.9%) died in the T-group and 77 (39.5%) in CTRL ($P < 0.0001$). Medication adherence to testosterone was 100% as all injections were administered in the medical office and documented.
Conclusion
In men with hypogonadism and obesity, long-term TTh improves anthropometric parameters which may be a contributing factor to the observed reduction in mortality.
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AEP163

Semaglutide reduces fat accumulation in the tongue of obese women with polycystic ovary syndrome: A randomized, placebo-controlled prospective study

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Objective
Fat depot in the tongue that represents 25–30% of the total tongue mass is largely unaddressed. It correlates with body mass index. The response to weight reduction induced by different anti-obesity modalities may vary between body fat compartments. Semaglutide, a long acting GLP-1 receptor agonist (GLP-1 RA), has the potential to reduce body mass with at least 2 to 3 times greater weight reduction than other studied GLP-1 RAs. This is the first study that assessed the effect of semaglutide on fat storage in the tongue in obese women with PCOS over 16 weeks.
Research design and methods
We conducted a single-blind, randomized, placebo-controlled prospective study comparing the effects of semaglutide versus placebo. 30 women (aged 33.7 ± 5.3 years, BMI 36.1 ± 3.9 kg/m^2, mean ± SD) diagnosed with PCOS by Rotterdam criteria, phenotype A, were randomized in a 1:1 ratio to semaglutide 1.0 mg (SEMA) or placebo group. Quantification of the tongue volume, fat and proportion of fat were obtained by MRI analysis. Total tongue volume was inferred via summation of the tongue mask voxels over all slices and multiplied by single voxel volume. Number of voxels defining the fat tissue was extracted with AFNI.
Results
25 patients concluded the study, 5 were excluded due to protocol violation associated with limitations due the COVID-19 pandemic. Weight reduction was significantly greater in SEMA when compared to placebo group (–5.2 ± 4.0 kg vs + 1.9 ± 5.6 kg, $P = 0.001$). BMI decreased by 1.9 ± 1.5 kg/m^2 in SEMA and increased by 0.7 ± 1.9 kg/m^2 in placebo group. The tongue fat reduction and reduction in tongue fat proportion were significantly greater in SEMA than in placebo (–1944 ± 5510 mm^3 in SEMA vs + 3116 ± 4868 mm^3 in placebo, $P = 0.022$ and –2% ± 7% in SEMA vs + 4% ± 6% in placebo, $P = 0.01$, respectively). Change in the total tongue volume did not significantly differ between the two groups. In SEMA, the tongue fat and tongue fat proportion were significantly reduced in 47% of patients whereas in the placebo group the tongue fat was reduced in only 17% of subjects. By correlation analysis we also found that the reduction of the tongue fat was associated with the reduction of body mass.
Conclusion
Compared with placebo, semaglutide treated patients lost significantly more fat in the tongue. Future studies are needed to assess the clinical

importance of the observed composition change in this unique therapeutic target, particularly in populations with obesity related sleep apnea, including PCOS.

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AEP164

The short-term effect of surgical and pharmacological intervention in obesity caused by MC4R deficiency: A single centre experience

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Introduction
Melanocortin-4-receptor (MC4R) deficiency is the commonest of the rare monogenic forms of obesity. Bariatric surgery (BS) is the most efficacious treatment modality in the more 'common' polygenic obesity. Effect of surgical and drug treatment in obesity due to MC4R deficiency is not well-established.
Aim
We aimed to explore the effects of BS and drug treatment among the confirmed cases of obesity due to MC4R deficiency and compare the short term weight loss was control group who were tested negative for MC4R mutations.
Methods
Based on a strong family history and phenotypic characteristics, genetic screening for MC4R mutation(s) was conducted in 27 morbidly obese ICLDC patients. Data on pharmacotherapy and surgical treatment, including treatment dates, and duration was retrieved from electronic patient records. Weight loss percentage at a median of 6 months post-intervention was compared between age- and sex-matched MC4R-deficient and wild-type controls.
Results
Of the 27 patients, 8 were confirmed to have MC4R mutations. Three specific mutations were identified: Val103Ile, Ile170Val and Thr162Ile (most common). Six MC4R deficient patients and eight MC4R normal patients underwent sleeve gastrectomy. Weight loss at median 6 months post bariatric surgery was not significantly different between MC4R deficient and MC4R normal patients (P = 0.065). However the weight loss post BS in MC4R deficient patients showed variation depending on the type of mutation [17.99(6.1–22.54)%]. Homozygous Thr162Ile did not benefit from BS in terms of weight loss compared to their age and sex matched controls. Heterozygous Thr162Ile and homozygous Ile170Val benefited similarly from BS compared to the controls. Response to Liraglutide treatment was comparable in MC4R Thr162Ile heterozygous patient and control.
Conclusion
Observations from our study suggest that efficacy of surgical and medical intervention in MC4R deficient patients might depend on the mutation type and zygosity. Thr162Ile homozygous individuals might require multiple surgeries or continued pharmacological intervention to maintain weight loss over longer period of time.

Table 1. Comparison of weight loss following surgical and pharmacological interventions between MCR4 deficient and age and sex- matched MC4R normal individuals

Type of intervention	Age	Sex	Mutation	Zygosity	Weight loss %	
					MC4R deficient	MC4R Wild type
Sleeve gastrectomy	33.5/32.2	F	Thr162Ile	Heterozygous	19.05	15.24
	23/18	M	Ile170Val	Homozygous	22.54	29.9
	18/17.8	M	Thr162Ile	Homozygous	8.08	35.27
	14/18	F	Thr162Ile	Homozygous	6.91	23.75
	24.5/18	F	Thr162Ile	Heterozygous	20.81	23.75
Liraglutide	22.9/18.2	F	Thr162Ile	Heterozygous	4.89	5.61
Orlistat	20.5/19.5	M	Ile170Val	Homozygous	–0.91	10.29
	12/14.5	M	Thr162Ile	Homozygous	–4.62	–4.1

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AEP165

Circulating microRNAs as predictive tool of the effectiveness of lifestyle intervention for weight loss

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Background and aims
Lifestyle modifications based on diet and exercise are common strategies for the treatment and prevention of obesity and related comorbidities. However, not all patients respond equally to similar weight loss intervention which compromise patient adherence. Strategies for predicting the individual response are required for improving intervention efficiency by personalized recommendations. microRNAs (miRNAs), small RNA particles which regulates gene expression, has been detected in the circulation and proposed as biomarkers for disease and treatment response. However, there are few studies analyzing the usefulness of circulating miRNAs (c-miRNAs) as predictive biomarkers for the response to lifestyle modifications. Furthermore, c-miRNAs has not been specifically analyzed regarding interventions based on Mediterranean diet, which has been associated with higher health-related quality of life. Thus, the aim of this study was to analyze the relationship of the response to hypocaloric Mediterranean diet and promotion of physical activity with c-miRNAs previously associated with Type 2 Diabetes (T2D) and obesity.
Material and methods
Obese subjects (BMI > 30 kg/m^2; n = 60) underwent a hypocaloric Mediterranean diet together with increased physical activity during 1 year and c-miRNA levels as well as biochemical and anthropometric parameters were determined before and at year 1. Participants were classified according to their 1-year weight loss in low-responders (LR) and high-responders (HR).
Results
There was a significant improvement in anthropometric and biochemical variables after intervention, together with significant modification in miR-150 levels. HR subjects had lower baseline miR-130a and miR-150 levels than LR group (P < 0.05). There were positive and significant (P < 0.05) correlations between baseline miR-130a levels and weight at year 1; baseline miR-150 levels and HbA1c and triglyceride levels at year 1; baseline miR-142–3p and weight, BMI and glucose levels at year 1. In a lineal regression model baseline miR-150 levels were independently associated with weight loss at year 1. Notably, In silico enrichment analyses of miRNA target genes showed an involvement in adiposity-related and metabolic pathways.
Conclusion
c-miRNAs might be predictive biomarkers for the interindividual response to dietary intervention based on Mediterranean lifestyle.

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AEP166

The ecology of the microbiome in children with obesity is associated to insulin resistance anddiet composition

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Introduction
In the pediatric population, the progression of obesity-related diseases can be delayed or prevented through lifestyle changes, including the promotion of a Mediterranean-like dietary (MD) pattern.
Objective
We aimed to evaluate the gut microbiome ecology in relation to dietary and clinical parameters in the pediatric subjects with obesity recruited at baseline in a protocol on an educational training to MD.
Methods
A total of 55 subjects (6 and 18 years) with obesity, diet naïve or with failure to a previous weight loss program were recruited. We collected auxological, metabolic, nutritional parameters (KIDMED score; IDEFICS food frequency questionnaire), and stool samples. DNA was extracted directly from 0.25 g of stool using the Power SoilKit. DNA was amplified with primers for the V3 and V6 regions of 16S rDNA tagged with Multiplex Identifier sequences using Microbiota Solution B Kit optimized for Illumina Miseq sequencing. Raw FastQ sequences were analyzed using MicrobAT Software. Statistical analyses were performed using R software.
Results
All the 55 subjects showed a Bacteroides enterotype: 38% Bacteroidetes, 34% Firmicutes, 22% Unclassified Bacteria, 4% Actinobacteria, 1% Proteobacteria. At baseline, clinical and metabolic characteristics were homogeneous among children while microbial communities associated with the different subjects showed statistically significant differences according to age, Tanner stage considering sex, fasting insulin levels, fasting insulin resistance (HOMA-IR 95° percentile), percentage of carbohydrates, and fiber intake with the diet. In particular, considering HOMA-IR, *Bifidobacterium pseudocatenulatum*, unclassified Faecalibacterium, Bifidobacterium sp., Unclassified Sutterella, and unclassified Blautia were correlated with higher insulin resistance while *Dialister invisus* and Barnesiella sp. were associated with lower insulin resistance. Moreover, we observed *Bacteroides dorei, Bacteroides vulgatus*, Unclassified Ruminococcaceae, and unclassified Faecalibaterium associated with a higher carbohydrate intake. Finally, with a greater daily intake of fibers (> 8.5 g/1000 Kcal) we observed a decrease in Unclassified Faecalibacterium and an increase in *Ruminococcus bromii, Gemmiger fomicilis*, and Prevotella sp.
Discussion
These preliminary results highlight as diet, insulin sensitivity, and microbiome are strictly related also in children with obesity. We identified several bacterial groups not previously described in obesity. These findings are of importance for clustering patients and studying tailored dietary programs.

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AEP167

Amniotic membrane treatment of an oxidative stress murine chronic diabetic wound model

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Background
To date, available animal models have failed to replicate the complex pathophysiology of chronic diabetic wounds. In a recent study we administered a regimen of antioxidant enzyme inhibitors (AIE) to develop a reliable and effective murine model. Here we use this model to test the efficacy of an amniotic membrane (AM) scaffold.
Methods
30 db/db mice received a pre-established AIE regimen and a 1 × 1 cm^2 full thickness skin wound was excised on their dorsum. The wounds of 15 mice were covered with AM and occlusive dressing (AM group). The remaining 15 received only occlusive dressing (Blank group). The wounds were photographed on day 0, 10, 14, 21 and 28 and mice were sacrificed at various time points with the tissue harvested for analysis.
Results
Histologically, the mice in the AM group had higher wound bed thickness, collagen deposition and keratinocyte proliferation than the Blank mice. The amniotic membrane appeared to improve the vascularization of the wound, both in terms of density and maturity of the vessels. Leucocyte infiltration was comparable between the groups and the wound healing rate of the AM group was similar to the untreated mice.
Conclusions
The AIE regimen arrested the wounds in the inflammatory stage of healing while treatment with amniotic membrane offers promising potential. Although the wound healing rate between the two groups was comparable, the scaffold improved the overall quality of the wound elucidating the mechanisms of function of the scaffold on chronic wound healing. Better understanding of the mechanisms of healing of chronic wounds will be instrumental for the development of more effective treatments.

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AEP168

Use of the thrombolysis in myocardial infarction risk score for heart failure in diabetes in a type 2 diabetes mellitus outpatient population

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Background
Type 2 Diabetes Mellitus (T2DM) and Heart Failure (HF) are two directly related diseases associated with considerable morbimortality. The prevalence of HF in T2DM populations is up to 20%, 4 times higher than the general population. Additionally, health-related quality of life, hospitalizations for HF (HHF) and mortality risk are more common when both are present. Hence, HHF risk assessment in T2DM patients may lead to prompt preventive interventions.
Aim
To assess the stratification accuracy of the Thrombolysis In Myocardial Infarction (TIMI) Risk Score for Heart Failure in Diabetes (TRS-HFDM) for predicting hospital admissions for HF in a T2DM adult outpatient population.
Material and methods
We conducted a cross-sectional study in T2DM adult outpatients between December 2015 and December 2020. The TRS-HFDM, a novel, practical and validated risk score, was applied for prediction of hospital admissions for HF. It comprises prior HF (yes = 1), history of atrial fibrillation (yes = 1), CAD (yes = 1), estimated glomerular filtration rate (yes = 1), and urine albumin-to-creatinine ratio (microalbuminuria [> 30 mg/g] = 1; macroalbuminuria [> 300 mg/g] = 2). The TRS-HFDM ranges from 0 to 7 points, where 0, 1, 2 and ≥ 3 points are graded as 'low risk', 'intermediate risk', 'high risk' and 'very high risk'. ROC curve analysis was used to find the most appropriate TRS-HFDM cutoff point for the highest possible combination of sensitivity and specificity in predicting the primary endpoints: emergency room (ER) visits and HHF. Mann-Whitney U test was performed to compare TRS-HDFM scores between patients with and without the aforementioned outcomes. Binary logistic regression was applied to characterize the relationship between these variables.
Results
This study encompassed 353 T2DM patients, 197 women (55.8%), with a mean age (SD) of 73 (9) years. HF was present in 109 (30.9%) patients. 48 (13.6%) individuals had ≥ 1 ED visits and 36 (10.2%) ≥ 1 HHF. A TRS-HFDM cutoff of ≥ 3 showed the best combination of sensitivity/specificity in predicting ER visits (97.9% and 76.1%, respectively) and HHF (100% and 73.5%, respectively). There was a statistically significant increase in scores between patients who had those outcomes and those who did not (ER visit: OR = 2.835, $P < 0.001$; HHF: OR = 2.886, $P < 0.001$).
Discussion and conclusions
Our analysis proposes a cutoff of ≥ 3 to identify T2DM outpatients at risk for hospital admissions for HF. Greater absolute reductions are expected if early patient-tailored protective interventions take place in higher scores. Therefore, this simple tool may help in diminishing morbimortality in T2DM outpatients.

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AEP169

Glycemic control and complication rate through pregnancy and thirteen-years post-partum in women with microalbuminuria (type 1 diabetes T1DM)

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The aim of the present work was to assess the degree of glycemic control and complications rate through pregnancy and thirteen-years post-partum in women with microalbuminuria (T1DM).

Materials and methods
In total 191 patients with T1DM were enrolled in the study. Based on albuminuria levels in the 1st trimester women were separated into 2 groups (Gr.). Gr.1 – 116 women with normoalbuminuria, Gr.2 – 75 women with microalbuminuria. Preconception care was performed in 46.5%- Gr.1 and 57.3% -Gr.2. Strict metabolic control was maintained and fetal surveillance was performed throughout the pregnancy. Repeated examinations –13 years post-partum.
Results
At entry HbA1c(%) levels for Gr.1 and 2 were: 7.42 (0.15) and 7.25 (0.14); by the end of the pregnancies they statistically decreased in both groups (Gr.1- $P = 0.000$, Gr.2 – $P = 0.000$). At entry percent (%) of retinopathy for Gr.1- 8.6 and Gr.2–20.0; by term the percent has not increased. The percent of women with macroalbuminuria increased, together with the growth of gestational age. By term macroalbuminuria was observed in 2.5% (Gr.1) and in 14.6% (Gr.2) of patients ($P = 0.0094$, OR-5.67). In Gr.1 percent of pre-eclampsia and preterm deliveries before 37 weeks of gestation was lower, than in Gr.2 (pre-eclampsia – $P = 0.0064$, OR –4.64; preterm deliveries $P = 0.048$; OR –2.8). Perinatal mortality was observed in Gr.1 – 0.8% and in Gr.2 – 6.6% of women ($P – 0.006$, OR – 7.73). Repeated examinations 13 years post-partum showed that HbA1c levels were statistically higher, than at the end of pregnancy: Gr.1–7.7 (0.41) ($P = 0.0002$), Gr.2 – 8.05 (0.26) ($P = 0.000$). Repeated examinations showed that percent of retinopathy, micro and macroalbuminuria, increased in both groups. Besides, patients from Gr.2 had statistically higher complications rate, than patients from Gr.1 (retinopathy – $P = 0.0002$, OR – 3.45; microalbuminuria – $P < 0.0001$, OR – 10.2; macroalbuminuria – $P = 0.0032$, OR- 3.03). Chronic kidney disease (stage 3–6) were observed in 36 patents. Nine patients from Gr.2 are on regular hemodialysis, and in two patient kidney transplantation was performed.
Conclusion
If microalbuminuria was detected in the 1st trimester, the risk of preeclampsia increased 4.6 times, the risk of preterm delivery increased 2.8 times and risk of perinatal mortality increased 7.3 times, compared to patients with normoalbuminuria. In both groups glycemia control deterioration was observed thirteen years post-partum. The higher complication percent was found if pregnancy proceeded with microalbuminuria, the risk of retinopathy increased 3.4 times and the risk of CKD increased 3 times compared to patients with normoalbuminuria.

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AEP170

Impact of social isolation and quarantine on the course of diabetes mellitus and its complications during Covid 19 pandemic in Adjara Region Country of Georgia

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Background
SARS-CoV-2 infection produces greater morbidity and mortality in people with cardiovascular disease, diabetes, and obesity. Quarantine and social distancing are necessary measures to prevent the virus from spreading but also lead to elevated levels of loneliness and social isolation. The aim of the study was to research impact of Social isolation and quarantine on compensation of diabetes and on progression of its complications.
Methods
A specific questionnaire was developed by us and was launched on the Google platform. In this Survey was participated 16 endocrinologists and 22 family and general practice doctors.
Resalts:
In the clinics patients application decreased by 79.9%; in 64.8% patients for communication was used mobile phone and social media. New diabetes cases manifestation was in 58.4%; HbA1c 6% to 23.5%, 7%-26.5%, 8%–41.2% and up 8.8% ketoacidosis (DKA) –4%; Hypoclicemia-22% anxiety and fear were observed on 82% of patients . 11.5% of ambulatory patients was switched on insulin therapy; stable angina pectoris attack increased by 35.5%, hospitalization MI was needed in 41.5%; BP levels increased in 88.2% of patients, high blood pressure hospitalization was declared in 50% cases, HF –35.5%, Nephropathy was complicated –4.9%, deterioration of vision was in 55.9% of patients; weight gain in 97.1%; cigarette consumption has increased on 35.3%; alcohol- 29.4%; Physical activity decreased in 29.8%.
Conclusion
According to doctors survey, social isolation and quarantine in diabetes reduces the availability of medical care, increases the weight of the patient, blood pressure, causes bad cigarette habits, increases alcohol consumption, and also worsens the emotional background of patients, which leads to the development of pre-existing cardiovascular diseases and other complications risk. The issue requires additional large-scale research.

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AEP171

Risk factors of cardiovascular autonomic neuropathy in patients with prediabetes and coronary artery disease

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Background
Cardiovascular autonomic neuropathy (CAN) is a chronic complication associated with high risk of cardiovascular morbidity and mortality either in patients with diabetes mellitus and prediabetes. However, risk factors of CAN in patients with prediabetes and coronary artery disease (CAD) was not fully investigated.
Aims
The aim of this study was to investigate risk factors of CAN in patients with prediabetes and CAD.
Materials and methods
We examined 32 patients with prediabetes and angiography confirmed stenosis of coronary arteries, 20 males and 12 females (aged 61.44 ± 1.92 years, HbA1c – 5.87 ± 0.1%) (data are presented everywhere as mean ± SEM). All patients were performed cardiovascular autonomic reflex tests (CARTs) by Ewing. The diagnosis of CAN was confirmed in patients with 2 and more positive tests. The statistical analysis was performed using SPSS statistical package version 25.0 for Windows.
Results
CAN detected by 2 abnormal tests of CARTs was diagnosed in 40.6% patients with prediabetes and CAD, by 3 abnormal tests – in 43.8%. We found positive correlation between the total score of CARTs: and levels of total cholesterol, ($r = 0.44$, $P < 0.05$), fasting insulin, ($r = 0.41$, $P < 0.05$), HOMA-IR ($r = 0.46$, $P < 0.01$), heart rate ($r = 0.4$, $P < 0.05$), and negative correlation with glomerular filtration rate, ($r = –0.39$, $P < 0.05$). We found that CAN diagnosed by 2 abnormal tests of CARTs had positive correlation with fasting glucose, ($r = 0.36$, $P < 0.05$) and HbA1c ($r = 0.4$, $P < 0.05$), but if there was no correlation of CAN detected by 3 abnormal tests of CARTs with these parameters.
Conclusion
CAN is the common complication of prediabetes and there are some risk factors for its development revealed in our study.

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AEP172

NaKATPase activity regulated by glycemia level in patients with DM

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Introduction
NaKATPase is membrane bound enzyme, necessary for maintenance of the cell potential and volume, ion flow, neuronal signal transduction. Previous studies showed decreasing of its activity in patients with diabetes mellitus (DM). Mechanisms regulated enzymes activity in DM is not clear yet. We proposed that glycemia is a main regulator of NaKATPase activity in erythrocytes at the DM.
Material and methods
In 76 patients with DM, 31 with DM type1 and 36 with DM type 2. In observed persons blood glycemia, HbA1c, blood plasma tryglycerides,

cholesterol level were measured. Erythrocytes separated from blood, washed out with buffer saline. NaKATPase activity measured by differences of the inorganic phosphorus level in media after incubation with ATP.
Results
Erythrocytes NKATPase activity were decreased by 25% in patients with DM1 and 29.9% ($P < 0.05$) in patients with DM2 ($P < 0.05$) compared with healthy subjects. Enzymes activity were not depends from age and gender in person younger than 40 years old. There were no any differences in enzymes activity between patients with DM type 1 and type 2. Blood glycemia, HbA1c, tryglycerides and cholesterol levels were significantly higher in patients with DM in compare with healthy subjects and suggest about metabolic disturbances. Erythrocytes NaKATPase activity shown negative correlation with glycemia and HbA1c level. Interestingly, NaKATPase activity significantly increased in those who achieved better glycemic control, whereas remain unchanged in those with poor glycemia.
Conclusion
Erythrocytes NaKATPase activity is decreased in patients with DM type 1 and 2, and negatively depends from glycemia and HbA1c level. Glycemia is an independent factor in regulation of erythrocytes NaKATPase activity.

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AEP173

Hirata's disease (Insulin autoimmune syndrome) in an Egyptian female patient: A case report

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Introduction
Insulin autoimmune syndrome (IAS), is rare cause of hyper-insulinemic hypoglycemia due to production of autoantibodies against the endogenous insulin in persons not formerly received insulin with no evidence of pancreatic lesions. Most described cases were in Asian peoples and this is the first case reported from Egypt.
Case report
A 64-year-old Egyptian female presented with repeated postprandial hypoglycemic attacks, approximately three hours after food ingestion, which improved on ingesting sweets. On one occasion, the patient lost her consciousness and was transferred to the nearest hospital where her plasma glucose was 26 mg/dl and she regained her consciousness after IV Dextrose 25%. Then, she was referred to our department for further assessment. She has no past history of chronic illness, nor family history of similar condition. She denied insulin or oral hypoglycemic drugs intake. Dietary history showed high intake of simple carbohydrates to overcome her frequent hypoglycemia. On physical examination: she was an obese female with BMI 38.9 kg/m^2, blood pressure 125/70 mmHg and heart rate 84/min with no signs of insulin resistance and her chest, abdomen, cardiac and neurological examination was unremarkable. Laboratory findings, including liver, kidney, adrenal, thyroid and glycemic profile were all normal except for elevated HbA1c (was 6.2%) and IGT (2-hpp glucose 186 mg/dl). She underwent prolonged (180-min) oral glucose tolerance test (OGTT) using 75 gm glucose. The patient began to develop hypoglycemic symptoms at 180-min of OGTT, during which her simultaneous plasma glucose was 49 mg/dl, serum Insulin > 1000 µiu/ml and C-peptide 17.22 ng/ml. These results were consistent with hyper-insulinemic hypoglycemia. Serum sulfonylurea drug screen was negative. Contrast-Enhanced triphasic CT abdomen was unremarkable with no evident of any pancreatic lesions. anti-insulin autoantibodies were found to be extremely high (> 100 u/ml). thus, the diagnosis of IAS was established. The patient was instructed to eat small frequent meals of low glycemic index. azathioprine 50 mg twice daily plus Prednisolone 60 mg were commenced. Her hypoglycemic attacks had completely subsided after two months of therapy, then the prednisolone dose was reduced gradually over the next three months with no recurrence of hypoglycemia, and repeated serum insulin and insulin antibodies showed a continual decline and her insulin autoantibodies became negative after 3 months of therapy.
Conclusion
IAS should be considered in any patient with hyperinsulinemic hypoglycemia, particularly if no detectable pancreatic or extrapancreatic neoplasm.

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AEP174

Severe postprandial hypoglycemia as a possible sequel of COVID-19

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Introduction
COVID-19 is an evolving disease and its clinical picture is constantly being updated. Severe hypoglycemia has not been usually recognized as a COVID-19 symptom (except when caused by hydroxychloroquine toxicity) but in our patient it has been apparently triggered by the disease.
Methods
Review of the patient's records and the relevant literature.
Clinical case
A 55 year-old woman (a licensed nurse) was referred to our Endocrinology Clinic for severe, frequent, invalidating episodes of hypoglycemia. She had primary hypothyroidism, correctly substituted with levothyroxine, and a history of gastroesophageal reflux, treated with a Nissen fundoplication the previous year, and was asymptomatic. In April 2020 she was admitted in our Hospital for severe SARS-CoV-2 respiratory infection and was discharged with residual emphysema. Immediately after the discharge she had almost daily episodes of postprandial hypoglycemia, occasionally severe with loss of consciousness, and she was admitted to our Emergency Room, with plasma glucose 40 mg/dl but normal insulin and C-peptide (respectively 9.34 µ/u/ml and 3.22 ng/ml) in the lab tests. An abdominal CT scan did not suggest insulinoma or other abnormal mass. The 72-hour fasting test did not suggest insulinoma either, and the 24-hour Holter monitoring was near normal, not suggesting triggering of the symptoms by arrhythmia. A gastric emptying scintigraphy did not suggest dumping syndrome. In our Clinic the patient was trained in a fractionated diet with servings of 30–40 g of complex carbohydrates 4–5 times daily, and in the use of a flash glucose monitoring device with alarm capacity. She was able to resume work but still had frequent non severe hypoglycemia during the afternoon and evening, but rarely in the night. Acarbose 50 mg was added at lunchtime, initially with minor intolerance symptoms (occasional meteorism) but the variability of her glucose profile was largely improved and the episodes of hypoglycemia became milder and infrequent (less than 1/15 days). The follow-up lab tests (December 2020) were: Glycemia 82 mg/dl, HbA_{1C} 5.3%, plasma insulin 8.32 µ/u/ml, proinsulin 1.6 pmol/l, C-peptide 2.77 ng/ml, normal free T4 and TSH.
Conclusion
Although postprandial hypoglycemia is frequent after gastric surgery, including fundoplication, there was a clear-cut temporal coincidence in our patient between the COVID-19 disease and the triggering of the hypoglycemic episodes, suggesting a causative or unmasking relationship.

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AEP175

Increased anxiety, depression and body dysmorphia in women with polycystic ovary syndrome: Results from blue morpho survey

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Background
Polycystic Ovary Syndrome (PCOS) is a common reproductive, endocrine and metabolic disorder. The UK National Institute of Health and Care Excellence (NICE) recommends evaluating emotional wellbeing in women with PCOS. Therefore, we conducted a health service evaluation to assess emotional wellbeing.
Methods
We invited women with PCOS via social media to complete an online survey in September 2020, supported by PCOS support groups: PCOS Vitality and Verity. The survey included questions on demographics and validated questionnaires including the Hospital Anxiety and Depression Scale (HADS; score 8–10 borderline; score ≥ 11 cases of anxiety and depression, respectively), Body Image Concern Inventory (BICI; score ≥ 72 suggestive of body dysmorphic disorder, BDD) and Beliefs About Obese Persons Scale (BAOP; higher score suggestive of weight bias), and Female Sexual Function Index (FSFI; higher score suggestive of psychosexual dysfunction). The results are reported as median and interquartile ranges (IQR).
Results
A total of 502 participants with self-reported PCOS completed the survey (48.4% were between 26–35 years of age; 74.1% identified as White British). The prevalence of anxiety and depression was 55.4% and 22.5%, respectively (HADS anxiety 11(8–14); depression 7(4–10)). According to BICI scores, 49.6% (n = 249) of women with PCOS suffered from body dysmorphic disorder. Scores for BAOP and FSFI questionnaires were 32(27–35) and 19.8(8.0–25.2), respectively. As expected, women with self-reported mental health diagnosis had higher HADS scores for anxiety (12(10–15) vs 10(7–13); P < 0.001) and depression (8(5–12) vs 6(2.25–8); P < 0.001). They also had higher body image concerns (BICI 74(64–82) vs 68(55.25–77.75); P < 0.001) and probable BDD (152 (58.9%) vs 97 (40.4%); P < 0.001). Presence of mental health diagnosis did not have an impact on perceived weight stigma (BAOP 32(28–36) vs 31(27–35); P = 0.346) or psychosexual function (FSFI 19.3(6.5–24.4) vs 20.6(11.3–26.1); P = 0.143). Borderline depression was more common in white ethnic women compared to non-white (n = 108 (25.3%) vs 74 (98.7%); P = 0.049). Based on ethnic group, results showed no difference in anxiety, depression, impact on body image concern, weight stigma and psychosexual function. Women with BDD had higher anxiety (HADS 13(10–15) vs 10(7–12.5)); P < 0.001), depression (HADS 8(6–11) vs 6(3–8.5); P < 0.001) and weight bias (BAOP 32(28–36) vs 31(26–35); P = 0.016). BDD did not impact psychosexual function (FSFI 19.8(6.8–24.8) vs 19.85(9.7–25.7); P = 0.453).
Conclusion
The study showed a high prevalence of anxiety, depression and BDD in PCOS, which was more severe in women with mental health disorders. It is important to address mental health and wellbeing in women with PCOS as part of their clinical care.

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AEP176

COVID-19 and diabetes: Impact on emergency department demand by diabetic patients. experience from a portuguese center

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Introduction
COVID-19 is an emerging disease caused by the new coronavirus (SARS-CoV-2) that has overburdened healthcare worldwide. In Portugal, schedule appointments were cancelled, postponed or changed to tele-consultation. The objective of the study is to assess the impact of the pandemic on the use of Emergency Department (ED) by diabetic patients.
Material and methods
Retrospective monocentric study of the ED demand by diabetic patients from the 1st March to the 30th of June of 2020, compared to the same period in 2019. Data collection was performed using discharge diagnosis according to ICD-9, and divided in four different groups: 'decompensated diabetes', 'diabetes complications', 'severe diabetes complications'. Chi-Squared test was used to compare the ED demand by the different diagnosis.
Results
The demand for acute care by diabetic patients diminished by 36.3% in 2020 compared to 2019. Cases of hypoglycemia and decompensated diabetes mellitus decreased in 2020 compared to 2019 (41.2% vs 33.1%, P = 0.137; 25.5% vs 21.5% in 2020, P = 0.409). On the other hand, complications of diabetes and serious complications of diabetes increased in 2020 (25.5%% vs 36.2%, P = 0.037; 7.8% vs 9.2%, P = 0.655). 23.8% of patients were hospitalized in 2020 vs 18.6% in 2019 (P = 0.251).
Conclusion
There was a decrease in the demand for urgent care by diabetic patients. However, in 2020 patients had more severe complications and a greater need for hospitalization. This is in line with other published studies. Long-term follow-up is needed to conclude if interruption in healthcare assistance has resulted in worsening of diabetic patients' health.

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AEP177

ER stress and toxic soluble misfolded proteins are present in diabetes and diabetic ketoacidosis in a sex dependent-manner

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Introduction
Diabetes, a metabolic disease, is responsible for 1.6 million deaths each year. Type 2 diabetes (T2D) is the most common type (90%) that usually occurs in adults. Type 1 diabetes (T1D) an autoimmune disorder, affects more children and adolescents. Diabetic Ketoacidosis (DKA) is the most common acute cause of morbidity and mortality in youth with T1D. Soluble protein oligomers (SPOs), are a class of misfolded toxic proteins released during endoplasmic reticulum (ER) stress and unfold protein response (UPR). Hyperglycemia leads to ER stress and activate the UPR pathway. We hypothesized that SPOs are increased in the plasma from patients with DKA. Also, ER stress induce SPO release and/or vice versa.
Methods
By using the dot blotting, we measured SPOs in plasma from young (8–18 years old) male (n = 4) and female (n = 6) DKA patients in three different time points: 6–12 hours of treatment; 2–3 weeks; and 3 months post-DKA correction. Mechanistically, we evaluated if vascular smooth muscle cells (VS MCs) from the tibial artery of a 45-year-old male with T2D in normal glucose, or human aortic endothelial cells (HAEC), from a 33 year old health woman, submitted to high glucose concentrations (35 nmol/l) for 48 hours, presents with ER stress and/or SPOs in the media. Some VS MCs and HAEC were treated with ER stress inhibitor (4-PBA 2 mmol/l), SPOs inhibitor (K01–162, 10 μmol/l), or vehicle (DMSO) for 48 hours.
Results
SPOs were present in plasma from patients with DKA at all-time points. Interestingly, SPOs levels increased in a time-dependent manner in females, but not males. On the other hand, SPOs were not detected in the media of VS MCs or HAEC patients. However, the C/EBP Homologous Protein (CHOP), a marker for ER stress, was expressed in VS MC from patient with T2D, and the treatment with ER stress inhibitor, PBA, but not SPOs inhibitor, decreased its expression (A.U.: Vehicle: 55.3 ± 5 vs . PBA: 40.1 ± 5* vs . K01–162: 64.3 ± 9; *P = 0.04 vs . Vehicle). CHOP was not detected in HAEC after high glucose treatment.
Conclusion:
In diabetes there is an accumulation of SPOs that may contribute to the systemic inflammation observed in young patients with DKA. Although there was ER stress in VS MC from T2D, SPOs were not detected in the supernatant from these cells nor HAEC treated with high glucose. More studies are necessary to evaluate the relation between SPOs, ER stress and vascular dysfunction in diabetes.

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AEP178

High prevalence of 1st trimester gestational diabetes mellitus in polish women is accompanied by insulin resistance similar to pcos cohort

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Back ground
Both pregnancy and polycystic ovary syndrome (PCOS) constitute insulin-resistant states, while gestational diabetes (GDM) is associated with adverse pregnancy outcomes. Though screening for GDM is typically performed later in pregnancy, some women demonstrate significant insulin resistance (IR) and develop GDM even in 1st trimester. We have endeavoured to compare surrogate IR indices in 1st trimester pregnant women and in women diagnosed with PCOS according to the Rotterdam consensus criteria.
Patients and methods
We performed 75 g Oral Glucose Tolerance Test (OGTT) with insulin measurements in 106 healthy 1st trimester pregnant women at 9.9 ± 2.6 weeks of gestation and in 418 women with PCOS. We also assessed the prevalence of GDM according to the IADPSG and WHO (1999) criteria.
Results
Despite lower BMI (24.93 ± 5.43 kg/m^2 versus 26.53 ± 6.83 kg/m^2, P = 0.027) pregnant women had either similar (QUICKI, Belfiore index, $Stumvoll_{0–120\_min}$) or greater IR than women with PCOS (e.g. HOMA-IR 3.85 ± 6.11 versus 2.64 ± 2.04, P = 0.002, and $Stumvoll_{demographics}$ 0.1054 ± 0.045 versus 0.085 ± 0.58, P = 0.003), while only Matsuda index demonstrated less IR in pregnant women. Though correlation between IR indices in pregnant women was highly significant, it showed marked variability ranging from r = 0.334 (HOMA-IR versus Belfiore index) to r = 1.0 (HOMA-IR versus QUICKI). This was accompanied by high prevalence of GDM (14.2% and 9.4%, IADPSG and WHO criteria, respectively). Women with GDM diagnosed according to IADPSG criteria demonstrated greater IR than pregnant women without GDM. In women with GDM diagnosed according to WHO (1999) criteria these differences were visible only for OGTT-derived IR indices (Belfiore, Matsuda and Stumvoll0–120 index).
Conclusions:
Depending on the choice of IR indices healthy 1st trimester pregnant women demonstrate either similar, or greater IR than women with PCOS and this is accompanied by high prevalence of early GDM. It remains to be established whether GDM screening should be performed in the 1st trimester.

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AEP179

Mother's education with type 1 diabetes and the risk of some neonatal outcomes

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Aim
To evaluate some neonatal outcomes, depending on the level of education of the mother with type 1 diabetes (T1DM).
Materials and methods
A retrospective single-center study was carried out among 430 children from mothers with T1DM, who were born in 2015-2020 years. Taking into account the level of education of mothers, newborns were divided into 3 observation groups. The first group (Gr1) consisted of 70 children from mothers with low education, the second (Gr2) - 204 from mothers with intermediate education, the third (Gr3) - 156 from women with high education. The experience of diabetes in mothers Gr1 was 11(6-16) years, Gr2 - 13(7-18) years, Gr3 - 11(6.5-17.5) years (P > 0.05). Physical development of newborns was assessed using the Intergrowth-21st.
Results
The body weight of newborns of Gr1 was 3320(2800–3730) g, Gr2 – 3550(3000–3945) g, Gr3 – 3585(3150–3885) g ($P_{1–2}$ = 0.02, $P_{1–3}$ = 0.01, $P_{2–3}$ = 0.74). Z-score body weigh – 1.65(1.08–2.41), 1.63(0.89–2.45), 1.61(0.90–2.49) (P > 0.05). There were 45.7% of preterm infants among newborns Gr1, which was statistically significantly higher than in Gr2 (27.0%) and Gr3 (24.4%). Large for gestational age (LGA) newborns among full-term newborns in Gr1 were 50.0%, Gr2 – 59.7%, Gr3 – 54.9% (P > 0.05), among premature babies 78.1%, 74.9% and 79.1% (P > 0.05). The newborns from mothers with T1DM and intermediate education, compared with children from women with low education, had lower chances of prematurity (OR = 2.28, 95% CI 1.62–3.21), chances of respiratory support as mechanical ventilation at the 5th minute of life due to the respiratory distress syndrome and a low Apgar score (OR = 1.55, 95% CI 1.00–2.32). Newborns from mothers with T1DM and high education, in comparison with children from women with low education, also had lower chances of preterm birth (OR = 2.61, 95% CI 1.79–3.81), mechanical ventilation at the 5th minute of life (OR = 1.52, 95% CI 0.98–2.36).
Conclusion
The influence of maternal education on the outcomes of newborns from mothers with T1DM in Belarus has been established. The low level of education of the mother with T1DM is an important factor associated with some adverse neonatal outcomes (prematurity, mechanical ventilation at the 5th minute of life). The mother's education level did not affect the birth rate of LGA newborns.

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AEP180

Vitamin B12 status and maternal-fetal outcomes among women with gestational diabetes

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Introduction
Vitamin B12 (vB12) deficiency has been associated with a plethora of hematologic, neurologic and metabolic abnormalities. In pregnant women, several studies have demonstrated an association with a greater maternal body mass index (BMI), maternal and offspring insulin resistance, gestational diabetes mellitus (GDM) and even later type 2 diabetes.
Aim of the study
Evaluation of maternal and fetal outcomes of pregnant women with GDM with and without vB12 deficiency.
Material and methods
Retrospective study based on data from 200 pregnant women with GDM evaluated between 2018 and 2019 that had B12 levels measured at the initial observation. It was considered vB12 deficiency if levels < 188 pg/ml.
Results
We considered two groups: Group 1 (n = 132) with vB12 within normal range; Group 2 (n = 68) with vB12 deficiency. Serum samples were collected at 27.6 ± 8 weeks of pregnancy. Mean vB12 level in Group 2 was 134 ± 106.2 pg/ml. GDM was diagnosticated in 46% vs 36.5% during the first trimester and in 54% vs 63.5% during the 2nd trimester. There was no statistical difference between groups in terms of age (33.3 ± 5.4 vs 33.5 ± 4.7years), initial HbA1c (5.4 ± 0.8% vs 5.3 ± 0.6%), HOMA-IR (3.1 vs 3.3), hemoglobin level (11.6 ± 1.6 vs 11.5 ± 2.1 g/l), percentile of fetal abdominal circumference in 3rd trimester (58 ± 19.5 vs 55 ± 22), gestational hypertension (3.7% vs 4.4%), pre-eclampsia (2.2% vs 1.4%), hydramnios (8.3% vs 8.8%) and pre-term delivery (4.5% vs 5.8%). All patients were already medicated with iron plus folic acid whereby deficiencies were not detected. The mean gestational age of delivery was 38 weeks without differences between groups. Group 2 had higher pregestational BMI (28.1 ± 7 vs 30.8 ± 5 kg/m^2; P = 0.03), 3rd trimester BMI (32.1 ± 3 vs 34 ± 6 kg/m^2; P = 0.04), higher rate of infectious complications in the postpartum period (0.7% vs 6.3%; P = 0.04) and tendency for macrosomia (4.3% vs 7.3%; P = 0.06). Although the rate of cesarean section was similar between groups (40% vs 36.7%, P = ns) the need to perform emergent cesarean section was higher in Group 2 (13.6% vs 60%; P = 0.01). Regarding the neonatal morbidity, the incidence of phototherapy due to hyperbilirubinemia was similar. Concerning postpartum reclassification, no statistical significance was observed between groups (diabetes mellitus in 6% for Group 1 and 9.7% for Group 2).
Conclusions
Pregnant women with GDM and vB12 deficiency had higher prevalence of obesity, emergent cesarean section and maternal complications in the postpartum period. More studies with a larger number of participants are needed to validate these results and, eventually, to find new associations with vB12 deficiency.

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AEP181

Glucagon levels in women with Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disease that manifests itself in the gradual loss of cognitive and behavioral functions. In humans, glucagon is processed in pancreatic alpha cells located next to insulin-secreting beta cells, suggesting a local interaction. Glucagon is also produced in the intestinal L-cells and in small amounts in the hypothalamus. The main function of glucagon is to counteract the effects of insulin and thus maintain balanced blood glucose level. In addition, glucagon also has the same neuroprotective effect as insulin on lowering glutamate in the central nervous system in diabetic rats, although both hormones have the opposite effect on glucose levels. Glucagon reduces glutamate in the central nervous system, reduces neuronal cell damage and improves neurological scores in mice. This study focused on glucagon levels in non-diabetic women with AD compared to controls, as well as on the changes of glucagon levels after five years in controls.
Methods
We evaluated the fasting metabolic parameters and glucose tolerance in 70 controls (median of age 68.2 years) and 41 women with AD (median age 74.7 years), both groups without type 2 diabetes. A group of 37 controls was re-evaluated after 5 years. The data were processed by GLM ANOVA (Statgraphics 18 × 64).
Results
Women with AD and controls had a similar body composition (median BMI [kg/m^2]: 25.7 (22.6, 29.4) vs . 27.7 (24.3, 30.2); $P = 0.13$), insulin resistance (median HOMA R: 1.74 (1.44, 2.74) vs . 2.05 (1.4, 3.67), $P = 0.91$) and insulin secretion (median HOMA F: 114 (79.8, 173) vs . 103 (78.8, 149), $P = 0.1$). Women with AD and controls had the same fasting glucose (median glucose [mmol/l]: 5.1 (4.8, 5.3) vs 5.3 (5, 5.8); $P = 0.06$), but women with AD had lower levels of glycated hemoglobin (median HbA1c [%]: 37 (35.3, 38.8) vs . 38 (37, 40.3); $P < 0.01$). Compared to controls, women with AD had significantly higher glucagon levels (median glucagon [pmol/l]: 51.1 (46.1, 57.3) vs . 41.5 (38.8, 46.5); $P < 0.001$). Long-term follow-up (5 years) of controls showed a decrease in glucagon levels with increasing age ($P < 0.001$).
Conclusion
Glucagon levels in women with AD are not associated with glucose tolerance or diabetes. Patients with AD have the same fasting blood glucose as controls, and even lower glycated hemoglobin (a long-term indicator of glucose metabolism). Women with AD could be resistant to glucagon, or it is a consequence of the brain's protective mechanism. The grants: NV 18-01-00399, MH CZ-DRO (EU 00023761).

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AEP182

Glycemic control in patients with different types of diabetes mellitus in Ukraine

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Introduction
The aim of this study, which was conducted for the first time in Ukraine, was to analyze a glycemic control in patients with different types of diabetes mellitus (DM), including neonatal (ND) and maturity onset diabetes of the young (MODY) and changing their treatment after the results of genetic testing.
Materials and methods
The Ukrainian Pediatric Diabetes Register was established in 2002 and included 9471 children with type 1 DM (a prevalence of 1 in 800 for the pediatric population), 47 children with type 2 DM (a prevalence of 1 in 161270), 65 patients with ND (a prevalence of 1 in 116610) and 48 patients with MODY (a prevalence of 1 in 157910) in 2019y. We analyzed the glycemic control in patients depending on the type of DM, namely: type 1 DM ($n = 9471$), type 2 DM ($n = 47$). HbA1c was analyzed also in patients with ND ($n = 16$) with KCNJ11 and *ABCC8* variants and MODY ($n = 16$) with *HNF1A*/*HNF4A* and *ABCC8* variants before genetic testing and after 3 and 12 months of sulfonylurea (SU) treatment. To confirm the nature of ND and MODY, targeting next-generation sequencing (tNGS) of all known neonatal and monogenic diabetes genes was performed.
Results
According to the Register in 2019, in Ukraine the average age of children with type 1 DM was 11.5 ± 1.4 years, and the level of HbA1c was unsatisfactory (8.8v2.01%). The proportion of children who had ideal or optimal glycemic control (HbA1c < 7.5%) was the smallest (28.15%). The Register included also 47 children with type 2 DM with an average age of 16.2 [15.5; 18] years old and HbA1c level 6.7 [5.7; 7.9]%. All patients with ND and MODY with confirmed mutations in *KCNJ11*, *ABCC8* and *HNF1A*/*HNF4A* genes and unsatisfactory glycemic control discontinued insulin therapy (or other inappropriate treatment) and were transferred to SU, which lead to the significant improvement in glycemic control (decreasing of HbA1c level) after 3 months and 12 months of SU treatment ($P < 0.05$).
Conclusions
The glycemic control in patients with type 1 DM in Ukraine was unsatisfactory compared to ND and MODY patients with mutations in *KCNJ11*, *ABCC8* and *HNF1A*/*HNF4A* genes, who received pathogenetically justified treatment with SU drugs, as well as in type 2 DM patients.

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AEP183

Increase in PUFA and in protein intake leads to reduction of liver fat independently of weight loss in 12 months: the NutriAct trial

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Background
Long-term effects of an increase in unsaturated fatty acids and protein on changes in intrahepatocellular lipids (IHL) are still unclear. We aimed to explore the impact of changes in individual macronutrients on IHL changes within the NutriAct intervention trial over 12 months in middle-aged and elderly subjects (50–80 yrs) at risk for age-related diseases.
Design
In the NutriAct randomized controlled trial, the effect of a high-protein and high-UFA diet was compared to the dietary recommendations of the German Nutrition Society. Individuals who completed 3-day food records and had IHL data both at baseline and at month 12 were included in this study. Intake (E%) of each macronutrient was calculated and IHL was measured by proton density fat fraction spectroscopy. Associations between changes in macronutrients intake and changes in IHL were analyzed, including mediation analysis to identify the role of weight loss as a mediator.
Results
248 participants were included in the analyses (34% male, median age 66y). BMI and IHL improved in both intervention groups in 12 months (both $P < 0.01$) and differed significantly between groups ($P < 0.05$). Participants with higher increase in protein and PUFA intake and a greater decrease in carbohydrate intake showed a stronger improvement in IHL ($P < 0.05$). Changes in protein, carbohydrate and PUFA, and IHL improvement are mediated by BMI changes. Increase in protein ($P = 0.05$) and in PUFA ($P = 0.01$) intake was also directly associated to IHL improvement (not BMI change-mediated).
Conclusions
Increase in intake of protein and PUFA, and decrease in carbohydrates intake led to IHL reduction after 12 months in middle-aged and elderly subjects. While these effects are partially mediated by weight loss, there is also a direct effect between increase in protein (trend) and in PUFA and IHL improvement. These results give insight into the understanding of a high-UFA diet on IHL changes in a long-term dietary intervention.

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AEP184

Diabetes mellitus is associated with a higher relative risk for Parkinson's disease in women than in men

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Introduction
In general, the risk to develop Parkinson's disease (PD) is higher in men compared to women. Besides male sex and genetics, research suggests diabetes mellitus (DM) is a risk factor for PD as well. In this population-level study, we aimed at investigating the sex-specific impact of DM on the risk of developing PD.
Research design and methods
Medical claims data were analyzed in a cross-sectional study in the Austrian population between 1997 and 2014. In the age group of 40–79 and 80+, 235.268 patients (46.6% females, 53.4% males) with DM were extracted and compared to 767.681 non-diabetic controls (51.9% females, 48.1% males) in terms of risk of developing PD.
Results
Men with DM had a 1.46 times increased odds ratio (OR) to be diagnosed with PD compared to non-diabetic men (95% CI 1.38–1.54, $P < 0.001$). The association of DM with newly diagnosed PD was significantly greater in women (OR = 1.71, 95% CI 1.60–1.82, $P < 0.001$) resulting in a relative risk increase of 1.17 (95% CI 1.11–1.30) in the age group 40 to 79 years. In 80 +-year-olds the relative risk increase is 1.09 (95% CI 1.01–1.18).
Conclusions
Although men are more prone to develop PD, women see a higher risk increase in PD than men amongst DM patients.

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AEP185

Anemia in diabetes and pre-diabetes with normal kidney function: Prevalence and long- term association with morbidity and mortality

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Background
Although anemia was previously described as a complication of diabetes mellitus (DM), it's prevalence and prognostic meaning in patients with DM and pre-DM with normal kidney function was not thoroughly investigated.
Methods
A retrospective analysis of patients with DM and pre-DM referred to the endocrine institute in Meir medical center during 2015. Patients with estimated glomerular filtration rate (eGFR) < 60 ml/min or any other recognized cause of anemia were excluded. Four-years outcome was assessed including development of microvascular complications, macrovascular complications and mortality.
Results
A total of 622 patients (408 with DM and 214 pre-DM) were included. Their mean age was 64 ± 10.6 years, and 69% women. Baseline HbA1 c was 7.1 ± 1.7% and eGFR was 86.1 ± 15.3 ml/min. The prevalence of anemia was 19% in DM and 11% in pre-DM. Multivariable analysis adjusting for several clinical and laboratory parameters demonstrated a negative correlation between baseline hemoglobin level (as a continuous variable) and mortality ($P = 0.035$), microvascular complications ($P = 0.003$) and eGFR decline ($P < 0.001$), but not with macrovascular complications($P = 0.567$).
Conclusions
Our study demonstrates a significant prevalence of anemia unrelated to renal failure, both in DM and pre-DM and its association with development of microvascular complications, eGFR decline and mortality. These results underscore the need for intensive lifestyle and pharmacological intervention in pattients with DM or pre-DM and anemia.

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AEP186

Cardiorenal outcomes and T2DM control in new users of SGLT2 inhibitors in combination therapy

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Introduction and objectives
SGT2i have changed the paradigm of T2DM management. Last guidelines insist on the importance of using newer glucose-lowering drugs with a demonstrated reduction in cardiovascular events (CVE). The aim of this study is twofold: to describe CVE, heart failure (HF) and renal function evolution; and to assess its efficacy in non-selected patients with T2DM initiating SGLT2i
Material and methods
Retrospective observational study that included T2DM patients with SGLT2i initiation (Empagliflozin, Dapagliflozin or Canagliflozin) between February 2018–2019 from 2 hospitals and 10 primary care centers for a 78.000 population area. We analyzed metabolic outcomes (changes in HBA1c, weight), renal function evolution and the development of CVE and HF at baseline and at the end of monitoring (February 2020).
Results
544 patients were included. 342 men (63%), with a mean age of 66 years (10.2% $N = 55 \geq 80$ years). The mean follow-up was 22.6 ± 6.3 months. Baseline HbA1c mean was 7.9 ± 1.3%, BMI 31.5 ± 5.8 kg/m^2, eGFR 83.6 ± 20.1 ml/min/1.73 m^2 (12% below < 60) and diabetes duration was 12.5 ± 7.7 years. 23.4% of patients had albuminuria and 10.7% was on loop diuretic. 38% of the sample had underwent a transthoracic echocardiogram (TTE) before the SGLT2i was prescribed: 63 (11.6%) had had previous HF and 23 of them a decompensation in the past year. TTE was available in 88.9% of them with a mean ejection fraction of 48% comparing to 60.6% observed in 31.4% of patients with no HF history ($P < 0.001$). 32.5% ($N = 177$) were on insulin and SGTL2i was added as second, third or fourth line of treatment in 33%, 26.2% and 26.9% respectively. 16%($N = 87$) of patients discontinued treatment due to side effects and they were older than those who continued the therapy (69.8 vs 65.3 years, $P < 0.001$). Nearly 50% were urinary tract and genital infections and in 31 subjects eGFR went < 30. CVE´s prevalence was 23.7% ($N = 127$) but new onset ones were infrequent and non-fatal ($N = 19$, 3.5%). HF occurred in 4.6% ($N = 25$) and 16 patients required hospitalization. During follow-up, there were 12 deaths (2.2%): 2 because of terminal HF (included in a palliative care program). At the end of monitoring, SGLT2i lowered HBA1c and BMI –0.9% and –1.3 kg/m^2 respectively ($P < 0.001$) whereas eGFR remained stable (79.4 ± 22.6 ml/min/1.73 m^2).
Conclusions
Our registry suggests that SGLT2i improve glycemic control and weight parameters while renal function was preserved with low rates of intolerance and/or adverse events such as heart failure, CVE and death.

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AEP187

Free T4 is associated with exenatide-related weight loss in patients with type 2 diabetes mellitus

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Introduction
Exenatide may provide weight loss in type 2 diabetes mellitus (T2D) via agonistic effect on GLP1 receptor. There is no study showing associations between free T4(fT4) and exenatide-related weight loss in T2D. We aimed to reveal the association between fT4 and exenatide-related weight loss, and change in thyroid functions with exenatide in euthyroid adult patients with T2D and obesity.
Materials and Methods
We included euthyroid adult patients with T2D and obesity under metformin, SGLT2 inhibitor and/or insulin treatment, whom exenatide was indicated. We excluded those < 18-year-old, with contraindication to exenatide, or history of thyroid dysfunction, or under levothyroxine or

antithyroid medications. We analyzed baseline demographic features, chronic illnesses (hypertension, hyperlipidemia), AntiTPO and lipid parameters. We evaluated change (level at 6th month of exenatide – baseline level) in body weight, body mass index (BMI), TSH, fT4, fasting blood glucose (FBG), HbA1c. We grouped them as weight gain vs weight loss (absent vs < 10% vs ≥ 10% weight loss).
Results
TSH change and fT4 change were –0.077(1.10) and –0.0123(0.20) in total (n = 106), respectively (P = 0.229 and P = 0.908, respectively). TSH was increased in weight loss group, but decreased in weight gain group (P = 0.018). fT4 at baseline and at 6th month of treatment were higher in weight loss group than weight gain group (P = 0.010 and P = 0.004, respectively). The ratio of patients having fT4 in upper-range was higher in weight loss group (P = 0.042). Decrease in BMI was positively correlated with fT4 level at 6th month of exenatide (r = 0.234 and P = 0.016) but not with baseline fT4.
Conclusion
Higher fT4, even in normal range, was associated with higher weight loss in the patients with T2D after initiation of exenatide. Thyroid function seems not to be affected by exenatide. Baseline fT4 may be considered when selecting exenatide in T2D especially if weight loss is targeted.

Tablo 1. Comparison of the patient characteristics according to the presence of weight loss

	Weight loss		
Parameters	Absent (n = 15)	Present (n = 91)	p value
	n		
Gender(female/male)	9/6	67/24	0.278
Hypertension(absent/present)	12/3	52/39	0.094
Hyperlipidemia(absent/present)	13/2	79/12	0.988
Metformin(absent/present)	1/14	10/81	0.611
SGLT2 inhibitor(absent/present)	10/5	63/28	0.842
Insulin(absent/present)	13/2	71/20	0.444
TSH first(lowerrange/upperrange)	11/4	71/20	0.688
TSH change(decreased/increased)	13/2	49/42	0.017
fT4 first(lowerrange/upperrange)	13/2	54/37	0.042
fT4 change(decreased/increased)	8/7	38/53	0.402
ATPO(negative/positive)	14/1	81/10	0.611
HbA1c first(< 6.5/ ≥ 6.5%)	0/15	28/63	0.012
HbA1c last(< 6.5/ ≥ 6.5%)	6/9	42/49	0.657
HbA1c change (decreased/increased)	13/2	70/21	0.396

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AEP188

Feasibility study of IoT telemonitoring for elderly patients with type 2 diabetes mellitus: Results of the Greek pilot of the ACTIVAGE multicenter randomised control trial

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Introduction
The aim of the present feasibility study was to examine the impact of an Internet of Things (IoT) telemonitoring program, for elderly patients with type 2 diabetes mellitus (DMT2) on glycemic control.
Methods
In this feasibility, prospective, randomized, single-blinded, multicenter study elderly patients with DMT2 capable to use the IoT telemonitoring device, with an HbA1c > 7.5 were followed-up for 6 months. They were randomly assigned in the telemonitoring group (IG, N = 24) and in the control group (CG, N = 20). The inclusion criteria of the study were: age ≥ 65 years old, no comorbidities or 1–2 diabetes chronic illnesses and no Activities of Daily Living (ADL) impairments and ≤ 1 Instrumental ADL impairment. The primary objective of the study was the reduction of the HbA1c from over 7.5 to 7. In the IG group patients' blood glucose profiles were collected weekly using an IoT Point of Care Testing (POCT) health platform. Allocated health professionals provided by phone the appropriate counseling on lifestyle and medication changes when required. Patients in CG group received usual care with face-to-face consultations.
Results
Baseline Hba1c in IG was 7.655 ± 0.7280 and in the CG 7.873 ± 0.7923 (P = 0.361). Glycemic control was improved statistically significantly in the IG within the first 3 months of the follow-up (IG HbA1c: 7.031 ± 0.4250 versus CG HbA1c:7.585 ± 0.7923, P = 0.026). At 6 months follow-up there was no statistical significant improvement of the glycemic control improvement (IG HbA1c: 6.882 ± 0.5879 versus CG HbA1c: 7.129 ± 0.2928, P = 0.321) . No severe hypoglycemia event was registered in either of the two groups.
Conclusion
IoT telemonitoring seems to have the potential for closer monitoring of the elderly patients with T2DM improving with safety the glycaemic control. These are only pleminary data and more patients are needed for safer an more accurate results.

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AEP189

Type 1 Diabetes and physical activity – which are the barriers to its practice and what is therole of therapeutic education?

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Background
Regular physical activity has a crucial role in the control of Type 1 Diabetes (T1D). Insecurity in the management of insulin therapy and fear for dysglycemia are barriers to the practice of exercise in T1D.
Aim
To identify barriers to regular physical activity in adult patients with T1D; to evaluate the impact of two educational sessions about exercise and strategies to achieve better glycemic control in this setting.
Materials and Methods
We conducted an online prospective study with adult patients with T1D, treated with functional insulin therapy (multiple daily injections regimen, exclusively). The patients had to perform physical activity regularly. Two 45 minutes Zoom webinars were carried out, with a two-day interval between them. In the first session, different types of exercises and strategies to adopt to minimize hipo- and hyperglycemias were explained. The second session was more practical with the debate of clinical cases brought by the speakers and the participants. The impact of the webinars in the knowledge of the attendees was evaluated through 15 questions applied before and after the sessions. For the assessment of perceived barriers to physical activity, the BAPAD-1 scale was used.
Results
We invited 67 patients to participate; 19 (28.4%) accepted and answered the BAPAD-1 scale. The majority were men (57.9%). Average age was 34 ± 8.8 years and median disease duration was 12.3 ± 10.4 years. In BAPAD-1, the average global score was 30.3 ± 12.3 points [maximum score: 77 (seven points per question)]; women had a higher global score (38.0 vs 24.7, P = 0.015). Fear of hypoglycemia was the main barrier to the practice of exercise (median score 5.0), in particular for women (P = 0.015). Weather conditions and the location of the gym were also frequent barriers in our population. Thirteen patients answered the pre-sessions' test. The average classification was 71.8 ± 10.6%. Ten patients attended both sessions and answered the after-sessions' test. The global score improved (92.7 ± 8.0%, P < 0.001). After the webinars, 80% of patients reported feeling confident/very confident in the management of their T1D in this particular setting. All the patients reported being satisfied with the sessions.
Conclusions
Patients with T1D face various barriers to the practice of exercise, mainly fear of hypoglycemia. Therefore, therapeutic education should pay special attention to hypoglycemia management. The webinars showed to be effective in increasing confidence and additional strategies to minimize

exercise-induced dysglycemia. The low rate of participation was reported to be due to constraints associated with work and with the COVID-19 pandemic.

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AEP190

The effect of increasing soluble diatery fibre content of meals on postprandial glycaemic and c-peptide response

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Background
Medical nutrition therapy is often the initial step in the management of Prediabetes and diabetes mellitus. Postprandial glycaemia contributes significantly to the glycaemic control of patients with diabetes mellitus. The beneficial effects of soluble dietary fibre in reducing postprandial glycaemia have been established. The 2017 global burden of disease (GBD) report shows that 97.000 deaths result from low fibre intake. Despite the this, the intake of fibre is low in many countries including European countries as shown by the 2009 European Nutrition and Health (ENH) report. The objective of this study is to evaluate the impact of increasing soluble fibre content of meals on postprandial glycaemic and c-peptide responses.
Methodology
This experimental randomised, crossover study was conducted among 20 healthy subjects. Anhydrous glucose drink (G) which was the reference meal was consumed in the first week. The participants were then randomized by balloting to consume one of the two test meals per week namely white fonio (*Digitaria exilis*) and white fonio (*Digitaria exilis*) fortified with 3 g of B-CAN soluble fibre. i.e. Non fortified fonio meal (NFFM) and Fortified fonio meal (FFM) respectively. All meals were served after an overnight fast with a washout period of one week between the test meals. Fasting and postprandial plasma glucose, serum concentration of pancreatic c-peptide were measured at 0, 30, 60, 90, and 120 minutes. All data were entered using Microsoft Excel and analysis performed using the Statistical Package for Social Science (SPSS) version 22.0. P-value was set at < 0.05.
Results
Twenty participants were enrolled in the study, but one participant could not complete the study, giving a participant response rate of 95%. The mean peak plasma glucose (PPG) level of FFM was lower than that of NFFM (6.1 mmol/l and 6.35 mmol/l respectively) and were significantly lower than the PPG level of the reference glucose drink which was 7.01 mmol/l. $P < 0.05$. The glycaemic indexes of NFFM and FFM were 85.9 and 77. 5, respectively. The peak serum postprandial c-peptide (PPCP) response was also lower for FFM than NFFM (3.553 ng/ml and 3.814 ng/ml respectively) when compared with PPCP of G (4.333 ng/ml). $P > 0.05$.
Conclusion
The finding and potential impact of this study is that the diet can be modified by increasing soluble dietary fibre to improve the postprandial glycaemic response and c-peptide responses.

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AEP191

Erythrocytosis in a patient on sodium glucose cotransporter-2 inhibitor

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Background
Sodium glucose cotransporter-2 (SGLT-2) inhibitors have proven valuable in the management of type 2 diabetes. These agents are particularly effective in reducing hospitalisations with heart failure and cardiovascular mortality. Adverse effects are primarily centred on urogenital infections and hypovolaemia. Here, we report the case of a patient who developed asymptomatic erythrocytosis while taking empagliflozin.
Case report
A 44-year-old male patient with type 2 diabetes for 12 years, presented to diabetes clinic for review of suboptimal glycaemic control. He was treated with sitagliptin/metformin (50/1000 mg) BD and empagliflozin 10 mg once daily. Nine months later, his blood work showed erythrocytosis with haemoglobin (Hb) 18.3 g/dl (13.5–17.5), red blood cells (RBC) 6.34×10^{12}/l (4.5–5.5), haematocrit (Hct) 0.53 (0.4–0.5), reticulocyte count 202×10^{9}/l (50–100), normal white cell count 7.2×10^{9}/l and normal platelet count 169×10^{9}/l. The patient was asymptomatic and had no history of smoking, sleep apnoea, malignancy, testosterone use or exposure to high altitudes. Oxygen saturation was 98% on room air and BMI was 26 kg/m^2. Subsequent investigations showed packed red cells and reactive lymphocytes on blood film, normal erythropoietin level, normal SPEP, normal Hb electrophoresis and negative JAK2 V617F mutation. In the meantime, the patient decided to stop all anti-hyperglycaemic medications and relied solely on lifestyle modification for diabetes control. Coincidentally, erythrocytosis resolved spontaneously (Hb 17.4 g/dl, Hct 0.49) six months after stopping anti-hyperglycaemic agents. Follow-up in diabetes clinic revealed worsening glycaemic control (HbA1c 75 mmol/mol). At this point, he was restarted on empagliflozin 10 mg once daily. 4 months later, investigations showed recurrence of erythrocytosis (Hb 18.9 g/dl, Hct 0.55, RBC 6.6×10^{12}/l). Empagliflozin was discontinued and 6 weeks later his blood work showed slight improvement in erythrocytosis (Hb 18.6 g/dl, Hct 0.53). CT thorax/abdomen/pelvis showed no evidence of hepatic, renal or adrenal masses. He is due to have repeat blood work.
Discussion
There are five reported cases of erythrocytosis during treatment with SGLT-2 inhibitors in the literature; two cases had no risk factors for increased haematocrit, two were associated with co-administration with testosterone and one was unmasking of polycythemia vera. Our patient did not have any risk factor for increased haematocrit and erythrocytosis appears to be coincidental with SGLT-2 inhibitor use. A degree of plasma volume depletion due to osmotic diuresis leading to a relative erythrocytosis would make mechanistic sense. As erythrocytosis may predispose to prothrombotic events such as myocardial infarction and stroke, our case highlights the importance of monitoring haematocrits in patients on SGLT-2 inhibitors.

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AEP192

Investigation of 5 alpha reductase-1 and aromatase enzyme levels, gene expressions and kisspeptin and nesfatin-1 levels in male patients with metabolic syndrome and hypogonadism

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Metabolic syndrome-associated hypogonadism is an important problem in men and is thought to occur by complex pathogenetic pathways. 26 men with metabolic syndrome-related hypogonadism, 26 men with metabolic syndrome with normal testosterone levels, and 26 healthy men were included in this study to examine the factors that may affect these pathogenetic pathways. Plasma nesfatin-1, kisspeptin, 5 alpha reductase-1 and aromatase levels and plasma 5 alpha reductase-1 and aromatase gene expressions were examined. As a result, plasma nesfatin-1 and kisspeptin levels of men with metabolic syndrome-related hypogonadism and only metabolic syndrome were found to be lower than healthy men ($P = 0.001$). There was no statistically significant difference for plasma nesfatin-1 and kisspeptin levels between the two groups with metabolic syndrome, with and without hypogonadism. Plasma 5 alpha reductase-1 and aromatase levels were also lower in men with metabolic syndrome-associated hypogonadism than healthy men ($P = 0.006$ and $P = 0.0001$, respectively). Plasma 5 alpha reductase-1 levels were not statistically significant in the metabolic syndrome group compared to the control group or the hypogonadism group. The difference between the aromatase levels between the two groups with metabolic syndrome with and without hypogonadism was not statistically significant. There was no statistically significant difference between the groups for 5 alpha reductase-1 and aromatase gene expressions ($P = 0.8$ and $P = 0.5$, respectively). A positive correlation was found between kisspeptin, nesfatin-1, plasma 5 alpha reductase-1 and plasma aromatase levels in all groups ($P = 0.0001$). Considering these findings, it can be thought that nesfatin-1 is an important mediator in the pathogenesis of metabolic syndrome and indirectly affects the development of metabolic syndrome-related male

hypogonadism. Although it has been shown in studies that kisspeptin is a regulator of the Hypothalamic-Pituitary-Gonadal axis at the hypothalamus level, it can be considered to be an important marker for the development of metabolic syndrome, and when the metabolic syndrome is associated with male hypogonadism, it is not effective in the pathogenesis alone, but may have a role in this pathogenesis through metabolic syndrome. It can be said that plasma 5 alpha reductase-1 levels are one of the important points in the development of metabolic syndrome-associated male hypogonadism. For aromatase, contrary to the classical view, it would be more appropriate to say it is a parameter that is affected by the process rather than the cause of hypogonadism and to review what we know about it.

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AEP193

Comparative analysis of the methods for differential diagnosis of non-diabetic hypoglycemia (NDH): Beta-hydroxybutyrate and glucagon test

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Introduction
some authors propose to conduct consistently two additional tests for differential diagnosis (DD) of NDH with the main purpose to confirm or exclude the autonomous hyperinsulinemia (AH; insulinoma): determination the capillary beta-hydroxybutyrate (BHB) during prolonged fasting test (FT), and glucagon test (GT) at the moment of hypoglycemia. GT is more labor-intensive, high-cost and lead to potential complications. Therefore, we assumed that the BHB determination alone is enough for NDH DD.
Objectives
To compare the efficiency of GT and BHB determination in AH diagnosis.
Methods
In 59 patients aged 44 (23, 74) years with suspected NDH we conducted FT (was interrupted if glycaemia ≤ 2.8 mmol/l with symptoms of neuroglycopenia or, if maintaining normoglycemia, after 72 h). At the end of FT BHB was determined, then GT was conducted: 1 mg of glucagon was administrated iv with venous blood sampling for glucose through 3, 5, 10, 15, 20, 30 min. BHB ≤ 2.7 mmol/l and increase in glycemia ≥ 1.4 mmol/l during GT confirmed AH, opposite results indicated hypoinsulinemia.
Results
63% (n = 37) of patients had hyperinsulinemia (group 1); 37% (n = 22) – hypoinsulinemia/not confirmed NDH (group 2). BHB was 0.2 [0.1; 0.3] mmol/l in group 1; 4.4 [2.3; 4.9] mmol/l in group 2, P < 0.001. Sensitivity, specificity, accuracy of method were: 97.3%, 72.7%, 88.1%, accordingly. ROC-analysis indicated the excellent quality of model: AUC 0.989 [0.967; 1.000]. All patients with false positive results (1.85 [1.60; 2.00] mmol/l; n = 6) had insulin resistance (HOMA-IR > 2.7), that likely blocked ketogenesis. False negative result (3.3 mmol/l) identified in one patient with exacerbation of pyelonephritis, associated with increased ketogenesis. Increase in glycemia after glucagon administration was 2.8 [2.0; 3.4] mmol/l in group 1; 0.8 [0.6; 1.1] mmol/l in group 2, P < 0.001. Sensitivity, specificity, accuracy of method were: 94.6%, 100%, 96.6%, accordingly. ROC-analysis indicated the excellent quality of model: AUC 0.974 [0.937; 1.000]. False negative results (1.03 and 0.68 mmol/l; n = 2), presumably, were due to the influence of any other hormones on the glucagon effect on liver. Results of BHB determination and GT were identical in 90% of cases.
Conclusion
BHB determination and GT are highly sensitive and highly specific methods DD of NDH at the laboratory stage, with a small advantage for GT. But GT is more labor-intensive, high-cost and lead to potential complications. We assume that BHB determination during FT (especially at the end) is mandatory; GT should be used in doubtful cases as an additional method.
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AEP194

Hedonic rating of sucrose is sub-regionally associated with striatal dopamine transporter in humans

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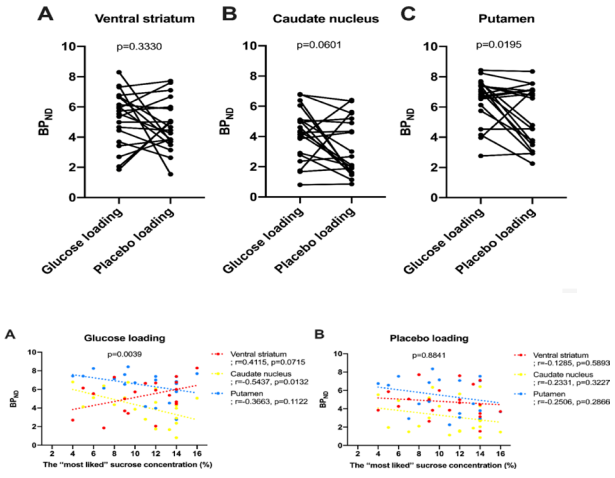
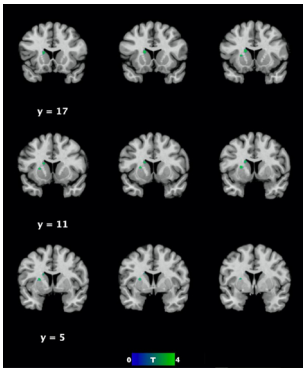
Eating behavior is determined by both homeostatic and hedonic values. We investigated the association of hedonic value with striatal dopamine transporter (DAT) availability sub-regionally. An intravenous bolus injection of ^{18}F-FP-CIT was administered after the infusion of glucose or placebo, and the emission data were acquired over 90 mins. DAT availability, binding potential (BP_{ND}), were measured via the simplified reference tissue method. Subjects were assessed with sensory taste test of sucrose solutions. The 'most liked' sucrose concentration (%) was determined as the hedonic rating for sucrose. Twenty healthy males with the mean age of 23.9 ± 1.7 years (range 22 ~ 28 years) were participated in this study. The 12% sucrose solution received the highest liking score. BMI was associated neither with the 'most liked' sucrose concentration (r = –0.1812; P = 0.4446). After glucose loading, BPNDs of putamen were significantly increased (P = 0.0195, mean percentage change of BP_{ND} ± standard deviation; + 33.7 ± 51.7%), and those of caudate nucleus showed the increasing trend (P = 0.0601, + 70.4 ± 113.6%), while those of ventral striatum were not significantly different (P = 0.3330, + 29.6 ± 94.0%) compared with those after placebo loading (Figure 1). The relationships between the 'most liked' sucrose concentration (%) and BPNDs were investigated both by VOI-based and voxel-based analysis. With a VOI-based analysis, after glucose loading, the 'most liked' sucrose concentration (%) was negatively associated with BPNDs of caudate nucleus (r = –0.5437, P = 0.0132) and showed the trend of positive association with those from ventral striatum (r = 0.4115, P = 0.0715). Slopes of regression lines were significantly different according to sub-regions of striatum (F = 6.150, P = 0.0039) (Figure 2A). After placebo loading, the 'most liked' sucrose concentration (%) was not associated with BPNDs of ventral striatum (r = –0.1285, P = 0.5893), caudate nucleus (r = –0.2331, P = 0.3227) and putamen (r = –0.2506, P = 0.2866) without the significant difference in slopes of regression lines (F = 0.1235, P = 0.8841) (Figure 2B). With a voxel-based analysis, the 'most liked' sucrose concentration (%) was not associated with DAT availabilities of brain regions except for left putamen (MNI coordinates; –24 12 8, k = 87, T = 3.51) and left caudate nucleus (MNI coordinates; –18 14 12; –16 –6 24, k = 104, T = 3.36; 3.07) negatively after glucose loading (Figure 3). In conclusion, we have highlighted that striatal DAT increased after glucose loading in dorsal striatum, not in ventral striatum. These changes of striatal DAT were sub-regionally associated with the hedonic rating of sucrose from each subject.





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AEP195

glycaemic control in patients with Gestational Diabetes requiring betamethasone – a quality improvement project with intravenous insulin infusion protocol

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Administration of antenatal steroids for foetal lung maturity is considered for all women at risk for preterm birth before 37 weeks. Administration of two doses of betamethasone 12 mg intramuscularly, 24 hours apart may result in a deterioration of glycaemic control for 2–3 days in patients with gestational diabetes (GDM), thereby potentially affecting foetal wellbeing. Current practice was noted to be inconsistent, and a protocol was drawn up for variable rate insulin infusion for all GDM patients requiring betamethasone. We sought to review effectiveness of the protocol to achieve better glycaemic control in those requiring betamethasone injections. Retrospective data was collected from chart review of 17 GDM patient who were treated with VRIII after betamethasone injections and subsequently monitored for up to 24 hours after last dose of betamethasone and glycaemic control was compared with the data of 17 GDM patients from before implementation of VRIII protocol Hourly glucose was monitored. There was no difference in glucose values in the first 14 hours. From 14 to 32 hours, mean glucose ± SD mmol/l were 7.8 ± 1.0 pre protocol, and 6.2 ± 0.4 post implementation of protocol (P = 0.002), We conclude that VRIII in GDM patients requiring betamethasone is effective in maintaining target glucose of 4 to 7 mmol/l.

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AEP196

Combined vildagliptin + metformin therapy can increase telomerase activity in patients with type 2 diabetes

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Introduction
Metformin and vildagliptin are the medications amongst first-line treatment options in type 2 diabetes patients. Few recent studies have explained positive pleotropic effects of metformin therapy by telomerase activation and telomeres length in leukocytes preservation. Knowing the primary role of insulin-signalling pathway in insulin resistance development and physiology of ageing, it is possible to suggest, that one of the protective mechanisms of metformin and vildagliptin therapy is their ability to increase telomerase activity and thus to prevent accelerated telomeres shortening.
Aim of the study
To investigate effects of combined therapy with vildagliptin and metformin and their influence on telomerase activity in patients with type 2 diabetes.
Materials and methods
Total of 50 patients with diabetes were included in the study. Mean age was 58.4 ± 7.90 years. Diabetes duration was 0.9 ± 0.09 years. The patients were randomized with 1:1 ratio to a group treated with metformin 2000 mg/day and a group, which was given vildagliptin + metformin 100/2000 mg/day combination therapy. There were no statistically significant differences in age, sex, blood pressure, main carbohydrate metabolism parameters and vessel wall state between two groups. All patients were given recommendations on lifestyle changes (diet and physical activity). In 12 months after the initiation of treatment we performed: pulse wave velocity measurement, carotid arteries duplex scan, telomerase activity investigation on monocyte fraction of blood cells and pre-prandial glucose and HbA1c measurements. Statistical analysis was performed using SPSS 23.0.
Results
Examination after 12 months of treatment demonstrated, that either metformin monotherapy or its combination with vildagliptin had led to a significant glycaemic control improvement. In group 1 (metformin only) HbA1c and glucose levels decrease was 8.28% and 3.2% respectively, and in group 2 (combination therapy) – 3.4% and 1.5% respectively, reaching the normal range. The number of patients, who reached HbA1c less than 7.5% goal was 87.6% in group 1 and 64.7% in group 2. In group 2 were revealed statisitically significant increase in telomerase activity from 0.87 to 1.15 (P < 0.01) in contrast with group 1, where we observed a significant decrease in telomerase activity from 0.89 to 0.64 (p=0.01). After comparing all the numbers between two groups, we found, that vildagliptin + metformin combination therapy had a positive effect on changes in pulse wave velocity (P < 0.001), body mass(P < 0.001) and telomerase activity (P < 0.001).
Conclusion
Based on the obtained results it is possible to suggest the finding of a new independent pleotropic effect of metformin + vildagliptin combination therapy – the modulation of telomerase activity.

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AEP197

Maternally inherited diabetes and deafness, associated with a novel mitochondrial mutation, complicated by sever hypertriglyceridemia: Case report

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Introduction
Mitochondrial diseases are a clinically heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial respiratory chain. it is genetically heterogeneous diseases characterized by multisystem involvement. Thus, its clinical description is incomplete. The aim of this case report is to highlight the association between mitochondrial diabetes and severe hypertriglyceridemia. In this study, we describe the case of a 22 year old Tunisian girl, with a strong familial history of diabetes, hypertension and kidney diseases. The patient was born to a non-consanguineous marriage, attaining developmental milestones appropriately. Her past medical history was remarkable for hearing impairment, congenital Pigmentary retinal dystrophy, congenital structural abnormalities of the urogenital system and Diabetes with severe insulin deficiency but without typical features of Type 1diabetes (such as autoimmunity, prompt insulin requirement, ketoacidosis). Mitochondrial disease was then suspected and confirmed, since the age of 11, when genetic analysis identified A novel MT-CO1 m.6498C > A variation associated with the m.7444G > A mutation in the mitochondrial COI/tRNASer(UCN) genes The follow up findings revealed a poorly controlled diabetes (HBA1c 10.8%) despite increasing insulin requirement up to 2 uI/Kg /day and severe hypertriglyceridemia up to (13 g/l).The patient weight was 52 kg and her body mass index was 24.4 kg/m^2. Physical examination and abdominal imaging didn't reveal any pancreatitis features, except the presence of Hepatosteatosis. Furthermore, cardiovascular examination was normal and there was no evidence of eruptive xanthoma. Serum sample was milky and turbid. Lipoprotein-electrophoresis of serum, under fasting conditions, showed high levels of plasma VLDL (33%) and the presence of a small amount of chylomicrons (8.1%) accompanied by decreased level of HDL .Metabolic syndrome was then concluded by association of diabetes, hypertriglyceridemia, hypoHDL and hepatosteatosis. Severe hypertriglyceridemia was successfully resolved by diet control fibrates insulin and hydration therapy. In the other side, the patient was suffering of spaniomenorrhea, hyperandrogenism with hirsutism (Ferriman Gallwey score of 8), and gradual weight gain. Biochemically, hyperoestrogenaemia was observed in association with raised serum luteinizing hormone (LH), follicle-stimulating hormone (FSH) and antimullerian hormone (AMH) concentrations in 2016. Moreover, pelvic ultrasound revealed polycystic ovarian disease.
Conclusion
To our knowledge, this is the first case report describing a severe hypertriglyceridemia and polycystic ovary syndrome in maternally inherited diabetes and deafness.

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AEP198

Elderly patients with Type 2 Diabetes and Covid-19: the impact of glycemic control on the outcomes

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Introduction
Diabetes mellitus (DM) is one of the major comorbidities in patients with Coronavirus disease (COVID-19) leading to poorer outcomes. Previous evidence showed that poorly-controlled hyperglycemia increases the

severity and mortality of COVID-19. Nevertheless, there is limited data on the role of in-hospital glucose control on the outcomes of elderly patients with type 2 diabetes mellitus (T2DM).
Objective
To access the impact of blood glucose control, assessed by the derived time in range (dTIR) and glycemic variability, on the mortality of elderly patients with T2DM and COVID-19.
Methods
We selected consecutive patients with laboratory confirmed COVID-19 who had been hospitalized in a general ward of our hospital between 25 March and 25 May 2020. From a total of 97 patients, we identified and included 38 patients with DM, with a median age of 80 years (IQR, 76–87). To assess glycemic control, all capillary blood glucose levels were extracted for each diabetic patient in the first seven days (four glucose tests per day). Individual derived time in range (percentage of time with plasma glucose between 70–180 mg/dl) was derived as the proportion of values within range (dTIR). dTAR (derived time above range) was derived as the proportion of values above range.
Results
The dTIR for all diabetic patients was 49%, and the dTAR was 52%. TIR > 70% was 36.8% for all diabetic patients. Nonsurvivors were more likely to have a lower TIR (38% vs . 73%, $P = 0.020$) and a higher TAR (62% vs . 27%, $P = 0.020$). Survivors were more likely to have TIR > 70% (50% vs . 14.3%, $P = 0.030$). There were no differences between groups regarding data estimates of glycemic variability: coefficient of variation (CV) (23.26 [17.46–35.76] vs . 29.15 [19.63–37.84], $P = 0.526$); high blood glucose index (HBGI) (13.78 [7.09–21.89] vs . 9.73 [3.35–17.03], $P = 0.151$); measure of stability of glycemia in comparison with an arbitrary assigned 'ideal' glucose value, 'R,' set to 100 mg/dl (M-100 index) (297.41[194.23–386.75] vs . 216.94 [147.00–321.54], $P = 0.123$) or measure of quality of glycemic control calculated as 0.001 × [mean + Standard of deviation (SD)] (J-index) (73.20 [45.82–104.39] – 56.99 [31.05–88.34], $P = 0.221$).
Conclusion
A poorer glycemic control, assessed by lower dTIR during hospitalization, was associated with in-hospital mortality. Clinicians should maximize TIR even in elderly patients, using a basal-bolus or continuous insulin infusion whenever needed, with appropriate surveillance.

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AEP199

Diabetes mellitus and COVID-19 – The bidirectional impact

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Introduction
SARS-CoV2 infection can worsen glycemic control regardless of history of Diabetes mellitus (DM) and may precipitate new-onset diabetes (NOD). DM is also a risk factor for a greater severity of COVID-19. At-admission hyperglycemia (AH) is a known predictor of critical illness in other diseases.
Aims
Assess the impact of AH, regardless of the presence of DM, on the severity of COVID-19 inpatients.
Methods
Retrospective observational study on COVID-19 patients admitted to the IMFU from 3rd March to 31st October 2020, in order to assess associations between AH and severity outcomes: respiratory support (oxygen therapy or invasive mechanical ventilation – IMV), admission to Intensive Care Unit (ICU), and mortality in inpatients with and without DM.
Results
In 374 patients, 209 (55.9%) were males. The average age was 68 ± 19.3 years. DM was present in 105 patients (28.1%) with a HbA1c of 7.2% [IQR 6.2–8.3]. NOD was diagnosed in 15 patients (4%) with a HbA1c of 7.6% [IQR 6.8–11.1] with 2 of them presenting with diabetic ketoacidosis (DK). Blood glucose at admission was evaluated in 360 patients. Considering diabetic patients with AH ($N = 68$; 64.8%) there was a statistically significant correlation with COVID-19 severity ($P = 0.03$), IMV ($P = 0.008$) and ICU admission ($P = 0.026$) but not with oxygen therapy or mortality. In diabetic patients without AH ($N = 33$; 31.4%), there wasn't a statistically significant correlation with any of severity outcomes. In nondiabetic patients with AH ($N = 51$; 17.5%) there was a statistically significant correlation with oxygen therapy ($P = 0.001$); IMV ($P = 0.01$) and ICU admission ($P = 0.03$) but not with mortality (P = NS). All 15 NOD patients had AH and 12 had severe/critical COVID-19, needing oxygen therapy. ICU admission occurred in one third of NOD patients ($N = 5$): 4 of them being submitted to IMV; the other admitted due to DK. Three NOD patients died. In NOD patients, no statistical significance was found between AH and severity outcomes (probably due to the small size of this group of patients).
Conclusion
The results support previous data regarding the impact of at-admission hyperglycemia on severity outcomes, and suggests a strong effect on short and long-term prognosis of COVID-19 inpatients, both with and without diabetes. We reinforce the importance to assess at-admission glycemia in all patients admitted with COVID-19.

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AEP200

IL-18 in the Glucose Continuum

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Background
Both obesity and diabetes are associated with chronic low-grade inflammation. IL-18 is a cytokine that stimulates various cell types and has pleiotropic functions. The aim of the present study was to investigate the circulating levels of IL-18 in different stages of glucose dysregulation from obesity through prediabetes to newly diagnosed diabetes
Methods
IL-18 levels were determined using a commercially available human enzyme-linked immune sorbent assay (ELISA) kit.
Results
The sample consisted of 388 subjects with mean age 53.3 ± 10.78 years, divided in three age and BMI matched groups-obesity, prediabetes and diabetes. The control group consisted of 42 healthy individuals. IL-18 levels were significantly higher in patients with obesity and/or prediabetes and newly diagnosed diabetes compared to the control group respectively (249.77 ± 89.96; 259.01 ± 95.70; 340.98 ± 127.65 vs. 219.47 ± 110.53, $P < 0.05$). Correlation analysis showed that the level of IL-18 positively correlated with BMI, waist, WSR, VAI, liver enzymes, fasting and post load plasma glucose and insulin, uric acid, TG and negatively with HDL. ROC analysis determined circulating IL-18 levels to be of value for differentiating subjects with carbohydrate disturbances and those with MS. The AUC for carbohydrate disturbances was 0.597 ($P = 0.001$; 95%CI 0.539–0.654) and for MS AUC was 0.581($P = 0.021$; 95% CI 0.516–0.647).
Conclusion
The levels of IL-18 were increased in patients with obesity and carbohydrate disturbances. Further studies will elucidate the role of this cytokine in development of type 2 diabetes and its complications.

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AEP201

Liraglutide for weight management in syndromic obesity: effects in overgrowth adult Beckwith–Wiedemann syndrome

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Context
Genetic obesity, including syndromic and non-syndromic forms, represent a minority of cases but gene dysregulations make their management particularly difficult. Among them, Beckwith–Wiedemann syndrome (BWS) is a multisystem human genomic imprinting disorder characterized by overgrowth, macroglossia, abdominal wall defects, hemi hyperplasia, enlarged abdominal organs, and an increased risk of embryonal tumours. The syndrome is caused by genetic and epigenetic changes on the chromosome 11p15 region, that include genes such as cyclin-dependent kinase inhibitor 1C (CDKN1C) or insulin like growth factor 2 (IGF-2), strong related to fetal and postnatal growth. Genetic and epigenetic alterations are frequently mosaic and lead to different clinical phenotypes, including early onset

obesity, although BWS is often an underestimated cause of syndromic obesity. Thus, less is known about obesity treatment in this syndrome.
Case description
We describe the first case of liraglutide treatment in an 18-year-old boy patient affected by BWS (Imprinting Center 1 Gain of Methylation (GoM IC1) associated with IC1 microdeletion) complicated by macroglossia, cryptorchidism, nephroblastoma, organomegaly, microscopic lymphocytic colitis, pharmacologically treated arterial hypertension, obesity and obstructive sleep apnea syndrome. He presented a normal cognitive development. BMI at the time of first transition visit in the adult endocrinology department was 40.6 kg/m^2 without glucose metabolism impairment. Lifestyles interventions failed because of a poor compliance. During 20 months of 3.0 mg liraglutide treatment weight loss of 19 kg (–13.3%) and BMI reduction of 6.8 points were registered without side effect. Normal glycemic and metabolic pattern was recorded without hypoglycemic episodes. Better control of blood pressure values was documented hesitating in improvement of quality of life.
Conclusion
liraglutide was effective on obesity in 7 subjects with Prader Willy Syndrome and 14 with melanocortin-4 receptor mutations. The efficacy of liraglutide in BWS could be related to a cross talk among glucagon like peptide (GLP)-1 system, mechanisms related to CDKN1C and dopamine mesolimbic circuit. Moreover, the causative mutation of BWS could interest genes such as IGF-2, implicated in postnatal overgrowth, and expresses by adipose tissue together with GLP-1 receptors. Thus, considering that GLP-1 promotes preadipocyte differentiation, reduces the expression of adipogenic and lipogenic genes, and enhances the expression of lipolytic markers, these could be some mechanisms targeted by liraglutide in BWS. On the other hand, the risk of hypoglycemia, although low during liraglutide, should be taken into account considering the intrinsic predisposition in BWS patients. Clinical trials aiming a tailored medicine in genetic obesity are needed.

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AEP202

Role of circulating cell-free deoxyribonucleic acid in the management of obese patients with breast cancer: Diagnostic impact, prognosis and relationship with obesity

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Introduction
Circulating cell-free deoxyribonucleic acid (cfDNA) is a topical subject that has proven its place in oncology. However, its regular use is always compromised by the relatively high cost of the technique. The objective of our study is to determine the usefulness of cfDNA in the management of obese patients with breast cancer as well as its prognostic impact.
Methods
Using real-time multiplex polymerase chain reaction (PCR), we studied the levels of circulating free DNA, with three different methods: fluorometry, Bglobin gene and ALU115 sequences, in samples. plasma from 105 patients divided into 4 groups (G1: 23 healthy controls, G2: 33 obese women, G3: 23 non-obese breast cancer patients and G4: 26 obese patients). To assess the applicability of cDNA as a biomarker for distinguishing between different study groups, we performed a Receiver Operating Characteristic (ROC) curve analysis. We also studied the relationship of the levels of molecular markers as well as the values of DNA integrity in the cancer group with the various clinicopathological parameters.
Results
While the levels of cfDNA in the two cancer groups were higher compared to the control groups, this result was only significant using the fluorometric method ($P = 0.045$) and ALU115 sequences ($P = 0.039$). The level of cfDNA was also associated with lymph node involvement ($P = 0.01$). In fact, the level of cfDNA was found to be significantly higher in both groups of obese women ($P < 0.001$). However, we have not found significant results by studying the different correlations between DNA integrity and cancer on the one hand and obesity on the other. Using the ROC curve analysis, we were able to distinguish between breast cancer cases and healthy controls using cDNA as a marker (cutoff: 7.91 ng/ml; sensitivity: 67.3%; specificity: 64.3%; $P < 0.001$). This threshold was higher taking into account the metabolic profile of the patients with a value of 10.15 ng/ml in the obese groups and of 7.04 ng/ml in the non-obese groups.
Conclusion
cfDNA is a valuable tool in the diagnosis of breast cancer but remains modifiable with the metabolic profile of the patients. But, more studies with larger cohorts are needed to validate the use of DNA integrity in cancer diagnosis and prognosis.

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AEP203

Is there an association between sex steroids and biopsy-proven non-alcoholic fatty liver disease in obese men? A cross-sectional analysis of 134 men

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Background and aims
Low levels of testosterone and non-alcoholic fatty liver disease (NAFLD) in obese men are both linked to the metabolic syndrome, but the independent association between testosterone and NAFLD needs to be elucidated. In this cross-sectional analysis the association between total testosterone (total T) and calculated free testosterone (cFT) on the one hand and NAFLD, non-alcoholic steatohepatitis (NASH) and fibrosis on the other hand was investigated in obese men.
Methods
Data of 134 men of 18 years or older and a body mass index of at least 25 kg/m^2 who underwent a liver biopsy after visiting the obesity clinic were collected. Liver biopsy was performed if there was suspicion of NAFLD. Individuals were classified into 4 categories: no NAFLD, NAFL, NASH (no fibrosis (F0) or F1) or NASH with advanced fibrosis (F2-F4). Because of an unequal distribution of fibrosis, the 5 stages were regrouped into F0–1 and F2–4.
Results
Mean age was 45 ± 12, median BMI was 39.6 kg/m^2 (range 25.0–64.9). Only 5.2% of the individuals had no NAFLD. Of the individuals with NAFLD, 15.7% had NAFL, 56.7% had NASH F0-F1 and 22.4% had NASH F2-F4. Fibrosis stage 0 to 4 were present in respectively 47.8, 26.9, 17.2, 7.5 and 0.7%. cFT and total T were below the limit of normal in respectively 63% and 23% of individuals. One-way ANOVA showed a tendency toward a difference in the level of cFT between the grades of NAFLD ($P = 0.053$) that did not persist after controlling for confounding variables. No significant difference was seen for total T. Ordinal regression analysis showed a decreasing level of cFT was associated with an increase in the grade of NAFLD ($P = 0.005$) that did not persist after controlling for confounding variables. No significant effect of total T on the grade of NAFLD was seen. When performing the same analyses for fibrosis and after controlling for confounding variables, no difference in the level of cFT or total T were seen between F0-F1 and F2-F4 and no effect of cFT or total T was seen on the stage of fibrosis.
Conclusion
To the best of our knowledge, this is until now the largest study investigating the association between sex steroid levels and biopsy-proven NAFLD. After controlling for confounding variables no association was found between the level of total T and cFT on the one hand and NAFLD, NASH or fibrosis on the other hand.

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AEP204

The role of vitamin D deficiency in the development of latent autoimmune diabetes in adults

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Introduction
Vitamin D deficiency is recognized as a global problem worldwide. Today, there is information about the relationship between vitamin D levels and the pathogenetic links in the development of classic forms of diabetes mellitus (DM). In particular, vitamin D deficiency has been shown to cause insulin

deficiency, progression of insulin resistance, and β-cell dysfunction. There is growing evidence that vitamin D deficiency may be a risk factor for diabetes. At the same time, the role of vitamin D deficiency in the development of latent adult autoimmune diabetes (LADA) needs further study. The aim of our study was to determine the relationship between the level of vitamin D with carbohydrate metabolism and the level of antibodies to glutamic acid decarboxylase in patients with LADA.
Materials and methods
A study of 90 patients with diabetes (26 patients with type 1 diabetes mellitus (T1DM),28-with type 2 diabetes mellitus (T2DM),36-with LADA),as well as 25 members of the control group. Evaluated complaints, history, objective examination, carbohydrate metabolism, levels of antibodies to glutamic acid decarboxylase (antiGAD) and vitamin D. Vitamin D < 10 ng/ml was regarded as a deficiency,10–30 ng/ml as a risk of insufficient consumption, > 30 ng/ml as the optimal level. Patients with LADA were divided into two groups depending on the level of antiGAD:LADA1 and LADA2.We studied the relationship between vitamin D levels and carbohydrate metabolism in the study groups.
Results
Vitamin D deficiency was found in most patients:T1DM-62%,T2DM-75%, LADA-67%, and 12% of healthy individuals. The indicator of the insufficient consumption was registered in 34% of patients with T1DM,25% of patients with T2DM,25% of patients with LADA and 40% of the control group. In the remaining patients of the experimental group and in 28% of the control, this indicator was registered at the lower limit of normal. 20% of the surveyed control groups had the optimal level of vitamin D. Patients with LADA have the highest frequency (71%) and the degree of deficiency of this vitamin in a subgroup with LADA2 phenotype (LADA1–63%). In patients with LADA, there was a negative correlation between vitamin D levels and antiGAD titres ($P < 0.05$), as well as HbA1C levels ($P < 0.05$), and a positive correlation between vitamin D and C-peptide levels ($P < 0.05$).
Conclusion
Most patients with LADA have vitamin D deficiency, which is associated with a higher degree of autoimmunity, loss of beta-cell function and poorer compensation of the disease, which may indicate its role in the development and progression of this variant of diabetes.

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AEP205

Prevalence of erectile dysfunction among the subjects with type 2 diabetes mellitus in the indian state of punjab

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Background
Erectile Dysfunction (ED) is one of the most common sexual dysfunction occurring in men with Type 2 diabetes mellitus (T2DM) but its evaluation is often neglected in routine clinical practice. There is hardly any data on the prevalence of ED among the males with Type 2 diabetes mellitus in the Indian state of Punjab.
Aims
This cross sectional study was conducted to find out the frequency and risk factors of ED in subjects with T2DM in the Indian state of Punjab.
Material and methods
Study was conducted on 520 male subjects with T2DM attending the outpatient department of an endocrinology speciality hospital. All participants underwent detailed clinical evaluation, anthropometric measurements and relevant lab investigations like fasting plasma glucose (FPG), HbA1c, creatinine, lipid profile,testosterone. The presence of ED by was determined by using the International Index of Erectile Function-5 (IIEF-5) questionnaire, which consists of 5 items; a sum score of 21 or less indicates the presence of ED. Statistical analysis was done using SPSS.
Results
The mean age of subjects was 53.4 ± 16.8 years. Out of the 520 subjects, 298 (56.4%) had ED. ED was mild in 14.8%, mild to moderate in 17.6%, moderate in 14.4% where as severe ED was present in 9.6% of the subjects. The subjects with ED had higher mean age, longer duration of DM, higher body mass index (BMI), higher HbA1c, higher FPG, higher serum creatinine and lower serum testosterone level than those without ED. Also the Subjects with hypertension, peripheral artery disease, dyslipidaemia had higher prevalence of ED.
Discussion
ED is defined as the persistent inability to achieve or maintain penile erection for successful sexual intercourse and it results from complex interplay between vascular, neurologic, hormonal and psychological factors. In our study a high prevalence of erectile dysfunction was observed in type 2 DM subjects in Indian state of Punjab. The IIEF-5 score showed significant negative correlation with age, duration of diabetes, HbA1c, fasting plasma glucose, serum creatinine and significant positive correlation with serum testosterone. Poor glycaemic control, testosterone deficiency, peripheral arterial disease were the modifiable risk factors for ED in diabetic subjects.
Conclusions
The prevalence of ED is high among T2 DM patients. ED is an important but often neglected complication of diabetes and its assessment should be included in the routine evaluation of all men with diabetes so as to ensure its early diagnosis and prompt treatment.

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AEP206

The effect of renin-angiotensin-aldosterone system inhibitors on binary and continuous renal outcomes in subgroups of patients with diabetes: an extensive meta-analysis

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Introduction
Diabetic nephropathy is the leading cause of end-stage-kidney disease (ESKD). Clinical practice guidelines recommend prescribing renin–angiotensin aldosterone system inhibitors (RAASi) to prevent diabetic nephropathy at any stage. We conducted this extensive meta-analysis to compare the effects of RAASi with placebo and other antihypertensives in adults with diabetes on binary and continuous renal outcomes to provide a comprehensive review of the class effect of RAASi on several subgroups of study participants.
Methods
A systematic search to identify randomized clinical trials of a duration of 12 months or more that recruited more than 50 adults participants with type 1 or 2 diabetes mellitus with any stage of chronic kidney disease and proteinuria was conducted. Electronic searches were conducted with the help of a librarian in MEDLINE, CINAHL, EMBASE, Cochrane library with no language or date restrictions. Studies were screened against the inclusion and exclusion criteria by two reviewers independently.
Results and discussion
In this meta-analysis, evidence was drawn from 26.609 patients with diabetes from 46 studies on the effect of RAASi on binary and continuous renal outcomes. Our analysis shows that RAASi were superior to placebo in reducing the risks of ESKD(OR:0.74; 95% CI: 0.56–0.97) and doubling of SrCr levels(OR:0.71; 95% CI: 0.55–0.91), but not in promoting the regression of albuminuria(OR:3.00; 95% CI: 0.96–9.37). RAAS inhibitors, however, were not superior to other antihypertensives in reducing the risks of these outcomes. RAASi were better than placebo in reducing SrCr (the raw mean difference (RMD) was −13.4umol/l (95% CI: −16.78; −10.01)) and albuminuria levels (standardized mean difference (SMD) −1(95% CI: −1.57; −0.44, I^2=96%)). Surprisingly, RAASi reduced GFR levels more than placebo (RMD:−0.82ml/min;95% CI: −5.54; 3.91), yet it was not a statistically significant finding. When compared to active treatments, RAAS inhibitors did not reduce SrCr levels (RMD:0.03 umol/l;95% CI: −6.4; 6.10, I^2=76%), caused a reduction of GFR levels (RMD: −1.12 ml/min; 95% CI: −4.51; 2.09, I^2=86%), and resulted in modest reduction of albuminuria levels (SMD:-0.55; 95% CI: −0.95;-0.16, I^2=90%). Patients with T2DM, macroalbuminuria and longer duration of DM had less risk to develop ESKD in placebo-controlled trials, while longer duration of DM, normal renal function, and hypertension increased the probability to achieve regression of albuminuria in active-controlled trials.
Conclusion
While our findings revealed the non-superiority of RAASi over other antihypertensives and portrayed class effect on several subgroups of study participants, it raised a challenging question on whether RAASi deserve their place as first-line therapy in managing diabetic nephropathy.

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AEP207

Correction of oxidative stress in experimental diabetes mellitus by means of natural antioxidants

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Associated with the increased generation of free radicals and reduced activity of antioxidant system, oxidative stress is a pathogenetic mechanism underlying the onset of diabetic complications. Antioxidants are known to facilitate normalization of lipid peroxidation, composition, structures and functions of biological membranes. Antioxidants are universal membrane-trophic agents protecting against damaging factors. Plant antioxidants play a significant role in treatment of diabetes mellitus (DM).
The work was initiated to study oxidative stress in experimental DM and its correction with natural antioxidants.
Materials and methods
Antioxidant properties of medications based on phenolic compounds isolated from the leaves of cotton *Gossypium hirsutum L.* (gossitan) and euphorbia *Euphorbia Fergansis* (euphorbin), as well as extract of safflower *Carthamus tinctorius* blossoms and quercetin were studied in the models of adrenaline autoxidation and ascorbate-dependent lipid peroxidation *in vitro*. Hypoglycemic effects of the medications were studied in the experimental model of alloxan diabetes in rats. Blood glucose reaching more than 9–11 mmol/l, the medications and gliclazide, a commercially available blood glucose lowering drug (Servier, France), as a control at the recommended dose *o.d.* for 10 days were administered to the animals by a gastric tube. The orthotoluidine test was used to measure blood glucose. Activity of the rat liver glucokinase was calculated by changes in concentrations of exogenous glucose in % to the control upon the 30-minute incubation with the liver homogenates from rat with alloxan diabetes before and after the 10-day administration of polyphenols.
Results
Demonstrating high antioxidant activity, gossitan, euphorbin, safflower extract and quercetin were found to cause reduction in blood glucose concentrations in animals with experimental diabetes, associated with a reduction in free-radical lipid oxidation and an increase in activity of enzymes involved in glucose utilization. The medications demonstrated significantly higher antidiabetic effect than gliclazide. The combination of antioxidative and hypoglycemic effects in the medications under study would make possible correction not only of glycemia, but also of the free-radical processes taking place in diabetes mellitus to decrease the risk of onset and progression of diabetic complications.

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AEP208

Clinical and biochemical differences in diabetic ketoacidosis in people with type 1 and type 2 diabetes mellitus

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Introduction
Once thought to typify type 1 diabetes mellitus (T1DM), diabetic ketoacidosis (DKA) in people with type 2 diabetes mellitus (T2DM) is also now increasingly recognized. We explored the clinical and biochemical differences in DKA in the two types of diabetes.
Methods
This retrospective cohort study included all the DKA episodes from April 2014 to September 2020 at a large tertiary care centre in West Midlands, United Kingdom. People admitted with DKA were classified as having T1DM or T2DM based on previously established diagnosis, treatment history, autoantibody status, and/or phenotypic features. The two groups were compared for differences in precipitating factors, biochemical profiles at presentation, management, and outcomes of the admission with DKA.
Results
A total of 786 DKA episodes were identified. Eighteen were excluded due to unclear underlying type of diabetes. 75.9% (n = 583/768) had T1DM, and 24.1% (n = 185/768) had T2DM. The most common precipitating causes in both groups were intercurrent illness (total: n = 272/768, 35.42%; T1DM: n = 198/583, 33.96%; T2DM: n = 74/185, 40.00%) and suboptimal compliance to treatment (total: n = 206/768, 26.82%; T1DM: n = 176/583, 30.19%; T2DM: n = 30/185, 16.22%). There was no clear precipitant in 16.15% (n = 124/768) (T1DM: n = 95/583, 16.30%; T2DM: n = 29/185, 15.68%). There was no significant difference in biochemical profiles on admission [median(Q1-Q3) pH (T1DM: 7.22(7.09–7.29); T2DM: 7.24(7.11–7.30); P = 0.3266), bicarbonate (T1DM: 11.90(7.13–16.78); T2DM: 13.20(7.75–17.80); P = 0.2192), glucose (T1DM: 28.00(20.45–34.80); T2DM: 26.55(16.21–35.09); P = 0.4496), lactate (T1DM: 2.6(1.8–4.3); T2DM: 2.6(2.04–4.21); P = 0.6532), serum osmolality (T1DM: 310.07(300.61–320.90); T2DM: 312.13(300.11–328.79); P = 0.2787)] between the two groups, except for urea, which was higher in T2DM [T1DM 7.1(5.1–10.6); T2DM 8.9(6.4–16.8); P < 0.0001]. There was no difference in appropriateness of fixed rate intravenous insulin infusion administered [T1DM: 100.00%(93.53–104.48); T2DM: 99.48%(90.00–102.27); P = 0.0688], proportion of hourly glucose measurements [T1DM: 99.49%(61.71–131.95); T2DM: 92.78% (64.33–120.22); P = 0.2143], proportion of hourly ketone measurements [T1DM: 46.39% (24.30–71.43); T2DM: 44.43% (20.90–70.74); P = 0.6485], and fluids administered [T1DM: 80.00% (58.33–100.00) vs 80.00% (50.00–112.50); P = 0.4978]. People with T1DM had more episodes of hypoglycaemia [T1DM 0(0–1); T2DM 0(0–0); P = 0.0056] during DKA management. Although there was no difference in the total DKA duration between the two groups [T1DM: 13.92(9.11–21.92); T2DM: 13.90(7.73–21.12); P = 0.4638], people with T2DM had significantly longer hospital stay [T1DM: 2.95(1.68–6.05); T2DM: 11.02(4.99–23.11)]; P < 0.0001].
Conclusion
Both cohorts had similar DKA severity, management, complications, and duration. People with T2DM required longer hospital stay, suggesting a more complex need for care, and increased economic burden. Increased awareness of DKA in people with T2DM is needed for improved prediction and prevention.

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AEP209

Clinical and biochemical assessment of erectile dysfunction in men with type 1 diabetes

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Background
Erectile Dysfunction (ED) is a common complication of diabetes, but also one of the most underdiagnosed. ED is considered a vascular impairment that shares many risk factors with cardiovascular disease (CVD) and could be an early marker of systemic endothelial dysfunction. The aim of our study is to assess the prevalence and risk factors for ED by using the International Index of Erectile Function- 5 (IIEF-5) in type 1 diabetic men undergoing a health investigation.
Methods
This is a cross-sectional, prospective study including 50 type 1 diabetic men. All men underwent a detailed health examination including physical assessment, evaluation of various life-style factors, medical history and a blood analysis. IIEF-5's Arabic version was used to assess the prevalence and the degree of ED. A hormonal assessment was performed including testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), free thyroxine (FT4) and Prolactin. Borderline hypogonadism was defined as the presence of total testosterone level < 3 ng/ml.
Results
The mean age the study group was 37.88 ± 9.31 years. According to the IIEF-5 score, 67% reported on any degree of ED, 25.7% had mild ED (IIEF-5 score 17–21), 18.9% mild to moderate ED (IIEF-5 score 12–16), 12.4% moderate ED (IIEF-5 score 8–11) and 10% severe ED (IIEF-5 score 5–7). The mean duration of diabetes in this group was 12.2 ± 7.9 years. The prevalence of comorbid conditions increased with ED severity (P < 0.05).

Risk factors for ED were microvascular complications of diabetes (OR: 1.02; 95% CI: 0.99–1.6), and hyperlipidemia (OR: 2.20; 95% CI: 1.55–3.5). Borderline hypogonadism was found in 10.5% of men with ED with mean testosterone level 2.2 ± 0.2 ng/ml. The prevalence of hypogonadism was higher in diabetics with diabetic nephropathy (32%) and diabetic retinopathy (28%).
Conclusions
ED is frequent in diabetic men; its frequency is correlated with the presence of microvascular complications and hyperlipidemia.

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AEP210

Diabetic bullosis: about 2 cases

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Introduction
Dermatological manifestations associated with diabetes affect approximately 30% of patients. Diabetic Bullosis is a rare complication of diabetes. It is a rare bullous dermatosis charecterised by the occurrence of bubbles on healthy skin with variable levels of cleavage.
Objective
We propose to study the epidemiological, clinical and evolutionary characteristics of Diabetic Bullosis in diabetic patients who are followed up at the Endocrinology Department of Sfax, Tunisia.
Patients and methods
Descriptive, retrospective study of diabetic patients over a period of 15 years (2005–2019). The disease was retained clinically.
Results
Diabetic bullosis was found in 2 male patients aged 69 and 87 years respectively at the time of diagnosis of bullosis. One was type 1 diabetic and the other type 2 diabetic. The diabetes had been progressing for 10.5 years. The recommended therapy was empirical insulin therapy in 1 case, oral antidiabetic drugs relayed by insulin in 1 case. Diabetes was complicated by sensitive polyneuritis in gloves and socks in one case and diabetic nephropathy in another case. No other skin or osteo-articular complications were objectified. Clinically, the skin lesions presented as multiple bullous lesions, without inflammatory areola, with clear content, occurring on healthy skin sitting on the hands in one case and on the big toe in another case. Therapeutically, local care was recommended in both cases, combined with antibiotic therapy in one case due to bacterial superinfection. An improvement of the lesions occurred in 1 case.
Conclusion
The bullosis of diabetics is a characteristic skin complication of diabetes. Its etiology is still unknown. Its evolution is benign and its treatment remains essentially preventive.

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AEP211

Selective sodium-glucose cotransporter inhibitors 2 (isglt2) in patients with high risk of amputation

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Introduction
The use of iSGLT2 remains controversial in diabetic patients with peripheral arterial disease.
Objectives
Assess metabolic effect and risk of amputations of iSGLT2 in diabetic patients treated in the Multidisciplinary Unit of Diabetic Foot (MUDF) comparatively with a control group.
Design and methods
Retrospective observational study in which the patients seen at the MUDF from December 2017 to January 2021 were recruited. A treatment group with iSGLT2 was selected and these data were compared with a control group. Clinical, metabolic, anthropometric variables and amputation rate were collected in both arms. Statistical analysis was performed using the SPSS program (SPSS, inc, v21.0).
Results
312 patients were recruited: 83 in treatment with iSGLT2 and 229 as a control group. The treatment group had a mean age of 65.99 ± 10.31 vs 68.14 ± 12.11 years of the control group ($P = 0.12$) and a disease evolution time of 17.33 ± 10.26 vs 18.10 ± 11.97 ($P = 0.52$). Weight of 86.88 ± 17.77 kg vs 82.65 ± 15.65 kg ($P = 0.57$) and a mean BMI of 31.07 ± 5.61 kg/m^2 vs 29.58 ± 4.91 kg/m^2 ($P = 0.03$). Basal HbA1c (iSGLT2 vs control group): 8.83 ± 1.67% vs 7.71 ± 1.72% ($P = 0.00$); mean reduction: 1.04 ± 1.32% vs 1.42 ± 2.34% ($P = 0.38$); Final HbA1c: 8.08 ± 1.37 vs7.42 ± 1.32% ($P = 0.05$). No statistical significant differences between the basal LDL values (96.29 ± 38.95 mg/dl vs 98.8 ± 40.93 mg/dl, $P = 0.67$)) or the reductions obtained in both arms (11, 28 ± 31.16vs12.25 ± 31.84, $P = 0.91$). Risk factors for amputation: higher proportion of hypertension (78.3% vs 72.2%), dyslipidemia (74.7 vs 71.1%), smokers (58.2 vs 49.8%) in the group with iSGLT2, as well as a greater history of chronic ischemia (41 vs 38.2%) and neuropathy (74.4 vs 70.9%). The rate of amputations after follow-up was 15.7% in the iSGLT2 group compared with the 12.3% control group ($P = 0.55$).
Conclusions
This study shows that treatment with iSGLT2 in a group of diabetic patients with a high risk of amputations is effective and safe, not increasing this rate comparing with control group of MUDF, despite presenting greater number of risk factors for it.

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AEP212

Influence of diabetes in heart failure with preserved ejection fraction

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Introduction
Heart Failure with Preserved Ejection Fraction (HFpEF) denotes a growing challenge due to the population aging and the rising prevalence of cardiovascular risk factors.
Aim
We aimed to evaluate the influence of the diagnosis of diabetes mellitus (DM) on the signs and symptoms, comorbidities and echocardiographic and vascular evaluation of patients with HFpEF in a stable phase.
Methods
Cross-sectional study including 94 patients with HFpEF in stable phase, followed in our center. Signs, symptoms and comorbidities were obtained by anamnesis, physical examination and patient medical records. The cardiac function was evaluated by echocardiography performed by expert cardiologists. Endothelial function (Reactive Hyperemia Index) was evaluated with the EndoPATTM2000 device, and carotid-femoral pulse wave velocity. The associations between DM and previously defined outcomes were assessed through linear and logistic regression models, adjusted for sex, age, systolic blood pressure (SBP) and body mass index (BMI).
Results
The included population ($n = 94$) has an average age of 73.8 ± 8.8 years and 53.8% are males. Average BMI is 29.4 ± 5.3 kg/m^2 and 52.7% of the patients have DM. Concerning signs and symptoms, no differences were recorded regarding oedema, NYHA class, orthopnea or nocturnal paroxysmal dyspnea. About comorbidities, patients with DM have higher SBP (OR 14.2 [5.0 to 23.4] mmHg; $P < 0.01$), and higher prevalence of both peripheral arterial (OR 15.5 [2.6 to 92.7]; $P < 0.01$) and cardiovascular atherosclerotic (OR 6.4 [1.5 to 26.8]; $P = 0.011$) diseases. The echocardiographic evaluation showed that patients with DM have an inferior isovolumetric relaxation time (ms) comparing to patients without DM (ß = –11.4 [-22.4 to -0.36]; $P = 0.019$). Patients with DM have a higher pulse wave velocity (m/s), comparing to patients without DM (ß=2.13 [0.92 to 3.33]; $P < 0.01$).
Conclusion
In patients with HFpEF, the presence of DM associates not only to higher prevalence of comorbidities but also to deleterious cardiac structural and vascular changes.

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AEP213

Analysis of lipid profile in a sample of patients with type 1 diabetes (T1D)

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Introduction
Dyslipidemia is a major cardiovascular risk factor, being its detection and control essential due to risk of serious complications. Numerous trials have demonstrated its relationship with T2D, but it has not been so well studied in T1D.
Objective
To obtain information about relationship between dyslipidemia and T1D and analyze its prevalence and control in a sample of patients.
Material and methods
Retrospective descriptive observational study that analyzes data from 235 patients with DM1 in Endocrinology Consultation at Virgen de la Victoria Hospital in Malaga.
Results
50.6% were women, with a mean age of 34.59 ± 12.6 years; BMI 25.47 ± 4.27 kg/m^2 and diabetes of 18.09 ± 10.15 years of evolution. From all of them, 93 (39.6%) had dyslipidemia with mean analytical parameters: glycemia 159 ± 74.4 mg/dl, HbA1c 8.6 ± 7.5%, total cholesterol 179.2 ± 7.5 mg/dl, HDL 59.9 ± 36.6 mg/dl, LDL 106.4 ± 76.9 mg/dl, triglycerides 104 ± 216.5 mg/dl. Only 74 (79.6%) received lipid-lowering treatment: 71 (76.3%) statins; 2 (2.2%) statins plus ezetimibe and 1 (1.1%) fenofibrate; with results at 6 months of: CT 163 ± 32 mg/dl, HDL 57 ± 16 mg/dl, LDL 88 ± 24 mg/dl, TG 90 ± 47 mg/dl. From them 17 (22.97%) achieved LDL < 70 mg/dl; 35 (47.29%) presented figures between 70–100 mg/dl and 22 (29.79%) LDL > 100 mg/dl. The sum of patients in treatment with LDL < 100 mg/dl was 52 (70.26%). In addition, they presented a higher percentage of comorbidities compared to non-dyslipidemic patients: hypertension 43 (18.3%) patients with dyslipidemia compared to 6.3% of non-dyslipidemic patients, smoker 29.8% vs 27.5%; taking antiaggregant 19.6% vs 8.5%; and complications: retinopathy 15.3% vs 9.2%; diabetic kidney diseases 13.2% vs 12.7%; neuropathy 3.8% vs 3.5% and a history of CVD 3% vs 0.7%.
Conclusion
There is a significant relationship between dyslipidemia and age, DM1 evolution time and BMI but not HbA1c. Furthermore, it is more frequent in those patients who present other cardiovascular risk factors.

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AEP214

ABSTRACT WITHDRAWN

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AEP215

Rare case of fluoroquinolone induced hypoglycaemia

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We would like to present an interesting unusual case of fluoroquinolone induced hypoglycaemia. As per FDA Adverse Event reporting System and medical literature published between 1987–2017, fluoroquinolones are said to have caused about 67 cases of life-threatening hypoglycaemic coma including 13 deaths and 9 permanent disabling injuries, most cases were associated with levofloxacin. Its hypoglycaemic effect is more common in elderly population who are on oral hypoglycaemic agents and insulin but can also happen in non diabetics. Our patient was a sixty seven year old woman who presented with an unwitnessed fall and decreased oral intake. She had a background of learning disability, hypertension, epilepsy, bronchial asthma, chronic iron deficiency anaemia, chronic mild lymphopenia, osteoporosis and previously treated uterine cancer. After clinical review an impression of hospital acquired pneumonia with possible aspiration pneumonia was made along with hyponatraemia secondary to dehydration. She was commenced on intravenous levofloxacin 500 mg twelve hourly and metronidazole 500 mg eight hourly. On first day of admission, venous plasma glucose was noted to be 7.1. She was not known to have diabetes. On third day of admission she was found unresponsive with an early warning score of four, capillary blood glucose was found to be 0.6 mmol/l, this improved with 10% glucose. Blood sugars continued to be low requiring further intravenous glucose. A medication review was undertaken and levofloxacin was discontinued. After 24 hrs of discontinuation of levofloxacin, the hypoglycaemic episodes resolved and her blood glucose later remained > 5 mmol/l throughout the admission.. A short synacthen test showed normal cortisol response (At 0 min – 262 nmol/l, 30 mins- 467 nmol/l). As the patient had no further hypoglycaemic episodes after stopping levofloxacin, a diagnosis of levofloxacin induced hypoglycaemia was made and no further investigation was deemed appropriate at that point. In experimental studies with rat islet cells exposed to quinolones, an increase in insulin secretion via blockade of adenosine triphosphate (ATP)–dependent potassium channels was observed. Thus, the possible mechanism could be increased insulin release via blockade of ATP-sensitive potassium channels in the beta-cells of the pancreas. Health professionals should be aware of the potential risk of severe hypoglycaemia with the use of Fluoroquinolones as it remains antibiotic of choice for many inflammatory conditions and blood glucose monitoring should be recommended if it is prescribed in elderly diabetic patients or in elderly patients who have poor oral intake or in those with other comorbidities to prevent life threatening hypoglycaemia.

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AEP216

Microvascular complications in type 1 diabetes diagnosed during adulthood: prevalence and predictive factors

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Introduction
Type 1 diabetes (T1D), also known as juvenile diabetes, commonly occurs in young individuals. However, autoimmune diabetes may be diagnosed in the elderly, with different clinical and biological aspects. The aim of our study is to identify the prevalence of and risk factors for microvascular complications related to T1D diagnosed during adulthood.
Patients and methods
A retrospective study, from 2010 to 2019, including 166 patients diagnosed with T1D occurred after the age of 20, with positive anti-pancreatic antibodies (Anti GAD, Anti ICA and/or Anti IA2). The incidence of microvascular complications and potential predictive factors were analyzed.
Results
Mean age was 31.81 years (95 males vs 71 females). Mean diabetes duration was 7.34 ± 6.73 years (2 months-44.5 years) and 57.8% of patients had diabetes that had progressed for at least 5 years. Microvascular complications occurred in 21.5% of patients. A total of 16 patients (9.6%) had diabetic retinopathy after a mean diabetes duration of 13.23–9.26 years (0.7–38 years). Diabetic kidney disease was observed in 6% of patients after an average duration of diabetes of 16.7 ± 6.68 years. The mean urea and creatinine level was 5.35 mmol/l and 75.8 umol/l,respectively. The prevalence of albuminuria was 7.2%. Seven patients underwent hemodialysis for *end-stage renal disease*. Peripheral neuropathy complicated diabetes in 18.1 % of patients after a mean duration of 9.66 ± 7.55 years (1–30 years). Only 15 patients had cardiovascular autonomic neuropathy: urogenital dysfunction in 14 patients, gastroparesis in 3 patients and orthostatic hypotension in 1 patient. Diabetic retinopathy and kidney disease were both significantly more common in men ($P < 0.05$).A higher prevalence of diabetic retinopathy was significantly observed in patients with longer diabetes duration ($P < 0.05$). Patients who developed diabetic kidney disease were significantly older ($P < 0.05$). Furthermore, there was a significant correlation between this complication and high blood pressure. Diabetic kidney disease was also significantly associated with an increased incidence of diabetic retinopathy, hypertension and macrovascular complications. Diabetic neuropathy was significantly related to diabetes duration, age, basal metabolic index (BMI) and creatinine clearance ($P < 0.05$).

Conclusion
Among adults who had been diagnosed with T1D, screening of microvascular complications remains a crucial step in T1D's management. Their early identification helps to reduce their adverse repercussions.

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AEP217

In the context of acute disease does the same hyperlactatemia cut-off point hold similar meaning in patients with and without Diabetes mellitus? A retrospective study

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Introduction
Hyperlactatemia is defined by a lactate value > 2 mmol/l and a lactate value above > 4 mmol/l is commonly used to define more severe hyperlactatemia. It is a common disorder in critically ill patients, associated with adverse prognosis. Diabetes mellitus (DM), however, can also be associated with increased lactate levels at baseline.
Objectives
To document the development of severe hyperlactatemia in acute situations in patients with and without DM; to analyze potential contributors to lactate elevation and its impact on mortality; to analyze whether lactate values > 4 mmol/l have equal prognostic significance in patients with and without DM.
Materials and methods
A retrospective cross-sectional study was performed with patients admitted to internal medicine wards in the context of acute disease, displaying lactate values ≥ 2 mmol/l. Data was collected regarding age, sex, independence-index, highest lactate values, contributors to hyperlactatemia, DM and mortality.
Results
A sample of 151 patients with lactate ≥ 2 mmol/l was analyzed, median age of 83.00 ± 17.00 years, 55.00% female. DM was present in 55.60% and these patients had higher lactatemia (5.35 ± 4.84 vs 3.90 ± 3.56 mmol/l, $P = 0.003$), with the majority reaching values > 4 mmol/l (vs 34.8% in non-DM patients). The most frequently identified potential contributors to the development of severe hyperlactatemia (lactate > 4 mmol/l) in DM patients were metformin consumption concomitantly with factors potentiating its accumulation, sepsis/septic shock, ischemia and neoplasia. In non-DM patients the last three factors were the most frequently found. The 30-day mortality rate was 25.82% and deceased patients also displayed higher lactatemia during hospital stay (5.93 ± 5.19 vs 4.52 ± 4.21; $P = 0.037$). Lactate values > 4 mmol/l were more frequently associated with mortality and these values were observed more often in patients with DM. However, a tendency towards higher lactate values in DM patients was registered not only in those who died, but also in the patients who survived. In multivariate analysis, lactate values > 4 mmol/l were an independent predictor of mortality in the global sample and in the subgroup without DM, but not in DM patients.
Conclusion
In our sample, patients with DM reached higher lactate levels than non-DM patients. Our analysis, however, raises the possibility that the same lactate values may not have equal capacity to assess prognosis in acute situations in patients with and without DM, since a lactate value > 4 mmol/l was an independent predictor of mortality only in non-DM patients. Large-scale studies are needed to optimize cut-off points for lactatemia in patients with high baseline values, such as DM patients.

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AEP218

Utilisation of fibrosis-4 (fib-4 score) for screening non-alcoholic fatty liver disease (nafld) in women with type 2 diabetes (t2dm) in real world setting

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Introduction
Limited evidence exists for hepatic fibrosis in Type 2 Diabetes (T2DM). NAFLD is an independent risk factor for incident diabetes with trends towards increased risk in women.
Methods
We conducted a cross-sectional, retrospective analysis in 438 women with T2DM.FIB-4 score was used to estimate extent of incidental finding of liver fibrosis.
Results
Mean fibrosis 4 score (FIB-4) was 1 (SD ± 0.66, 95% CI 0.98 to 1.1), Vs (HbA1c <7%, $n = 117$, 1.11) and uncontrolled group of diabetes (HbA1c ≥ 7%, $n = 321$, 1.02); $P = 0.21$. Mean AST, ALT (u/l) and platelet (109/l) were 23, 24 and 301, respectively. Patients were grouped based on FIB-4 scores (group 1: < 1.45, group 2: ≥ 1.45 < 2.67, group 3: ≥ 2.67 < 3.25, group 4: ≥ 3.25) for HbA1c, duration of diabetes and age (Table 1). Difference in age groups was statistically significant ($P < 0.0001$) with youngest patients (56.8 years) lowest FIB-4 scores
Conclusion
FIB-4 score was a simple, cost effective tool to identify T2DM women who are at risk of hepatic outcomes without any apparent clinical symptoms of liver disease. Patients with FIB-4 score in the range 1.45–2.67 were provided lifestyle modification and managed by pharmacotherapy options of pioglitazone, vitamin E, SGLT2 inhibitors, GLP-1 agonists and saroglitazar and patients with higher scores (≥ 2.67) were timely referred to hepatologists

Table 1. Age, Duration of Diabetes and HbA1c by FIB-4 range (mean ± SD, 95% CI)

	Overall	Group 1 FIB-4 < 1.45	Group 2 FIB-4 ≥ 1.45 < 2.67	Group 3 FIB-4 ≥ 2.67 < 3.25	Group 4 FIB-4 ≥ 3.25	p value (comparison across FIB-4 range)
No. of patients	438	368	58	5	7	
Age	58 ± 10.0, 95% CI 57.0 to 59.0	56.8 ± 10.2, 95% CI 55.8 to 57.9	65.9 ± 7.0, 95% CI 64.0 to 67.7	64.8 ± 9.9, 95% CI 52.4 to 77.1	60.4 ± 6.9, 95% CI 54 to 66.8	< 0.0001
Duration of Diabetes	10 ± 7.3, 95% CI 9.3 to 11	9.7 ± 7.3, 95% CI 9.0 to 10.5	10.7 ± 6.9, 95% CI 8.8 to 12.5	7.62 ± 4.5, 95% CI 1.9 to 13.3	15.2 ± 5.6, 95% CI 10.0 to 20.4	0.16 (NS)
HbA1c	7.9 ± 1.5, 95% CI 7.8 to 8.1	7.8 ± 1.4, 95% CI 7.7 to 8.0	8.2 ± 1.8, 95% CI 7.7 to 8.7	7.5 ± 1.2, 95% CI 6.0 to 9.0	7.3 ± 1.0, 95% CI 6.4 to 8.3	0.30 (NS)

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AEP219

Comparative evaluation of dapagliflozin and empagliflozin influence on the biomarkers of fibrosis and inflammation in patients with type 2 diabetes and very-high risk of cardiovascular events

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Recently, sodium-glucose cotransporter 2 inhibitors (SGLT2i) have demonstrated cardioprotective effects. However, findings for major adverse CV events (MACE) outcomes with dapagliflozin are not concordant with the empagliflozin studies and the possible mechanisms of cardioprotective effects are not fully understood. The aim of the study was to compare the two distinct SGLT2i, empagliflozin and dapagliflozin, in their influence on the biomarkers of fibrosis and inflammation.
Materials and methods
Sixty two patients with type 2 diabetes (T2DM) and 3 major risk factors for cardiovascular events were included in the study. Patients were randomized into either empagliflozin group (10 mg/day) or dapagliflozin group (10 mg/day). Duration of the study was 6 months. The outcome measures included changes in glycated hemoglobin (HbA1c), galectin-3, tissue inhibitor of metalloproteinase-1 inhibitor (TIMP-1), procollagen type I carboxy-terminal propeptide (P1CP), matrix metalloproteinase-9 (MMP-9), paraoxonase 1 (PON1), ST-2, C-reactive protein (CRP) and interleukin-6 (IL-6).
Results
Baseline characteristics were not different in the empagliflozin and dapagliflozin group. After 6 months of treatment, patients in both groups showed significant improvements in body mass index (BMI), fasting glucose (FG), and HbA1c levels. There were no significant differences in galectin-3, P1CP, MMP-9, ST-2, CRP, IL-6, TIMP-1 and PON1 concentrations between groups after 6 months of treatment.

Conclusion
Our study demonstrated that dapagliflozin and empagliflozin did not differ in their influence on biomarkers of fibrosis and inflammation. However, larger studies are needed to clarify exact cardioprotective mechanisms of SGLT2i.

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AEP220

Visceral adiposity index and atherogenic index of plasma: Simple markers of insulin resistance in type 2 diabetic patients

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Introduction
Homeostasis model assessment for insulin resistance (HOMA-IR) is widely used as a marker of insulin resistance. However, it reminds an expensive maker requiring insulin dosage. Several studies tried to found simple alternative predictors of insulin resistance such as triglycerides to HDL-C ratio with conflicting reported findings. The aim of our study was to investigate the usefulness of the atherogenic index of plasma (AIP) and the visceral adiposity index (VAI) as insulin resistance markers.
Methods
We conducted a transversal study in 55 patients with type 2 diabetes mellitus treated with oral antidiabetic drugs. All participants had physical examination and laboratory investigations. HOMA-IR index, AIP and VAI were calculated.
Results
The study population included 29 women and 26 men. Their mean age was 54.6 ± 10.1 years. Seventy seven percent of patients had well-controlled diabetes. The mean of fasting insulin levels was 9.7 ± 5.1 miu/l. Sixty two percent of patients had insulin resistance. The mean of VAI was 2.5 ± 1.7 with extremes of 0.46 and 8.75. According to VAI level, adipose tissue dysfunction was absent, mild, moderate, and severe in 46, 9, 25 and 20% of patients, respectively. The VAI was positively correlated with insulin level ($r = 0.557$; $P < 10^3$) and HOMA-IR index ($r = 0.569$; $P < 10^{-3}$). Patients with insulin resistance had significantly higher VAI than those without insulin resistance ($P = 0.033$). The AIP demonstrated a low risk in 47%, an intermediate risk in 15% and a high risk in 38% of patients. This index was positively correlated with insulin level ($r = 0.432$; $P = 0.001$) and HOMA-IR index ($r = 0.468$; $P < 10^{-3}$). However, no significant difference was found between patients with or without insulin resistance ($P = 0.069$).
Conclusion
AIP and VAI are commonly used as markers of atherosclerosis and cardiovascular risk. However, our results demonstrated that they could be used as simple and inexpensive markers of insulin resistance instead of insulin dosage and HOMA-IR index.

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AEP221

Plasma angiopoietin-like 4 protein: Long term evolution after 3 different techniques of bariatric surgery

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Introduction
Angiopoietin-like 4 protein (ANGPTL-4) is importantly produced in adipose tissue, mediates the inhibition of lipoprotein-lipase and has been recently related with the risk of atherosclerosis and type 2 diabetes (T2D). Bariatric surgery has demonstrated improvements in lipid profile, T2D and cardiovascular risk. But information about ANGPTL-4 circulating levels in severe obesity and after bariatric surgery is scarce.
Objective
To evaluate the evolution of circulating ANGPTL-4 seven years after 3 different techniques of bariatric surgery and its relationship with improvement in lipid profile.
Results
ANGPTL-4 circulating levels and lipid profile were analyzed in 23 non-diabetic women (age 37.7 + 9.3) with severe obesity (BMI 48.9 ± 6.5 kg/m^2) before and 6.9 ± 2.1 years after bariatric surgery: sleeve gastrectomy ($n = 8$), gastric bypass ($n = 8$) and biliopancreatic diversion ($n = 7$) (weight loss 42.0 ± 16.3 kg) as well as in 8 control lean women. ANGPTL -4 levels (ng/ml) decreased significantly (304.53 ± 48.75 pre vs 197.77 ± 64.10 post; $P < 0.001$; control 172.51 ± 28.01; $P < 0.001$ vs pre, and without differences with post-surgery levels ($P = 0.293$). There were no differences in ANGPTL-4 change among groups. Triglycerides and HDL-cholesterol, as expected, improved as well after surgery. Correlations were found between ANGPTL-4 and improvement in HDL-cholesterol ($r = –0.48$, $P = 0.028$).
Conclusion
Plasma ANGPTL-4 is markedly elevated in women with severe obesity and 7 years after bariatric surgery it decreases to levels comparable to control lean subjects, in parallel with triglycerides and HDL-cholesterol improvement. These findings suggest that ANGPTL-4, mainly derived from adipose tissue, could be an important mediator of lipid improvement after bariatric surgery.

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AEP222

Insulin resistance in association with cardiovascular risk factors and thyroid function

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Insulin resistance (IR) occurs as part of a cluster of cardiovascular-metabolic abnormalities. Given the seriousness of the cardiovascular diseases data there is the increasing burden of diabetes.
The aim of the study was to investigate insulin resistant in association with cardiovascular risk factors among 45–84-year-old citizens of Palanga.
Methods
A randomized epidemiological study was performed with 850 subjects. All participants were evaluated for sociodemographic, clinical, cardiovascular risk factors and biochemical analysis (including glucose, insulin, thyroid hormones (TH), total cholesterol, LDL and HDL and triglyceride). IR was evaluated by homeostasis model assessment of IR (HOMA-IR).
Results
All study participants were stratified into groups without IR (HOMA-IR≤2.7) 67% ($n = 557$) and with IR (HOMA-IR > 2.7) 33% ($n = 278$). Participants with IR were more likely to be older, female and have lower education. The analysis between two groups showed some significant relationships between IR and cardiovascular risks factors, e.g. triglyceride levels was significantly higher (respectively 1.7 and 1.2 mmol/l) and HDL significantly was lower (respectively 1.3 and 1.6 mmol/l) in group with IR compared with group without IR. The IR group had a statistically significant higher incidence of metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM) (51.4% and 16.2%, respectively) compared with group without IR (11.0% and 3.1%, respectively). There were no significant differences of TH between groups according to RI. However in groups according to MetS, concentrations of TSH, FT3 and FT3/FT4 ratio differed significantly. Significantly higher TSH and lower FT3 was in the group with MetS. The predictable accuracy was presented using receiver performance characteristics curves for HOMA-IR scores in women and man separate. If the HOMA-IR score is higher than 3.45, he or she is significant more likely to have T2DM. In men cut-off was higher (3.52), with higher sensitivity (94.1), but slightly lower specificity (79.9) compared with women (respectively 3.35, 65.0 and 84.4). These data demonstrated invariant relationship between HOMA-IR and presence of T2DM.
Conclusions
The results showed several significant associations between IR and cardiovascular risk factors, as well as between higher TSH, lower FT3, and MetS. HOMA-IR cut-offs can predict the presence of T2DM and HOMA-IR can be used not only for indicating the presence of IR.

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AEP223

Free T4 level may be associated with insulin requirement in gestational diabetes mellitus

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Introduction
Gestational diabetes mellitus (GDM) may frequently be overcome by nutrition therapy alone, but insulin regimen may be necessary in about 30 % of the patients with GDM. It was known that thyroid hormones were associated with glucose metabolism. Therefore, we aimed to investigate the association of fT4 level with insulin requirement in euthyroid pregnant women with GDM.
Materials and methods
We consecutively included euthyroid patients with GDM, and excluded those with thyroid dysfunction or any previous history of use of levothyroxine or antithyroid drug. The diagnosis of GDM was based on ADA criteria. Demographic features, previous history of GDM, gestational hypertension, insulin requirement (absent vs present or basal vs intensive regimen) and dose, nutrition and exercise adherence, and HbA1c, TSH, fT4, fT3, 25(OH) vitamin D3 levels were analyzed. We grouped the patients according to fT4 levels: lower than mid-normal (group A) vs upper than mid-normal (group B), or lower than normal range vs in normal range. We assessed the patients in 3rd trimester after 34th weeks of the pregnancy.
Results
Of total (n = 228), insulin was necessary in 58 patients. Insulin use was more frequent in the patients with fT4 level lower than normal range than those with normal fT4 (P = 0.003, OR:5.69 (95% CI 1.60–20.24)). Number of insulin injections was higher in group A than group B (0.022). fT4 level was not associated with insulin dose, HbA1c level, previous history of GDM, or diet adherence.
Conclusion
Lower fT4 level even in normal range may worsely affect glucose metabolism in euthyroid pregnant women with GDM. Our findings suggest that euthyroid hypothyroxinemia in pregnancy may be associated with difficulty in control of hyperglycemia. GDM would be an indication for treatment with levothyroxine in euthyroid hypothyroxinemia.

	Insulin use		
Parameters	*Absent (n = 170)*	*Present (n = 58)*	*p value*
	X(±SD)		
Age(year)	*31.75(4.86)*	*31.97(4.49)*	*0.793*
Gravida	*2.04(1.03)*	*2.19(1.17)*	*0.471*
Parity	*0.87(0.88)*	*1.0(0.95)*	*0.385*
Insulin dose(U/day)	*NA*	*19.60(13.27)*	*NA*
HbA1c(%)	*5.26(0.44)*	*5.58(0.64)*	*0.003*
TSH(miu/l)	*1.50(0.80)*	*1.69(0.80)*	*0.104*
fT4(ng/dl)	*0.95(0.13)*	*0.93(0.13)*	*0.689*
fT3(pg/ml)	*2.58(0.48)*	*2.69(0.41)*	*0.071*
25(OH) vitamin D3(ng/ml)	*15.87(9.14)*	*16.90(6.95)*	*0.453*
	N		
Hypertension(absence/presence)	*169/1*	*55/3*	*0.022*
Previous GDM(absence/presence)	*156/14*	*51/7*	*0.383*
Diet adherence(absence/presence)	*3/167*	*4/54*	*0.050*
Exercise adherence(absence/presence)	*119/51*	*33/25*	*0.068*
Insulin use(absence/presence)			
Number of insulin injections(≤2/ > 2 per day)			
HbA1c(< 5.7/≥ 5.7 %)	*135/35*	*39/19*	*0.060*
HbA1c(< 6.5/≥ 6.5 %)	*169/1*	*49/9*	*0.001*
TSH(< 2.65/≥ 2.65 miu/l)	*155/15*	*51/7*	*0.470*
fT4(< 1.09/≥ 1.09 ng/dl)	*146/24*	*50/8*	*0.951*
fT4(in normal range/lower than normal range)	*166/4*	*51/7*	*0.003*

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AEP224

Treatment transition in a recently described HNF4α-MODY variant: Better late than never?

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Introduction
Maturity Onset Diabetes of the Young (MODY) type 1 is characterized by mutations in hepatocyte nuclear factor 4ń (HNF4ń) gene, leading to progressive dysfunction of pancreatic beta-cells with optimal response to sulphonylurea treatment. However, most of these patients are initially misdiagnosed as having type 1 diabetes and inappropriately treated with insulin. Data on adequate transferring from insulin to sulphonylureas following genetic diagnosis in this setting is limited.
Case
We report the case of a 45 year-old male with a so-called type 1 diabetes, diagnosed at 10 years-old. He was under metformin and glibenclamide for twelve years, and then insulin therapy was initiated. He was not overweight and presented significant family history of diabetes: mother, grandmother, father and a 12 year-old daughter (diagnosed two years ago, under insulin regimen). Further investigation revealed negative pancreatic antibodies, low C-peptide and poor metabolic control throughout the years, with diabetic retinopathy. Given these data, genetic testing for MODY was performed and identified a heterozygous missense variant of HNF4ńgene (c.602A > C, p.His201Pro), recently described in the literature (also found in his daughter). In December/2020, he was under an intensive basal-bolus insulin regimen (insulin detemir 14 units twice daily and insulin glulisine before meals; total daily dose 34 units, body weight 75.4 kg). Laboratory workup showed glucose 274 mg/dl, C-peptide 0.37 ng/ml (0.81–3.85), HbA1c 8.5%. Flash glucose monitoring system revealed estimated A1c 9.1% and marked glycemic variability: 67% above target, 32% in target and 1% below. Transferring of treatment was performed under medical surveillance: we stopped rapid-acting insulin, maintained long-acting insulin dosage and started gliclazide 80 mg/day. Close patient monitoring was maintained and three weeks later he presented a much more stable glycemic pattern with estimated A1c 7.6% and glucose values 37% above target, 63% in target and 0% below. Basal insulin was reduced to 20 units/day and gliclazide dose increased to 120 mg, with continuous glycemic improvement (estimated A1c 7.0%), on ongoing monitoring.
Discussion
Recent data on HNF4ńMODY suggests that sulphonylurea should be added to existing insulin therapy, rather than replacing it, in subjects with longer duration of diabetes who are overweight and have high HbA1c at the time of genetic diagnosis, as found in our case. Nonetheless, this commonly forgotten diagnosis should be seeked, given that treatment change could have significant clinical impact, with improvement of glycemic control and patient quality of life (as a pill replaced three insulin injections per day).

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AEP225

The effect of obesity on the association between type 2 diabetes mellitus and polycystic ovary syndrome: a meta-analysis of observational studies

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Objective
The exact risk of type 2 diabetes in women with polycystic ovary syndrome (PCOS) is unknown. It is also unclear if obesity independently increases the risk in this population. The aim of this study was to systematically review and synthesize the best available evidence regarding the association between PCOS and type 2 diabetes, stratified according to obesity status.
Methods
A comprehensive search was conducted in PubMed, CENTRAL and Scopus databases up to October 31, 2020. Data are expressed as relative risk (RR) with 95% confidence interval (CI). The I^2 index was employed for heterogeneity. Research design and methods: The eligibility criteria were fulfilled by 23 studies (319.780 participants; 60.336 PCOS and 8847 type 2 diabetes cases). Women with PCOS demonstrated a higher risk of type 2 diabetes than those without PCOS (RR 3.45, 95% CI, 2.95–4.05, $P < 0.001$; I^2 81.6%). This risk remained significant both in studies matched or unmatched for participants' age. With regard to body mass index, the RR for developing type 2 diabetes in obese and non-obese PCOS women compared with their non-PCOS counterparts was 3.24 (95% CI 2.25–4.65; $P < 0.001$; I^2 30.9%) and 1.62 (95% CI 0.14–18.50; $P = 0.70$; I^2 89.9%), respectively. The RR in obese compared with non-obese women with PCOS was 3.85 (95% CI 1.99–7.43; $P < 0.001$; I^2 46.2%). This was also the case for overweight compared with normal-weight women with PCOS.
Conclusion
Women with PCOS present an increased risk of type 2 diabetes compared with non-PCOS women only if they are obese/overweight.

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AEP226

Features of bacterial metabolism of the colon in patients with type 2 diabetes mellitus (T2D) and non-alcoholic fatty liver disease (NAFLD)

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The key factor in the pathogenesis of both T2D and NAFLD is insulin resistance, which causes the lipids accumulation in hepatocytes and an increase of the lipid peroxidation, the production of reactive oxygen species and the development of inflammation. It has been shown that the main metabolic products of the saccharolytic microflora-short-chain fatty acids (SCFA), such as acetic (Ac), propionic (Pr) and butyric (Bu), can have an anti-inflammatory effect through their suppression of histone deacetylase (HDAC) activity (Arpaia N *et al*., 2013).
The aim
To study the features of bacterial metabolism in the colon in patients with T2D and NAFLD in comparison with the activity of the lipid peroxidation process.
Materials and methods
The study included 46 patients with T2D and NAFLD, mean age – 56.4 ± 7.2 y. The activity of lipid peroxidation process was assessed by conc. of malondialdehyde (MDA) in blood. The concentrations of fecal SCFA (Ac, Pr, Bu, valerian acid and their isoforms) were determined by GLC- method.
Results
It was shown that the average blood MDA level in T2D + NAFLD patients was increased by 70% and amounted to 17.4 ± 1.3 mmol/l vs norm (N) - 10.1 ± 0.8 mmol/l ($P < 0.001$). The value of total SCFA (TSCFA) was reduced and averaged 8.6 ± 2.8 mg/g vs N 10.6 ± 2.6 mg/g, $P < 0.01$. In the structure of the metabolites, there was a decrease in the proportion of butyrate (T2D + NAFLD 12.1 ± 0.8% vs N 16.0 ± 0.6%, $P < 0.001$) and an increase of propionate one (T2D + NAFLD 23.1 ± 0.5% vs N 20.0 ± 0.6%, $P < 0.001$). In T2D + NAFLD patients in stage of steatohepatitis, there was a more pronounced decrease in total metabolic activity due to a decrease in conc. of butyrate. In addition, there was an increase in the proportion of iso-acids, metabolites of the proteolytic microflora (9.4 ± 0.7% vs N 6.3 ± 0.04%, $P < 0.02$). In order to assess the degree of anti-inflammatory action of microbiota, a correlation analysis was performed between conc. MDA and SCFA. There were significant correlations between the TSCFA ($r = –0.437$; $P = 0.049$), acetate ($r = –0.4550$; $P = 0.024$), propionate ($r = –0.375$; $P = 0.037$) and conc. MDA.
Conclusion
Thus, a decrease in the total metabolic activity of the colon microflora in T2D + NAFLD occurs due to a decrease in the activity of Bu-producing and an increase in Pr – producing bacteria. Inverse correlation conc. SCFA and MDA indicate a pronounced effect of the luminal SCFA on the processes of inflammation in T2D with NAFLD patients.

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AEP227

Diabetes and cftr gene mutations: Prevalence and correlation in patients with cystic fibrosis

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Aim
To establish a relationship between the severity associated with cystic fibrosis transmembrane conductance regulator protein (CFTR) mutations and the prevalence of abnormal glucose tolerance and diabetes in patients diagnosed with cystic fibrosis (CF).
Methods
Observational, cross-sectional, clinical research in patients with CF evaluated at Hospital Universitario Reina Sofía (Córdoba).
Results
29 patients were selected for the study. Age: 34.41 ± 8.95 years, with a CF evolution time of 26.22 ± 10.43 years. 55% women. 72.41% of patients had two severe mutations (class I, II and III mutations) while the remaining 27.59% had at least one mild mutation (class IV and V mutations). After the oral 75g-glucose test (OGTT) 17.2 % patients were diagnosed with cystic-fibrosis related diabetes (CFRD), 41.4% with impaired glucose tolerance (IGT) and 41.4% showed a normal glucose tolerance. 66.7% of patients with two severe mutations were diagnosed with CFRD or IGT, compared to 37.5% of patients diagnosed with CFRD or IGT who had at least one mild mutation ($P < 0.001$).
Conclusions
In our series, there are statistically significant differences in the prevalence of CFRD and IGT depending on the type of mutations in the CFTR protein, with a higher prevalence in those patients with severe genotype.
Keywords: diabetes, cystic fibrosis, genotype, complications

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AEP228

Association of IDO polymorphism with oxidative status, metabolic control and inflammation in patients with type 2 diabetes mellitus

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Introduction
The Indoleamine 2.3-dioxygenase (IDO) is an enzyme involved in tryptophan metabolism, encoded by the IDO1 gene in humans. In Caucasians, the rs9657182 polymorphism of IDO gene was found to be associated with neurobehavioral complications, especially depression. Several studies in Type 2 Diabetes Mellitus (T2DM) describe psychological factors as barriers to the successful implementation of a healthy eating plan. According to our knowledge there is a lack of data that relates the IDO polymorphism with oxidative status and inflammation in T2DM.
Aim
1) To evaluate the distribution of the genotypic and allelic isolated and combined frequencies of the IDO polymorphism; 2) To study a possible association of this polymorphism with biomarkers of oxidative status, diabetes metabolic control and inflammation.
Material and methods
Observational analytical epidemiological study in 150 Caucasian adults with T2DM aged 40–75 years. Two groups were formed: GI75 patients with angiopathy and GII75 patients without angiopathy. The IDO genotypes were identified using the endpoint analysis method. Blood levels of malondialdehyde, ascorbic acid (AA), homocystein (Hcy), Hemoglobin A1c, vitamins B6, B12 and B9 were measured by HPLC methods. Creactive protein (CRP) serum levels were achieved by ultrasensitive immunoturbidimetric assay. Statistical analysis was performed using SPSS, version 26.0. Statistical significance was considered for $P < 0.05$.
Results
CT genotype was the most prevalent (GI: 52.9%; GII: 38.5%) and the CC genotype was the least frequent (G: 13.7%; GII: 21.2%). There were no significant differences between groups in the distribution of genotypic and allele frequencies of the IDO polymorphism, but there were differences between sexes ($\alpha = 0.025$). The average blood concentrations of AA and vitamin B12 were significantly higher ($\alpha = 0.049$; $\alpha = 0.025$; respectively) in subjects with the TT genotype compared to the CC + TC genotypes. Mean value of CRP was statistically lower in TT genotype ($\alpha = 0.044$). Having the TT genotype seems to be associated with a decreased risk of having low AA blood levels (OR = 0.363 [0.155–0.850]; $\alpha = 0.020$) and higher CRP plasma levels (OR = 0.310 [0.126–0.762]; α=0.011). This genotype was also associated with an increased risk of having higher concentrations of Hcy (OR = 3.238 [1.340–7.824]; $\alpha = 0.009$).
Conclusion
The TT genotype of the IDO gene rs9657182 polymorphism seems to offer protection against inflammation (< CRP levels) and cardiovascular disease (< Hcys values), as well as, favoring the antioxidant capacity by association with higher vitamin C concentrations in patients with T2DM.

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AEP229

Treatment of psoriasis in patients with type 2 diabetes

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Skin diseases in patients with type 2 diabetes mellitus (T2DM) are increased. Patients with T2DM and psoriasis have an increased risk of psoriasis exacerbations.
Objective:
to study the influence of T2DM on the psoriasis treatment.
Materials and methods
We studied hospitalized patients with T2D and psoriasis in dermatological clinic during 5 years ($n = 47$) - the main group. Comparison group 1- patients with psoriasis without T2D ($n = 40$), comparison group 2 - patients with T2D without psoriasis ($n = 37$). Patients were excluded: with the psoriatic arthritis, GFR ≤ 45 ml/min/1.73 m^2.
Results
Patients of the main group (women-53.2%, men-46.8%, mean age 61.0 ± 7.7 years), comparison group 1 (women-55%, men- 45%, mean age 60.5 ± 7.5 years), comparison group 2 (women-54%, men-46%, mean age 62.0 ± 7.8 years) were same in clinical, anthropometric, anamnestic and laboratory data (AST, ALT, total cholesterol, creatinine, $p > 0.05$). Patients of the main group and comparison group 1 differed in serum glycaemia ($P = 0.005$), HbA1c ($P = 0.009$). Patients of the main group had an increase HbA1c (11.8 (7.9–12.3)) compared with the comparison group 2 (6.8(6.1–7.3), $P = 0.006$) in the exacerbation of psoriasis period.
Duration of inpatient treatment of psoriasis until remission in patients of the main group was significantly longer (16.1 ± 2.4 days) compared with the comparison group 1 (13.0 ± 2.1 days, $P = 0.041$). The number of patients who needed the use of systemic glucocorticosteroid was higher in patients of the main group (14.9 %) compared with the comparison group 1 (2.5 %), F=0.05, $P = 0.048$.
Conclusions
There is probably a correlation between psoriasis exacerbation and T2DM decompensation. T2DM in patients with psoriasis can lead to a more severe exacerbation of psoriasis, which increases the duration of treatment and the frequency of systemic glucocorticosteroid use, which can lead to a decrease in DM2 control.

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AEP230

Use of continuous glucose monitoring for control assessment in type 2 diabetes patients

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Continuous Glucose Monitoring (CGM) is proved to be useful for dose adjustment in patients treated with multiple insulin injection regimens or with continuous subcutaneous insulin infusion. CGM give precise information about glucose variability in type 1 diabetes but are rarely used in type 2 patients. We assessed continuous glucose monitoring systems (CGMs) as control assessment tool in patients with type 2 diabetes receiving different treatment regimens. We studied 85 patients (50 men, 35 women; mean age 43.93 ± 10.87 years, mean disease duration 21.91 ± 6.07 years) with type 2 diabetes (31 receiving non-insulin therapy, 33 treated with pre-mixed insulin, 21 on multiple insulin injections. Continuous glucose monitoring by using iProTM was performed for seven days and HbA1c was measured at the end of this period. High positive correlation was found between HbA1c (7.46 ± 1.19%) and average glucose level during CGM period (7.45 ± 1.57 mmol/l) ($r = 0.73$), AUC above limit ($r = 0.75$) and percentage of time spent with glucose above 7.8 mmol/l (38.26 ± 26.38%, $P < 0.05$, $r = 0.69$). There was similar but negative correlation between HbA1c and percentage of time within the limit 3.9–7.8 mmol/l for all groups (56.07 ± 24.28%, $P < 0.05$, $r = –0.63$). Comparing CGM results in different treatment groups we found similar correlations of HbA1c and percentage of time spent within limit (non-insulin treated group 55.65 ± 25.99%, $phi_1 = –0.48$; premixed insulin treated group 54.33 ± 24.85%, $phi_2 = –0.67$; intensified insulin treatment group 59.62 ± 21.36%, $phi_2 = –0.58$). No correlations were found between HbA1c and number of all, positive and negative excursions. These results do not differ for age and gender. We conclude that performing CGM in patients with type 2 diabetes could give more precise information about the overall control nevertheless short time reflected and could present details about glucose deviations and hypoglycemic episodes and thus be useful for current treatment adjustment.

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AEP231

Factors influencing pregnancy planning of women with diabetes

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Introduction
For diabetics, preparation for pregnancy is essential; it allows conception in the best conditions, in order to reduce the risk of fetal malformation and abortion. The objective of this study is to determine the factors involved in pregnancy planning.
Materials and methods
Descriptive retrospective study, including 200 patients with pre-gestational diabetes followed in the department of gynecology and obstetrics between October 2019 and October 2020.
Results
The study included 200 patients with an average age of 31.9 years (19–49). 31.2% had type 1 diabetes and 68.8% had type 2 diabetes. The mean presentational BMI was 23.36 kg/m (14–47). Glycemic control during

pregnancy was not achieved in 70.7% of patients. The average duration of diabetes was 6.5 years (1–20) with an HbA1c of 8.16%. Among the patients, 24.7% had planned their pregnancy (HbA1c less than 6.5%) compared to 75.3% who had not. In terms of motivation, pregnancy was highly desired in 75.2% of patients who had planned their pregnancy compared to 56.2% of other patients. Regarding the presence of previous obstetric complications, patients who had planned their pregnancy had a history of fetal death in utero in 19.51% vs 10.2%. In addition, there was no difference with respect to socio-economic level or the presence of social security coverage or the other obstetrical histories studied, or the type of diabetes.
Discussion
The occurrence of pregnancy in a woman with diabetes potentially carries many risks for both mother and child. Pregnancy programming involves therapeutic adaptation to achieve perfect glycemic control and screening for possible complications. All diabetic women of childbearing age should be educated in this regard.

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AEP232

Long-term testosterone therapy improves lipid profile in men with functional hypogonadism and overweight or obesity: 12-year observational data from a controlled registry study in a urological setting

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Background
Effects of testosterone therapy (TTh) on lipid parameters are inconsistent and may depend on treatment duration, route of administration, and adherence. While in short-term studies, testosterone usually lowers HDL, long-term studies seem to increase HDL. Total cholesterol, LDL and triglycerides are either reduced by TTh, or effects are neutral.
Material and methods
After excluding men with primary hypogonadism, 723 men with functional, symptomatic hypogonadism were either overweight or obese. 367 men received testosterone undecanoate injections 1000 mg/12 weeks following an initial 6-week interval (T-group), 356 men decided against TTh and served as controls (CTRL). Measurements were performed 1–4 times a year for approximately 6.913 patient-years. The lipid accumulation product (LAP) as an indicator of metabolic syndrome was calculated according to Kahn 2005. 12-year data are reported. Changes over time between groups were compared and adjusted for age, weight, waist circumference, fasting glucose, blood pressure, lipids and quality of life to account for baseline differences between the two groups.
Results
Mean baseline age (years): 58.8 ± 5.9 (T-group), 63.1 ± 4.9 (CTRL) (P < 0.0001). Mean (median) follow-up: 9.3 ± 3.0 (10) years (T-group), 9.8 ± 2.6 (11) years (CTRL). Lipids at 12 years (mmol/l), mean±SE: Total cholesterol decreased by 2.6 ± 0.1 (T-group) and increased by 1.4 ± 0.1 in CTRL, estimated adjusted difference between groups: -4.0 [95% CI: -4.1;-3.8] (P < 0.0001 for all). HDL increased by 0.5 ± 0.0 (T-group) and decreased by 0.4 ± 0.0 (CTRL), between-group difference: 0.9 [95% CI: -0.8;-0.9] (P < 0.0001 for all). LDL decreased by 1.7 ± 0.0 (T-group) and increased by 1.0 ± 0.0 (CTRL), between-group difference: -2.8 [95% CI: -2.9;-2.6] (P < 0.0001 for all). Triglycerides decreased by 1.0 ± 0.0 (T-group) and increased by 0.7 ± 0.0 in CTRL, between-group difference: -1.7 [95% CI: -1.7;-1.6] (P < 0.0001 for all). Non-HDL decreased by 3.0 ± 0.1 (T-group) and increased by 1.8 ± 0.1 (CTRL), between-group difference: -4.8 [95% CI: -5.0;-4.6] (P < 0.0001 for all). Remnant cholesterol decreased by 1.5 ± 0.1 in the T-group and increased by 0.6 ± 0.1 in CTRL, between-group difference: -2.1 [95% CI: -2.4;-1.8] (P < 0.0001 for all). LAP (cm*mmol/l) decreased by 90.3 ± 3.6 in the T-group and increased by 60.8 ± 3.6 in CTRL, between-group difference: -151.0 [95% CI: -162.9;-139.2] (P < 0.0001 for all). 27 patients (7.4%) died in the T-group and 98 (27.5%) in CTRL (P < 0.0001). Medication adherence to testosterone was 100% as all injections were administered in the medical office and documented.
Conclusion
In men with hypogonadism and overweight or obesity, long-term TTh improves the lipid profile which may be a contributing factor to the observed reduction in mortality.

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AEP233

Efficacy and safety of gp40081 (insulin aspart biphasic 30) compared to novomix 30 flexpen in type 2 diabetes mellitus patients

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Introduction
A biosimilar is a biological medicinal product that shows high similarity to another already approved medicine product containing biotechnology-derived protein as active substance. The similarity depends on the biosimilar development program that includes comparative studies of physical and chemical properties, *in vitro* pharmacodynamics, pharmacokinetics and pharmacodynamics in humans. Insulin aspart biphasic 30 is one of the most convenient insulin formulations providing both prandial and basal insulin in a single injection. Russian biopharmaceutical company GEROPHARM has developed insulin aspart biphasic 30 that showed similarity to an originator NovoMix 30 FlexPen (NN-Asp30) in all abovementioned studies. The last stage of the biosimilar development program is comparative immunogenicity and efficacy study of insulin biosimilar and reference drug. Therefore, the aim of this study was to compare the immunogenicity and the efficacy of insulin aspart biphasic 30 (GP40081 (GP-Asp30)) with originator insulin NN-Asp30.
Methods
This was a multicenter, randomized, open-label, active-controlled, non-inferiority phase 3 clinical trial in parallel groups, conducted in order to compare safety (immunogenicity) and efficacy of GP-Asp30 with these parameters of NN-Asp30. This 26-week clinical trial enrolled 264 participants with type 2 diabetes mellitus (HbA1c 7.6–12.0%), randomized 1:1 to once-daily GP-Asp30 (n = 132) or NN-Asp30 (n = 132). The primary safety endpoint was immune response (development of anti-insulin antibodies (AIA)) at week 26. Secondary immunogenicity endpoints included the change of mean AIA concentration from baseline to weeks 12 and 26, the formation of neutralizing antibodies and clinically significant immune response at week 26. Efficiency endpoints included HbA1c change at week 26 from baseline, change of fasting plasma glucose (FPG) at week 26 from baseline and change in seven-point glucose profile (SPGP). Non-inferiority margin for HbA1c was 0.4 %.
Results
The frequency of immune response was similar in GP-Asp30 and NN-Asp30 (PP-population) both at week 12 (P = 0.107), and at week 26 (P = 1.000). The change of mean AIA concentration was not also significantly different in GP-Asp30 and NN-Asp30 (ITT-population) both at week 12 (P = 0.191), and at week 26 (P = 0.435). The frequency of clinically significant immune response was similar in GP-Asp30 and NN-Asp30 (P = 0.861 for ITT-population, P = 0.858 for PP-population). Inter-group difference of HbA1c change at week 26 was 0.12 (95% CI [-0.14, 0.38]). FPG, SPGP and insulin dose were similar between the groups.
Conclusions
GP-Asp30 and NN-Asp30 demonstrated similar safety (immunogenicity) and efficacy.

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AEP234

Vildagliptin is a safe and powerful oral antidiabetic drug for elderly adults with type 2 diabetes

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DPP4 inhibitors are special class of drugs that not only improve metabolism in a glucose dependant manner, but also suppress the glucagon axis. Due to its glucose dependant insulinotropic action, vildagliptin is thought to be relatively safe for people who are at risk of developing low glucose episodes. We studied the glucose lowering potential and hypoglycemic effects of vildagliptin among elderly diabetics who were uncontrolled with at least 2 oral antidiabetic medications. For this study, we recruited elderly adults (aged more than 60 years) with type 2 diabetes and elevated HbA1c (> 8%). All the participants were on at least 2 OADs at the time of enrollment, but not on insulin or GLP-1 agonists within 3 months. After due consent they were administered vildagliptin 50 mg twice daily in addition to their existing therapy and were evaluated 6 months later. Data of 386 elderly adults (Males/Females: 275/111) were available for analysis. The mean age of the sample was 62.7 ± 10.8 years and the duration of diabetes was 10.6 ± 6.6

years respectively. At the time of enrollment into the study, their mean FPG and PPG were 149.5 ± 47.1 mg/dl and 221.0 ± 61.8 mg/dl respectively, which declined to 128.5 ± 235.4 mg/dl and 186.8 ± 50.5 mg/dl in order after 6 months' treatment. During the same period, HbA1c was reduced in a statistically significant fashion. The change in HbA1c was 1.7 ± 1.6% from a baseline HbA1c of 9.8 ± 2.3%. Although overall incidences of hypoglycemia was not frequent, more number of cases occurred among individuals who were on sulfonylurea therapy ($P < 0.05$). There was no significant increase in the liver enzymes post treatment. The subjects did not experience any weight gain after the treatment. Our study showed that vildagliptin is a safe agent for the management of elderly diabetics and was found to reduce the glycemic parameters significantly. Addition of vildagliptin in elderly individuals improved the HbA1c by 1.7 ± 1.6% in 6months of treatment. Vildagliptin was also found to be weight neutral, which is important for the elderly population as they find it difficult to go for regular exercise due to the age related issues.

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AEP235

The relation between cortisol and anthropometric measurements throughout lifespan: A systematic review and meta-analysis

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Introduction

Recently, cross-sectional studies report associations between long-term glucocorticoid levels in scalp hair (HairGC) and obesity. However, there is a wide variation in studied outcomes and associations, possibly caused by differences in population characteristics, e.g. age, sex, dispersion of adiposity, and used laboratory methods. The aim of this systematic review and meta-analysis was to investigate the relation between HairGC and anthropometrics and to explore possible moderators of this association.

Methods

We searched the Medline, Embase, Cochrane, Web of Science, Scopus, Cinahl, PsycInfo, and Google Scholar databases for articles that relate HairGC to measures of adiposity (date 11–16–2020). Primary outcomes were correlations between hair cortisol (HairF) and cortisone (HairE), and anthropometrics: BMI, waist circumference (WC) and waist-hip-ratio (WHR). Authors were contacted to provide missing outcome information. Pooled correlation coefficients were calculated using random effects models. Assessment of heterogeneity was performed using the I^2 statistic. Exploratory moderator analyses were performed with subgroup analyses and meta-regression. This systematic review was performed in accordance to the PRISMA guidelines.

Results

Our systematic search identified 150 cohorts, comprising a total of 37.107 unique individuals, of which 15.033 sampled from population-based cohorts. For BMI, the pooled correlation for HairF was 0.121 (95% CI 0.083–0.158, $n = 26.941$; I^2 94.2%, $P < 0.001$) and for HairE 0.108 (95% CI 0.047–0.167, $n = 7.250$; I^2 52%, $P < 0.01$). For WC, the pooled correlation for HairF was 0.111 (95% CI 0.058–0.164, $n = 10.290$; I^2 63%, $P < 0.01$) and for HairE 0.200 (95% CI 0.137–0.264, $n = 2.198$; I^2 0%, $P = 0.42$). For WHR, the pooled correlation for HairF was 0.102 (95% CI 0.040–0.163, $n = 6.865$; I^2 27%, $P = 0.14$) and for HairE 0.261 (95% CI 0.195–0.330, $n = 1.314$; I^2 0%, $P = 0.40$). A higher percentage of male participants was related to stronger correlations with WC ($P < 0.001$), but not with BMI and WHR. Mean age, mean BMI, and mean HairGC levels of the cohorts did not significantly moderate the pooled correlations, neither did the used laboratory techniques (immunoassays vs mass spectrometry-based assays).

Conclusion

This unique, large meta-analysis demonstrates that long-term endogenous glucocorticoids as assessed by HairGC show small but consistent correlations to measures of obesity, despite a large heterogeneity between the included cohorts. The strongest associations were found between HairE and WC and between HairE and WHR. This suggests that glucocorticoid levels in the high-normal range, especially cortisone, may contribute to or reflect the state of specifically central adiposity, even within the general population.

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AEP236

The intensity of menopausal hot flushes is associated with values of the hepatic steatosis index

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Introduction

Menopausal transition is associated with an increase in the cardiovascular risk, possibly related with the sharp decrease of estrogen levels. Menopausal symptoms and more specifically hot flushes have been previously linked with an increase in cardiovascular risk. On the other hand, non-alcoholic fatty liver disease is considered as another presentation of the metabolic syndrome, conferring additional cardiovascular risk to the affected individual. This study aimed to evaluate any possible link between the severity of menopausal hot flushes and indicators of liver steatosis or fibrosis, expressed indirectly by the Fibrosis 4 score (Fib4) and the hepatic steatosis index (HSI).

Methods

This was a cross sectional study, consisting of 5.995 non-obese postmenopausal women, retrieved from the Menopause Clinic of the Aretaieio Hospital, Athens, Greece. All participants underwent hormonal and biochemical assessment and the HSI as well as Fibrosis 4 score (Fib4) were calculated, according to the biographically available algorithm. The intensity of hot flushes was evaluated as none, mild or moderate-to-severe.

Results

Our women were aged 56.7 ± 7.5years, with a menopausal age 8.9 ± 6.7years and body mass index 25.0 ± 2.7 kg/m^2. HSI values were 34.8 ± 4.2 (range 23.7–62.3), Fib4 values were 1.15 ± 0.4 (range 0.11–4.70), Fib4 values < 1.45 were found in 20.1% of women, while Fib4 values > 3.25 were found in 0.3% of women. HSI > 36, implying likely NAFLD, was evident in 75.5% of the sample. Moderate to severe hot flushes were evident in 18.3% of our women (993/5438). We observed a gradient linear increase in mean values of HSI and linear decrease in mean values of Fib4, according to increasing severity of hot flushes (none vs mild vs moderate-to-severe: HSI, 34.6 ± 4.1 vs 34.7 ± 4.1 vs 35.6 ± 4.4; Fib4, 1.17 ± 0.45 vs 1.14 ± 0.43 vs 1.08 ± 0.41 P-value < 0.001 ANOVA for linear trend, univariate). Multivariable logistic regression analysis showed that presence of moderate to severe hot flushes was associated with mean values of HIS (OR=1.060, P-value=0.002) and menopausal age (OR=0.884, P -value < 0.001) in a stepwise model that also included age, BMI, triglycerides, HDL, HOMA-IR, smoking alcohol, physical activity. No linear or dichotomous associations were observed between Fib4 values and the severity of hot flushes.

Conclusion

Mean levels of HIS were associated with the severity of menopausal hot flushes, in this large sample of postmenopausal women. We did not observe any associations between mean values of the Fib4 index and the severity of hot flushes.

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AEP237

Elevated circulating cell-free deoxyribonucleic acid in obese individuals

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Introduction

Altered levels of circulating cell-free deoxyribonucleic acid (ccf DNA) have been found in several pathologies and might have a diagnostic value. With the steadily growing number of studies in the issues related to obesity

research, it is proven, that obesity might be related to wide number of body disorders. In the current opinion, we hypothesized that there is a correlation between obesity and elevated cfDNA levels in the circulation.
Methods
This is a prospective analytic study about 56 cases. The sample included individuals who have no medical or surgical history. They were categorized according to their body mass index (BMI) groups: Group 1: normal group with BMI: [18.5–24.9 kg/m^2] and Group 2: obese group with BMI > 30 kg/m^2. Using Beta Globin 110, we investigated the levels of ccf DNA in plasma samples from obese women (n = 33) and from controls (n = 23). We also studied the relationship of the levels of this molecular marker with the various clinicopathological parameters of obesity.
Results
The study population included 56 females with a mean age of 31 ± 10.6 years. The average body mass index (BMI) was 22.5 kg/m^2 in group 1 and 39 kg/m^2 in group 2. In the serum, the mean concentration of ccf DNA was significantly higher in the obese patients as compared to the controls (P < 0.001). There were positive correlations between cfDNA levels and different parameters of obesity, with the weight (P = 0.001), the BMI (P < 0.001) and the waist circumference (P = 0.002).
Conclusion
There is a correlation between the obesity and elevated cfDNA levels. This correlation based on free radicals and oxidative stress hypothesis of cellular molecules damage and cell injury which in turn leads to a disorder in the whole body, but it still needs to more study and investigation.

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AEP238

Effect of a 16-week physical activity program on body composition and aerobic capacity parameters in a population of obese youth

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Introduction
The prevalence of childhood obesity continues to increase nowadays but also its long-term complications, particularly metabolic and cardiovascular, and this is due in large part to all the current modern conditions and means that promote sedentary lifestyle and lack of 'physical activity
Material and methods
We developed a 16-week aerobic exercise program (four 60-minute sessions per week at 70–85% FCM), in addition to school physical education and without dietary intervention; including Twenty-eight obese children divided into 2 groups with the same characteristics at inclusion (G1: exercise group; G2: control group) in order to be able to study the beneficial effects of this program on the body composition and aerobic capacity of obese children.
Results
After the training program, only G1 showed a significant reduction in BMI and waist circumference compared to baseline (P < 0.001). A signi fi cant decrease in fat mass was observed only in G1 while a significant increase in lean mass was observed in both groups but more marked in G1. There was a significant increase in the maximal metabolic equivalent of the METmax task (P < 0.05) in G1, and no significant change in this parameter was observed in G2.
Conclusion
This training program has beneficial effects on body composition and aerobic capacity parameters in obese children. Our intervention has the advantage of offering a sustainable and reproducible school and community approach to the management of childhood obesity.

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AEP239

The efficacy of complex kinesiotherapy in weight loss and improving of carbohydrate metabolism in obesity patients

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Aim of the study was to estimate the effect of complex with 4 kinesiotherapy methods on body weight loss and carbohydrate metabolism in patients with obesity.
Material and meth
ods. 80 people were enrolled in the study. 40 people in the first group (G1) -54–63 years old with obesity (mean age 57 [54;63] years, weight 100.5 [89.5;114.8]kg, BMI 35.6 [32.8;43.2] kg/m^2, waist circumference WC 105.5 [100.3;118.3] cm, hip circumference HC 117.5[108.5;127.3] cm. 40 people in the second group (G2) 58 [53;66] years old with obesity (weight 107[94.3;127] kg, BMI 41.7[34.2;46.9] kg/m^2, WC 109[105;125.8] cm, HC 127[112.3;139.8] cm. Complex kinesiotherapy administrered daily for 3 weeks included interactive sensorimotor training on double platform,complex of physical exercises in the gym and ergocycle. In addition, in G2. patients included kinesitherapy in a pool. Weight, WC, HC, carbohydrate tolerance test (TT HC), insulin last 3 weeks was measured at baseline and after the treatment was completed.
Results
There was a significant improve in body weight in G1 (100.5 [89.5;114.8]kg vs 98[87.5;111.3] kg in 3 weeks; P = 0.000), BMI (35.6 [32.8;43.2] vs 34.6 [32;42.1]kg/m^2; P = 0.000), WC (105.5 [100.3;118.3] vs 103.5[97;114.3]cm; P = 0.000), HC (117.5[108.5;127.3] vs 115.5[107;122.8]; P = 0.000). Body weight in G2 (107[94.3;127] kg vs 104.5[93.3;123.5] kg; P = 0.000), BMI (41.7[34.2;46.9] vs 39.3 [33.9;45.4]kg/m^2; P = 0.000), WC (109[105;125.8] vs 107[98.8;120]cm; P = 0.000), HC (127[112.3;139.8] vs 121[109.5;133.5] cm; P = 0.000). We registered statistically significant elevation in insulin levels of G2 vs to G1. With Z=2.63 in G1, P = 0.003 and Z=1.96, P = 0.002 in G2, and Z=2.87 when assessing the significance elevation between G1 and G2, P = 0.023. Significantly improved performance of TT HC in G1. Z=2.02, P = 0.04, in G2. Z=3.004, P = 0.002. When assessing the significance of differences between G1 and G2 after treatment, Z=2.3, P = 0.017.
Conclusions. Complex treatment with 4 methods of kinesiotherapy helps to reduce body weight, WC, HC, insulin, TT HC in obesity. Intensification training using kinesitherapy in a pool showed more significant improvements in carbohydrate metabolism.

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AEP240

Impact of sleeve gastrectomy on uric acid metabolism in a Tunisian obese group

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Introduction
Facing the repeated failures of the medical management of obesity, bariatric surgery offers a promising therapeutic option in terms of achieving weight loss and metabolic benefits. Our study aimed to assess the impact of sleeve gastrectomy on uric acid metabolism in obese subjects.
Methods
This was a repeated retrospective cross-sectional study including 40 obese patients who were followed up at the Research Unit on Obesity at the National Institute of Nutrition and Food Technology in Tunis up to 12 months after sleeve gastrectomy. The preoperative clinical and biological data and those checked at six and 12 months after surgery were collected from the patients' medical records.
Results
The mean patients' age was 34.65 ± 8.17 years and the sex-ratio was 0.21. The mean body mass index (BMI) was 50.23 ± 8.3 kg/m^2. The average uricemia was 325.3 91.6 µmol/l. The frequency of hyperuricemia in our population was 7%. After sleeve gastrectomy, the mean excess weight loss was 55.8% at 12 months. Uric acid levels decreased in patients with initial hyperuricemia. The hyperuricemia remission was observed in two out of three patients. However, we noted an improvement of the uric acid level in the patient who retained this abnormality. For patients who did not initially suffer from hyperuricemia, we saw an insignificant increase in uricemia, six months after the sleeve gastrectomy. Indeed, three patients developed this abnormality at six months post-operative. This was followed by a significant decrease in uric acid levels one year after the intervention.
Discussion
After bariatric surgery, weight loss would decrease uric acid levels, on the one hand, by reducing the production of urate and on the other hand, by increasing urate renal excretion following insulin sensibility enhancement since urate renal clearance has an inverse relationship to insulin resistance [1]. Referencet

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AEP241

GLP-1 receptor agonists and bariatric surgery in nonalcoholic steatohepatitis

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Rationale
Obesity is associated with multiple comorbidities including nonalcoholic steatohepatitis (NASH). Despite its association with increased morbidity and mortality, treatment options are limited. Some studies have suggested that glucagon-like peptide-1 receptor agonists (aGLP-1) are associated with NASH resolution. Additionally, the effects of bariatric surgery on NASH-associated liver fibrosis are controversial.
Methods
Clinical and biochemical variables of 399 patients with obesity were recorded. Different treatment-groups were analyzed: aGLP-1 in monotherapy, bariatric surgery (BS) or the combination of both. Intrahepatic fibrosis was assessed by non-invasive liver index Fib-4 before and after 6 months of treatment.
Results
The whole cohort included 62.4% females (mean age 48-y old); 37.3% had T2DM, 82% underwent BS. Mild fibrosis degree (F0-F1) was observed in 68.7% of patients, without differences among treatments groups. Serum transaminases significantly improved in patients with T2DM compared with patients without T2DM that underwent BS ($P < 0.05$). Patients treated with aGL1 before surgery had increased weight loss 6 months after BS than patients that were not treated with aGLP-1. Improvement of Fib-4 score was observed in 4.3% of patients that received aGLP-1 (3.5% of weight loss); in 2.11% of patients that underwent BS (26% of weight loss); and in 21.7% of patients that received both treatment options (23.5% of weight loss).
Conclusions
aGLP-1 in combination with BS represents a valuable therapeutic option for NASH in patients with obesity. Further studies in patients without T2DM and/or obesity are still required.

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AEP242

Post hip-fracture rehabilitation outcomes of diabetic and non-diabetic elderly patients

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Background
Although patients with diabetes mellitus (DM) are at higher risk of hip fracture, data regarding the effect of DM on rehabilitation outcomes is limited.
Methods
A retrospective population-based study was conducted comparing diabetic and non-diabetic elderly patients with a recent hip fracture who were admitted to a geriatric rehabilitation facility during 2014–2019. The Functional Independence Measure (FIM) was used to assess physical and cognitive function. Delta-FIM was calculated by subtracting admission FIM from discharge FIM. One-year mortality, hospitalizations and fractures were assessed.
Results
Six hundred and thirty post hip-fracture elderly patients were included, mean age 83 ± 7 years, 70.48%(444) females. Of them 30.63% (193) had DM. The diabetic patients were younger (81.41 vs. 84.28 years, p value < 0.01) and had higher rates of co-morbidities including hypertension, chronic kidney disease, ischemic heart disease and cerebrovascular diseases. Baseline cognitive and motor scores were similar between groups. Delta motor-FIM was similar in diabetics and non-diabetics (15.56 ± 8.95 and 14.78 ± 8.79, respectively, $P = 0.35$). Similar rates of patients were discharged to nursing care facilities. on Multivariate regression analysis motor FIM improvement was positively correlated with higher BMI, male gender and younger age but not with DM. Cognitive FIM did not change significantly during rehabilitation in both groups, and there was no difference in 1-year hospitalizations or fractures rates. One-year all-cause mortality was higher in diabetic patients (10.9% and 6.6%, respectively, $P = 0.07$). After adjusting for covariates, DM was associated with higher mortality risk (OR = 2.78, CI[1.28, 6.04], $P = 0.01$).
Conclusions
Diabetic patients have similar post-hip fracture rehabilitation potential compared with non-diabetics, in spite of higher prevalence of co-morbidity. These results support resource allocation for post-hip fracture rehabilitation in patients with DM. The higher 1-year all-cause mortality in patients with DM reinforces the need for close follow-up and control of co-morbidities in this population.

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AEP243

Impact of supervised physical activity on cardiovascular autonomic status in type 2 diabetes patients

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Background
Cardiac autonomic neuropathy (CAN) is a serious complication of diabetes mellitus (DM) that is strongly associated with increased risk of cardiovascular mortality. The significance of CAN has not been fully appreciated. Treatment of CAN includes physical activity.
Aim
To detect CAN status and measure the influence of physical activity on the autonomic nervous system using cardiovascular autonomic reflex tests (CARTs).
Methods
The study included 51 patients with type 2 diabetes: 30 were allocated to the control group (Con, $n = 30$) and the rest to the interval training (IT, $n = 21$) group. IT group exercised 3 times a week for 60 minutes for 4 month using a mobile device application. CAN was assessed on tilt table testing using 5 CARTs proposed by Ewing *et al.* (1985): parasympathetic function: heart rate (HR) response to the Valsalva manoeuvre (Valsalva ratio), HR response to deep breathing (E/I ratio) and HR response to standing (30 s/15 s ratio). Sympathetic function was measured by blood pressure (BP) responses to lying and standing as well as BP response to a sustained handgrip. Each test was assessed with a score of 0 for normal, 0.5 for borderline, and 1 for an abnormal result. Patients who had Ewing score ≥ 2 were classified as CAN positive.
Results
At baseline, CAN was detected in 33 (65%) patients. Ewing score in the CAN positive patients was 2.61 ± 0.74 and in CAN negative patients 1.08 ± 0.58. Probability of CAN before and after the intervention was 0.65 (95% CI - 0.38, 0.85) and 0.48 (0.22, 0.76) in the control group and 0.80 (0.48, 0.94) and 0.58 (0.27, 0.84) in the IT group. After the intervention between group (Con vs IT) change in CARTs and Ewing score was: Valsalva ratio 1.13 to 1.17 mm vs 1.12 to 1.25 mm (*P*-0.091); E/l ratio 12.85 to 12.51 mm vs 13.09 to 12.88 mm (p-0.902); 30s/15s ratio 1.04 to 1.06 mm vs 1.03 to 1.09 mm (p-0.233); BP response to lying and standing 8.69 to 9.45 mmHg vs 11.91 to 15.54 mmHg (*P*-0.420); BP response to handgrip 25.03 to 26.30 mmHg vs 26.76 to 22.70 mmHg (*P*-0.268); Ewing score 1.94 to 1.69 vs 2.04 to 1.74 (*P*-0.885).
Conclusions
CAN is a common complication of diabetes that often goes unrecognized. Physical activities can improve autonomic status.

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AEP244

Optimization of surgical treatment of patients with diabetic foot syndrome

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Background
The development of purulent-necrotic complications of the lower extremities is one of the most dangerous complications of diabetes. According to the Internationale Diabetes Federation, the number of hospitalized patients with foot lesions due to diabetes is 25–47%, and subsequently causing high amputations in 12% of such patients. That is why the comprehensive approach of the surgeon and endocrinologist is the key to successful treatment of such patients. The purpose of the study is to improve the quality of surgical treatment of patients with diabetic foot syndrome by improving the method of surgical treatment of the stump and fixation of the skin after phalangeal amputation.
Materials and methods
The analysis of the results of treatment of 88 patients, age from 46 to 72 years treated in the surgical department with purulent-necrotic complications lesions of toes with type II diabetes mellitus was done.
Results
The methods of surgical treatment of the foot and the fixation of the skin flap proposed by us improve the existing other methods, where the execution of amputation of the dead part of the phalanx of the finger or even the heads of the metatarsals is carried out using a cut-off metal disk rotating at a speed of 20.000 rpm (revolutions per minute), followed by gradual polishing of the cutoff point of healthy bone tissue. The fixation of the skin flap is carried out by seamless method after preliminary treatment with certain aqueous solutions of antiseptics and an even distribution of the amorphous component, which is formed as a result of mechanical treatment of the stump with a corundum grinding nozzle up to 10 mm in diameter in the form of a layer for 1–2 minutes at a speed of 10.000 rpm.
Conclusions
The proposed method of amputation of the phalanx of the finger is characterized by rapid and qualitative cut off of the dead part of the phalanx, absence of additional traumatization of the stump of the bone and surrounding tissues. This approach to treatment of purulent-necrotic wounds in patients with diabetic foot syndrome provides significant acceleration of wound healing, reduces the risk of implantation infection, eliminates additional tissue injuries during overlaying and sewing, and, accordingly, reduces the patient's stay in hospital treatment to 5 to10 days.

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AEP245

Necrotizing external otitis in diabetic patients: Role of imaging

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Purpose
To describe the role of imaging in diagnosis and detection of complications of necrotising external otitis in diabetic patients.
Material and methods
Our retrospective study included 43 diabetic patients who suffered from necrotising external otitis, from 1992 to 2020. All our patients had CT scan of the temporal bones and the brain. MRI was performed in 4 cases.
Results
The mean age was 69.4 years with female predominance. The average duration of diabetes follow up was over 10 years. In 33 cases, the causative agent was bacteria; fungal pathogens were found in 11 cases. In all cases, CT scan showed thickening soft tissue and cortical bone erosion of the external auditory canal. In 31 cases, it revealed opacification of the mastoid air cells and middle ear (erosion of the ossicular chain in 8 cases). Periauricular soft tissues inflammatory changes was noted in 10 cases. In the complicated cases, CT scan revealed: an anterior extension of the infection to the temporomandibular joint (5 cases), a bone destruction of the intratympanic facial canal (2 cases), an erosion of the tegmen tympani (2 cases), a parapharyngeal (2 cases) and parotid (1 case) involvement, a retropharyngeal abscess (1 case), an extension to the nasopharynx (2 case), a skull base extension (4 cases), an extension to the cervical vertebra (1 case) and an extension to the petrous apex (1 case). The CT angiography revealed venous obstruction of the sigmoid sinus (1 case), cavernous sinus (1 case) and internal jugular vein (3 cases), an osteolysis of the carotid canal (2 cases) and the jugular bulb with thrombosis of this latter and the petrous part of the internal carotid artery (1 case). MRI, performed in 4 cases, showed: a retropharyngeal abscess with skull base extension (1 case), cervical vertebra extension with epidural abscess (1 case) and thrombosis of the sigmoid sinus and the internal jugular vein (1 case).
Conclusion
Necrotizing external otitis remains a serious invasive infection which must be highly suspected mainly in diabetic patients. Imaging is necessary to establish the diagnosis and to detect complications.

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AEP246

Risk factors associated with diabetic foot amputation among patients hospitalized for diabetic foot ulcer in a public hospital

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Introduction
Diabetic foot is one of the most devastating of chronic complications of diabetes mellitus (DM) and is responsible for about 25% of hospitalizations. Worldwide, the diabetic foot represents the main cause of non-traumatic lower limb amputation.
Aim of the study
Identification of risk factors for foot amputation among in patients hospitalized for diabetic foot in a tertiary public hospital in Portugal.
Material and methods
Retrospective observational study of data collected from April 2017 to April 2020.
Results
There were 279 admissions involving 233 patients;161(69%) were males. Mean age was 68 ± 11.5 years and 219 (94%)] presented type 2 DM. The mean diabetes duration was 18.4 ± 10.5 years. Patients were divided into two groups: Group 1 (n = 140) patients not submitted to amputation; Group 2 (n = 93) patients submitted to amputation. There was no statistical difference between groups in terms of age (68.4 ± 11.6 vs. 67.5 ± 11.4 years), mean DM duration (18.1 ± 9.8 vs 18.8 ± 10.5 years), history of previous foot amputation (21.7% vs 30.1%), documentation of microvascular complications [retinopathy (50.4% vs 46.8%), neuropathy (75.8% vs 74.4%) and nephropathy (47% vs 52.2%)], smoking (26% vs 28.7%), high blood pression (84% vs 85%) and neuroischemic foot lesions (71.7% vs 78.5%). However, Group 2 presented higher HbA1c (8.1% vs 9.4%; P = 0.03), higher prevalence of osteomyelitis (28% vs 47%, P = 0.02) and higher prevalence of macrovascular complications: peripheral arterial disease (21.7% vs. 91.3%; P < 0.001) and ischemic heart disease (30% vs. 45%; P = 0.02). Regarding Grade 4 Wagner foot ulcer classification (localized gangrene) it was predominant in Group 2 (40% vs 10.8%; P = 0.01); all five patients with Grade 5 (extensive gangrene) were submitted to foot amputation. The global rate of mortality during hospitalization was 6.8% (n = 16) without significant differences between groups (5.8% vs 8.6%). The cause of death was sepsis in 7 cases, stroke in 2, sudden cardiac death in 3, acute myocardial infarction in 1, subdural hemorrhage in 1, and unknown cause in 2 cases.
Conclusions
Worse metabolic control and presence of peripheral arterial disease, ischemic heart disease or osteomyelitis as well as higher degrees in the classification of foot ulcers were risk factors for lower limb amputation among patients with DM. These results point to the need for an aggressive approach in this population, through preventive strategies, careful monitoring and management by multidisciplinary teams.

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AEP247

Clinical characteristics and outcomes of elderly type 2 diabetic patients with SARS-COV2 infection: a retrospective single centre study

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Introduction
Diabetes mellitus (DM) and older age are frequent comorbidities as well as factors associated with poorer outcomes in patients with Coronavirus disease (COVID-19). The reason for worse prognosis in patients with diabetes is likely to be multifactorial.
Objectives
We aimed to evaluate clinical characteristics and their impact on the outcomes of elderly patients with and without DM hospitalized with COVID-19.
Methods
In this retrospective study, we included 97 hospitalized patients (38 with DM, 59 without DM). We compared demographic characteristics, comorbidities, chronic medications, admission findings and outcomes between patients with and without DM.
Results
The mean age was 80 (± 9) and 75 (± 15) years in the group with DM and without DM, respectively. A higher prevalence of arterial hypertension (92.1% vs. 59.3%, P = 0.001), previous medication with RAAS inhibitors (64.9% vs. 44.1%, P = 0.047), chronic heart failure (55.3% vs. 32.2%, P = 0.024) and chronic pulmonary disease (28.9% vs. 11.9%, P = 0.035) was observed in patients with diabetes. There were no differences between groups regarding laboratorial and radiological findings at admission or fatality rate (36.8% DM vs 27.1% non-DM, P = 0.312). Among DM patients, nonsurvivors presented with higher Pneumonia Severity Index (PSI) score (159 ± 36 vs. 109 ± 30, P = 0.001), a higher NT-proBNP (5521 [4256–15280] vs. 1541 [288–2349] pg/ml, P = 0.047), a lower PaO2/FiO2 ratio (214 [181–259] vs. 300 [248–347], P = 0.033) and were more likely to have bilateral lung involvement at admission (78.6% vs. 29.2%, P = 0.013). Rates of acute kidney injury (85.7% vs. 33.3%, P = 0.003), acute heart failure (57.1% vs. 25.0%, P = 0.048) and secondary bacterial infection (64.3 vs. 26.1%, P = 0.022) were higher in deceased patients. When comparing deceased patients with survivors, there were no differences on the likelihood of being previously treated with insulin (60% vs 37.5%, P = 0.269), metformin (50% vs. 41%, P = 0.730), or DDP4i (40 vs. 33.3%, P = 0.775).
Conclusions
Elderly diabetic COVID-19 had a striking high risk of mortality. A more severe disease at presentation correlates with mortality. Organ disfunction reflects a rapid disease progression, significantly influencing the risk of death. These findings emphasize the frailty of diabetic and elderly patients with comorbidities, that should be regarded as high risk patients.

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AEP248

Effect of coronavirus disease on the clinical course of diabeticketoacidosis (DKA) in people with type 1 and type 2 diabetes

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Introduction
Coronavirus disease (COVID-19) in people with diabetes is associated with a disproportionately worse prognosis. DKA is an acute complication of diabetes with a mortality rate of approximately 0.67%. Little is known about natural history of DKA in the presence of COVID-19 infection. This study aimed to explore the effects of COVID-19 infection on presentation, clinical course and outcome in patients presenting with DKA.
Methods
We undertook a retrospective cohort study of all people admitted with DKA in our institution from 01 March 2020 to 30 May 2020. Based on the SARS-Coronavirus-PCR test results, they were categorised into COVID-positive and COVID-negative groups. A pre-COVID group was established using data from 01 March 2019 to 30 May 2019 as an additional control. DKA was diagnosed as per Joint British Diabetes Society guidelines in the UK. For all patients, we recorded demographic data, diabetes type, various biochemical measurements at the time of admission, time to resolution of acidosis, time to resolution of ketosis, need for admission to ITU, length of stay and final outcome. The data were analysed using GraphPad Prism Version 6.07. One-way ANOVA was used to compare the differences between groups. P-values provided are two-tailed, and value of < 0.05 was considered as statistically significant.
Results
A total of 88 DKA episodes were included in this study. There was no significant difference in the severity or duration of DKA between the three groups (12.5 hours vs 14.9 hours vs 17.9 hours for COVID-positive, COVID-negative and pre-COVID groups respectively; COVID-positive vs. negative, $P > 0.99$; COVID-positive vs. pre-COVID, P = 0.8772; COVID-negative vs. pre-COVID $P > 0.99$). COVID-positive T1DM ([60 mmol/l (35.9–60.0)] were more hyperglycaemic on admission compared to COVID-negative ([31.4 mmol/l (28.0–39.1)] and pre-COVID groups ([24 mmol/l (20.2–33.75)]. There was an over representation of T2DM in COVID-positive group with DKA (n = 15/20) than in pre-COVID (n = 8/37) or COVID-negative groups (n = 2/31). Six people with COVID and four people without COVID required intensive care. Five (1/31 COVID-negative and 4/20 COVID-positive) died. In patients with T2DM, all deaths occurred in COVID-positive group.
Conclusion
COVID infection appears to influence the natural history of DKA differently in T1DM and T2DM. Patients with T1DM and COVID-19 presented with more hyperglycaemia. Patients with T2DM were unusually presenting in DKA when infected with COVID with more ITU need and higher mortality rates.

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AEP249

Efficacy of liraglutide in weight reduction in a patient with HAIR-AN syndrome - case report

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HAIR-AN is a rarely recognized syndrome which is characterized by hyperandrogenism (HA), insulin resistance (IR) and acanthosis nigricans (AN). In the course of the syndrome, anovulation and metabolic disorders can develop, too. It is therefore suggested by some authors that HAIR-AN is an extreme phenotype of the polycystic ovary syndrome (PCOS). Generally, considering wide spectrum of metabolic and endocrine disorders which can be associated with the syndrome, it still remains therapeutic challenge. We present a case of a 32-year-old woman with HAIR-AN syndrome in whom introduced treatment regimen including liraglutide therapy improved her metabolic and procreative status. The patient was admitted to the Endocrinology Clinic because of 3rd degree obesity (BMI 50.22 kg/m^2), severe hirsutism, acanthosis nigricans and secondary amenorrhea. At that moment the patient was already treated with metformin which was prescribed by gynaecologist a few months prior to the hospitalization. In the laboratory tests, severe hyperandrogenemia, impaired glucose tolerance with hyperinsulinemia and atherogenic dyslipidemia were stated Hypercortisolemia, congenital adrenal hyperplasia or high prolactin level were ruled out. Eventually, the diagnosis of HAIR-AN syndrome was proposed. The treatment with metformin was continued. Low-calorie diet and systematic physical activity were recommended – the patient has undergone education in this field. Furthermore, as the therapy with only metformin did not improve patient's health status, liraglutide (1.2 mg/day) was added to the treatment. After six month therapy, a 33 kg reduction in body weight was achieved with BMI decline to 33.2 kg/m^2. The patient started to menstruate again. She also observed hirsutism reduction. Clinical amelioration was accompanied by metabolic and hormonal profile improvement – decline in insulin glucose and androgens' level; improved lipids' profile. The presented case shows the importance of body loss in the treatment protocol for HAIR-AN syndrome and the role of liraglutide in the therapy. Liraglutide, a drug from the group of GLP-1 analogues, ameliorates the symptoms related to HAIR-AN most probably not only due to its potential in body mass reduction. Several small studies confirmed already improve in insulin resistance, decline in androgen levels and normalization of menstrual cycle in PCOS patients who received liraglutide. Based on the case presented, it seems that HAIR-AN patients would also profit from liraglutide therapy and thus such a therapy deserves attention.

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AEP250

Evaluation of the results of weight loss at 1 year after bariatric surgery at the regional university hospital of malaga

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Introduction
Morbid obesity is a very prevalent disease, bariatric surgery being a fundamental pillar in its treatment.
Objective
To analyze the results of weight loss at 1 year in patients operated on gastric bypass and sleeve at the Regional University Hospital (HRU) of Malaga.
Methods
Retrospective observational study, with a follow-up period of 1 year, of 215 patients with morbid obesity who underwent bariatric surgery at the HRU of Malaga with systematic data collection and complete follow-up. 90 subjects had undergone gastric bypass surgery (between May 2003 and November 2018) and 125 by gastric sleeve (between January 2009 and July 2019).
Results
Of the total number of patients, the mean age at the date of the intervention was 44 years, 30.5% were men. The mean BMI before surgery was 50.15 kg/m^2 and the mean weight 136 kg. One year after surgery, the mean weight loss achieved in the case of gastric bypass was 46.94 kg (range 4.60–111.60 kg) with a mean percentage of excess weight loss of 72.59% (range 14–137%); while with the sleeve technique, there was a mean weight loss of 48.21 kg (range 20–109 kg) with a mean percentage of excess weight loss of 70.09% (range 29–113%). Regarding the global results, the percentage of patients with excess weight loss above 50% was 87.9%, while 70% achieved the double objective of excess weight loss above 50% + BMI below 35 kg/m^2.
Conclusions
Satisfactory weight results are observed in the short term, with no significant differences between the 2 techniques used in terms of the mean weight loss and the percentage of excess weight loss.

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AEP251

Bupropion/naltrexone associated psoriasis in an obese patient

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Introduction
The prevalence of obesity has risen dramatically worldwide in the last three decades. Due to this obesity pandemic, a growing demand for weight-loss drugs has emerged. The increased use of these drugs has consequently lead to an increase in the report of adverse reactions.
Case report
A 45-year-old woman with past medical history of class I obesity and psoriatic arthritis, presented with an itchy rash, developing one day after starting a weight-loss drug, naltrexone/bupropion. Physical examination revealed an erythematous maculopapular rash on the trunk and upper limbs, without mucosa involvement. Seeing as a drug reaction was suspected, naltrexone/bupropion was discontinued and prednisolone 0.5 mg/kg/day was initiated. Two days later, the rash progressed to form multiple, non-follicular, pinhead-sized pustules, on an edematous disseminated erythema, extending to the face and lower limbs. The patient was admitted to the hospital, and cyclosporine 3 mg/kg/day and prednisolone 0.5 mg/kg/day were administered, with good response. Nevertheless, cyclosporine had to be suspended after one week due to hepatotoxicity. Histological assessment of a skin biopsy was consistent with pustular psoriasis. After two weeks, the patient was discharged with a slow tapering plan of prednisolone. She later relapsed with classic psoriatic plaques, occasionally studded with pustules, on the limbs. Treatment with adalimumab was subsequently initiated. Patch tests were performed on the upper back six months later with naltrexone/bupropion, naltrexone, and bupropion (each 30% pet.). Readings on day (D) 3 showed positive reactions to naltrexone/bupropion and bupropion. A biopsy of this reaction confirmed an allergic dermatitis.
Conclusion
Psoriasis can be triggered or exacerbated up by certain drugs. Several cases of severe bupropion-associated skin drug reactions and psoriasis have been reported, including one case of psoriasis related to the anti-obesity drug naltrexone/bupropion. Nonetheless, the exact mechanism by which bupropion triggers psoriasis is unknown. In our case, the positive patch test to bupropion suggests that an initial acute generalized exanthematous pustulosis caused by bupropion might have elicited psoriasis as a result of the Koebner phenomenon. To the best of our knowledge, this is the first report on a type IV hypersensitivity reaction to bupropion documented through patch testing. There is a known association between psoriasis and metabolic syndrome, a frequent diagnosis in obese patients. Hence, special precautions should be taken when prescribing naltrexone/bupropion to patients with a known history of psoriasis.

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AEP252

Inhibition of ATG3 ameliorates liver steatosis by increasing SIRT1 in an autophagic-independent action

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Background and aims
Nonalcoholic fatty liver disease (NAFLD) is a major health threat in both developed and developing countries and is a precursor of the more advanced liver diseases including nonalcoholic steatohepatitis (NASH), liver cirrhosis and liver cancer. One of the numerous molecules participating in the development of liver steatosis is p63. Although p63 is mainly known for its roles as a tumor suppressor and cell maintenance and renewal, we have recently reported that it is also relevant in the control of lipid metabolism. More specifically, TAp63α isoform is elevated in the liver of animal models of NAFLD as well as in liver biopsies from obese NAFLD patients. Furthermore, downregulation of p63α in the liver attenuates liver steatosis in diet-induced obese (DIO) mice. Autophagy is a critical intracellular pathway that targets cytoplasmatic components to the lysosome for degradation. A specialized form of autophagy that degrades lipid droplets, is known to be a major pathway of lipid mobilization in hepatocytes. Its impairment has been associated with the development of fatty liver and insulin resistance. Thus, it is established that autophagy acts as a protective mechanism in the pathogenesis of NAFLD. Autophagy-related gene 3 (ATG3) is an enzyme mainly known for its actions in the LC3 lipidation process, which is essential for autophagy. Despite it is implicated in different biological functions, its role in lipid metabolism and its contribution to NAFLD remains unknown.
Results
We found that autophagy-related gene 3 (ATG3) was modified by TAp63α activation and downregulated after p63α inhibition. Further *in vitro* and *in vivo* experiments demonstrated that ATG3 is elevated in several animal models of NAFLD and in the liver of patients with NAFLD, who also show a positive correlation between ATG3 and steatosis grade and NAS score. Genetic overexpression of ATG3 increased the lipid load in hepatocytes, while its repression alleviated TAp63α- and diet-induced steatosis. Unexpectedly, ATG3 exerted its role in lipid metabolism by regulating SIRT1 independent of an autophagic action.

Conclusion
Our findings indicate that ATG3 is a novel gene implicated in the development of NAFLD.

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AEP253

Association between obesity and anxiety: A cross-sectional study in Sfax, Southern Tunisia

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Introduction
Obesity is recognized to be one of the greatest public health problems worldwide. In addition to physical health problems, obesity is also linked to an increased risk of mental health disorders such as anxiety. The objective of this study was to determine the prevalence of anxiety in obese adults and the factors associated with anxiety in this population.
Methods
We conducted a cross-sectional study on June and July 2020. We included all obese adults aged 19 to 64 years consulting at the basic health centre of Sfax and having a BMI greater than or equal to 30 kg/m^2. We excluded pregnant and nursing women and patients with severe decompensated organic disease and psychiatric disorder. We used the Hospital Anxiety and Depression scale (HAD) to evaluate anxiety.
Results
One hundred and fifty patients were included in our study. The sex ratio (male/female) was 0.3. The median age of patients was 50 years (IQR 37–58 years). Among the study population, we noted 40 diabetic patients (27.2%), 58 hypertensive patients (38.7%) and 12 smoking patients (8.0%). Thirty-four (22.7%) subjects had a heavy workload. Out of the 150 patients, 44(29.3%) had an extreme preoccupation of the body, 88(58.7%) had a low to moderate preoccupation of the body and 18 (12.0%) did not have a preoccupation of the body. The average anxiety score was 13.05 ± 3.3. We found that 113 (75.3%) of obese adults had definite anxiety symptoms and 26 (17.3%) had depression. We found that certain anxiety was more common among patients with extreme preoccupation to the body (88.6% vs 73.9% vs 50%, P = 0.003) and among those who have a heavy workload (88.2% vs 71.6%, P = 0.047). Nevertheless, there was no significant association between certain anxiety and depression (84.6% vs 73.4%, P = 0.2).
Conclusion
Anxiety was relatively high among people with obesity. Our study confirms the data from the literature, and underlines the need to set up a program to detect and act early on psychiatric disorders of obese.

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AEP254

Characterization of glycemic profile and glucose-lowering treatment in hospitalized patients of a central hospital by main diagnosis and length of stay

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Introduction
Glycemic control during hospitalization has an impact on the length of hospital stay (LOS) and infection rates. This knowledge has led to a growing concern with hyperglycemia and its repercussions.
Objectives
This study aims to evaluate the glycemic profile and diabetes mellitus (DM) treatment paradigm of hospitalized patients in a central hospital by main diagnosis and LOS.
Methods
We performed an observational cross-sectional study on the 9th October 2020 that included non-critical adult patients admitted to Centro Hospitalar Universitário do Porto (except pregnant/puerperal women), with DM and a minimum of 24 hours of hospitalization. The diagnosis of DM was made by consulting the clinical file and glycemic control was assessed using capillary blood glucose (CBG) values in the previous 24 hours. The main diagnosis of hospitalization was categorized as infection/non-infection and the LOS as A (1–3 days), B (4–7 days), C (8–14 days), D (15–30 days) and E (> 30 days). Statistical analysis: SPSS version 20.0.
Results
A total of 128 patients (57.8% male, mean age 73.7 ± 11.6 years) were included, with medians of LOS of 11.0 (19.0) days and mean CBG of 166.2 (69.4) mg/dl (95.5–392.0). Regarding the diagnosis, 51 (39.8%) had infection and 7 (5.5%) were hospitalized for DM or its complications. The median mean CBG was higher in the group of patients diagnosed with infection [183.7 (65.2) vs 160.1 (75.1) mg/dl, P = 0.099]. A larger proportion of patients without a diagnosis of infection was being treated exclusively with glucose-lowering drugs (6.5% vs 3.9%, P = 0.702) and a lower percentage was insulin-treated (26.0% vs 37.3%, P = 0.239) compared to infected patients. There were also considerable percentages of patients only under sliding scale regimen, especially in the group without infection (44.2% vs 37.3%, P = 0.468). By LOS, the median maximum CBG was higher in groups B to D (P = 0.025) and there were no significant differences in terms of median minimum/mean CBG. The percentage of insulin-treated patients was minimal in group A (9.1%) and maximum in group D (43.3%, P = 0.133).
Conclusion
The diagnosis of infection is common in hospitalized diabetic patients and tends to be associated with higher median CBG values. The rates of exclusive use of the sliding scale regimen are still higher than desirable, particularly in infected patients. LOS between 4 and 30 days also seem to be associated with higher CBG values and there appears to be an increased insulin therapy use as hospitalization time increases.

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AEP255

Audit on GLP-1 mimetics monitoring in East Kent university hospitals UK

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Aims/objectives
The aims of the audit were to assess the monitoring of GLP-1 analogues if they were in accordance in monitoring to National institute of clinical excellence guidelines and appropriate in continuation and 6 months review with these guidelines.
Methods
A retrospective audit of 81 patients with Type 2 diabetes who were taking GLP-1 analogues between January 2010 and July 2019 at East Kent university hospitals was performed across both hospital sites in August 2019. The review time from initiation of the drugs varies between 10 years and 8 months. The data was collected from the hospital software systems and hard copy notes.
Results
The collected data demonstrated that 34.5%[28 patients] of patient's continue to take the drugs despite that they were not meeting the criteria's [reduction of at least 1% of HbA1c and 3% reduction of body Wight after 6 months] 51.% [[41 patients] of the patients met the criteria at assessment time but none reviewed in appropriate time, 13.58% [11 patients] never reviewed since initiation of treatment however only one patient stopped from taking these drugs.[because of side effects]. The audit demonstrates significant failure of our trust to be adherent to nice guidelines in monitoring of these drugs [reviewing after 6 months and continuation if reduction of at least 1% in HbA1c and 3% of body Wight reduction was achieved]. Conclusions: The audit demonstrated that standards for initiation were met but significant failure in reviewing and continuation criteria's. We recommended GLP-1 mimetics monitoring form to be kept with patients of type2 DM notes and to be assessed by physician with each visit Were audit in July 2020 and the re audit data showed considerable improvement as 35% of the reviewed patient [28 patients] stopped from taking these drugs because they were not meeting the nice guidelines criteria's for continuation.

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AEP256

Real-world experience of Evolocumab for treatment of hyperlipidemia in an outpatient population

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Background
Use of Evolocumab as a monotherapy or in combination with other lipid lowering drugs reduces LDL-C by up to 60% in patients with or without familial hypercholesterolemia (FH), diabetes mellitus (DM), or coronary artery disease (CAD). Data regarding the efficacy of PCSK9 inhibitors in MENA populations is lacking.
Method
Retrospective case review of all patients initiated on Evolocumab treatment at Imperial College London Diabetes Centre, Abu Dhabi, between 2017 and 2020.
Results
A total of 183 individuals were identified, of which six (3.3%) were diagnosed with FH (four heterozygous, two homozygous), 141 (77.0%) primary hyperlipidemia and 36 (19.7%) mixed hyperlipidemia. Mean + SD age 51.5 + 12.4 years, 51.4% (n = 94) male, 129 (70.5%) Diabetes Mellitus (DM), of which 125 (96.9%) Type 2 and four (3.1%) Type 1. The most commonly stated indication for use was statin intolerance in patients with primary hyperlipidemia (n = 59, 32.3%). Baseline median (IQR) LDL-C was 4.03(3.01–5.08), HDL-C 1.18(1.02–1.40), total cholesterol (TC) 5.70(4.45–6.86), and triglycerides (TG) 1.93(1.34–2.70). Significant reductions in median LDL-C (48.3%, P < .001), TG (16.1%, P < .001) and TC (34.7%, P < .001) occurred in the first 90 days of administration together with an increase in HDL-C of (8.3% P < 0.001). A total of 165 (90.2%) patients achieved a ≥ 30% reduction in LDL-C on initial 90 days of treatment; of these 158 (86.3%) maintained this reduction at each follow-up visit over a follow-up period of at least 1.5 years. However, 25 (13.7%) patents did not maintain this reduction on at least two occasions during their follow-up. This was attributed to unavailability of medication in nine (36%) individuals, non-concordance in ten (40%) or withdrawal of treatment in six (24%) cases.
Conclusion
Clinically meaningful, statistically significant and sustained reductions in LDL, TG and TC levels were observed, affirming the role of PCSK9 inhibitors in management of hyperlipidemia in the Emirati population.

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AEP257

The optimal HbA1c threshold for predicting diabetes mellitus defined by OGTT in a high-risk population in Algiers about 500 cases

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Introduction
Type 2 diabetes mellitus chronic hyperglycemia resulting from a defect in the secretion of insulin or the action of insulin or from these two associated abnormalities.
Aim of the study
To try to establish an optimal threshold of HbA1C to predict diabetes mellitus on a sample of Algiers population not known to be diabetic but at high risk compared to the gold standard OGPO.
Method
500 patients (345 women, 155 men) aged ≥ 40 years consulting at the level of primary care structures, volunteers, but at high risk of diabetes, are subjected to a questionnaire, then to screening by carrying out a hyperglycemia caused by oral route (OGTT), HbA1c (HPLC TOSOH G8 method), SNSF, and ophthalmologic examination (fundus). The sensitivity and specificity of HbA1c at different thresholds for the diagnosis of diabetes and pre-diabetes were studied by ROC curve. The diagnostic performance of HbA1c was assessed by the areas under the ROC curve (AUC) estimated by the DeLong method.
Results
53.2% of patients present with dysglycemia: 23.8% with diabetes mellitus, 29.4% with pre-diabetes: 6.8% with moderate fasting hyperglycemia (HMJ). 22.6% ITG glucose intolerance. The optimal HbA1c threshold for the diagnosis of diabetes mellitus is 6.27% with a sensitivity of 78% CI (0.9134–0.924) and a specificity of 88%, PPV: 67.88%, NPV: 92.83%. For the diagnosis of pre-diabetes, the optimal HbA1c threshold is 5.83%, with a sensitivity of 71% CI (0.6221–0.8016) and a specificity of 81% (0.7268 - 0.8950), PPV: 80.6%, NPV: 72 %. The HbA1c at the threshold ≥ 5.7% of ADA seems more interesting for screening the maximum number of diabetics (98%) than that of prediabetes (67%). Our HbA1c threshold ≥ 5.83% being less sensitive to detect dysglycemia compared to that of ADA (92% of type 2 diabetes mellitus and 54% of prediabetes).

Seuil d'HbA1c %		Normal	Pré diabète	Diabète
ADA American Diabetes Association	< 5.7	156(65%)	47(33%)	2(1.6%)
	5.7–6.4	76(32%)	79(55%)	36(30%)
	≥ 6.5	6(2.5%)	17(12%)	81(68%)
Algiers Belkacem	< 5.83	192(80.6%)	66(46%)	9(7.5%)
	5.83–6.26	33(14%)	46(32%)	17(14%)
	≥ 6.27	13(5.5%)	31(22%)	93(78%)
	total	238(100%)	143(100%)	119(100%)

Conclusion
The use of HbA1c by the standardized method may be a means of screening in high-risk subjects. This HbA1C screening strategy must be verified at the level of the general Algerian population and involves periodic evaluation.

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AEP258

HbA1c threshold to predict prediabetes in a non-diabetic population but high risk of diabetes

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Introduction
When we talk about the prevalence of diabetes on a planetary scale, we can speak of a global epidemic or even a pandemic. Its prevalence continues to increase and the detection of individuals at risk of developing this disease remains a major concern.
Aim of the study
To attempt to establish standards for HbA1c by assessing the validity of this test in the diagnosis of pre-diabetic conditions and in normal subjects. This test has not yet been validated by Algerian national studies.
Material and methods
345 women, 155 men consultants at the level of primary care structures, volunteers, but at high risk of diabetes, are subjected to a questionnaire (specifying all the anthropometric parameters and the risk factors of diabetes: family and personal history of Type 2 diabetes mellitus (Type 2 DM), hypertension obesity, dyslipidemia.), then screening by performing an OGTT/HbA1c (HPLC), blood count and ophthalmologic examination. The correlation between 2 qualitative variables was analyzed by the Pearson correlation coefficient. The significance level of the tests was $P \leq 0.05$ (5%). The sensitivity and specificity of HbA1c at different thresholds for the diagnosis of diabetes and pre-diabetes were studied by ROC curve. The diagnostic performance of HbA1c was assessed by the areas under the ROC curve (AUC) estimated by the DeLong method.
Results
For the diagnosis of pre-diabetes, the optimal HbA1c threshold is 5.83%, with a sensitivity of 71%) and a specificity of 81%, PPV: 80.6%, NPV: 72%. The HbA1c at the threshold ≥ 5.7% of the ADA seems more interesting for screening the maximum number of diabetics (98%) than that of prediabetes (67%). Our HbA1c threshold ≥ 5.83% being less sensitive to detect dysglycaemia compared to that of ADA (92% of (Type 2DM) and 54% prediabetes).
Conclusion
The use of HbA1c by the standardized method may be a means of screening in high-risk subjects. This HbA1C screening strategy must be verified at the level of the general Algerian population and involves periodic evaluation.

	Estimation	IC 95% Limit inferior	IC 95% upper limit
Area under the curve	0.81	0.77	0.85
HbA1c optimal.threshold	5.83 %	5.73	6.04
Specificity.optimal.threshold	0.81	0.72	0.90
Sensitivity.optimal.threshold	0.71	0.62	0.80
positive predictive value (PPV)	0.80	0.74	0.85
negative predictive value(NPV)	0.72	0.66	0.77
Specificity, threshold 5.7%	0.65	0.59	0.71
Sensitivity, threshold 5.7%	0.77	0.71	0.81
PPV	0.75	0.70	0.80
NPV	0.76	0.70	0.81

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AEP259

Clinical and immunological profile of newly diagnosed diabetic patients in a cohort of young adults of national hepatitis C Virus survey in Egypt

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Background
Type 2 diabetes has traditionally been considered a disease affecting older age groups. In recent years, however, Type 2 diabetes has become increasingly common in children, adolescents and young adults.
Aim of the work
To estimate the prevalence of T2D among a sample of Egyptian youth aged (18–30) and to highlight the challenges in differentiating T1D from T2D in early onset diabetes depending on clinical and laboratory characteristics.
Methodology
Our cross sectional study was performed on two hundred newly diagnosed diabetic patients aged (18–30) years. All patients were subjected to full medical history and thorough clinical examination. Laboratory investigations included FBS, HbA1C, fasting C peptide and GADA. Patients with Medical disorders that would potentially confound results or patients receiving drugs that may affect blood glucose level as steroids were excluded from the study.
Results
About 59% (118) of our patients were T2D while (82) 41% were T1D. T1DM was more dominant than T2DM in age group less than 25 years (T1DM 79% vs T2DM 21%, $P < 0.001$), while T2DM was more than T1DM in age group more than 25 years (T2DM 93% vs T1DM 17%, $P < 0.001$). GADA was detected in 74 % of T1DM patient and it was high titer while GADA was detected in only 8% of T2DM with low titer, in addition GADA positive patients were significantly younger than negative patients, age (20.9 ± 2.5 years vs 26.4 ± 3.5 years respectively) ($P < 0.001$). C peptide was predominantly higher in T2D than T1D (1.4 ± 0.5 ng/ml T2D vs 0.7 ± 0.3 ng/ml T1D $P < 0.001$), but there was no difference in C peptide between GADA positive and negative neither T1DM nor T2DM patients. DKA was higher in T1DM than T2DM in both the GADA positive and GADA negative patients (92.7% in T1D, vs 5.1% in T2DM), but surprisingly higher in GADA negative than GADA positive in both T1DM and T2DM patients ($P < 0.001$). Also, family history of diabetes was more common in T2DM (T2DM 70.3% vs T1DM 26.8%, $P < 0.001$), history of autoimmune diseases was more common in T1DM (T1DM 18.3% vs T2DM 2.5%, $P < 0.001$).
Conclusion
The prevalence of diabetes mellitus especially T2D is increasing among youth may be due to changing lifestyle and genetic background, collection of detailed clinical and laboratory data has become fundamental to correctly evaluate diabetes trends in youth and to describe optimal treatment to different cases.

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AEP260

The role of bile acids in the pathogenesis of non-alcoholic fatty liver disease and type 2 diabetes mellitus

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Bile acids (BA) regulate glucose and lipid metabolism, provide bile flow, increase lipase activity by 10–15 times. With the development of inflammation, violations occur in the membrane proteins of glucose transporters.
Aim
Determine the total pool of bile acids in NAFLD with diabetes mellitus (DM) and impaired glucose tolerance (IGT). Determine the content of inflammation markers lipoprotein-associated phospholipase (Lp-PLA2), endotoxin (ET) in the blood serum of NAFLD patients.
Material and methods
On a biochemical analyzer 'Olympus' using test systems * Randox * (England), the total content of BA was determined by the enzymatic method. 80 patients with NAFLD with type 2 diabetes and ITG were examined. BMI 36–40 kg/m^2. During ultrasound, fatty hepatosis or diffuse liver damage was detected. Analysis of biochemical parameters showed a significant increase in aminotransferases in 90% of cases. Lp-PLA2 was determined by the enzyme immunoassay using the PLAC TEST diagnostic kits (USA), and the LAL test (USA) was used to determine ET.
Research results
In 59 NAFLD patients with diabetes, there was a significant decrease in the fatty acid content by 45% compared to the control, the level of bile acids in the blood serum was 2.97 ± 1.02 μmol/l, and with ITG 8.88 ± 4.94 μmol/l and a high content of PLA2 median 605 (504–826) ng/ml. In patients with NTG, PLA2 was significantly lower and amounted to a median of 430 (324–497) ng/ml. The content of Et in patients with diabetes is increased 12-fold. This activates Ca2 + channels on the membrane of smooth muscle cells, which leads to the activation of PLA2.
Conclusions
In NAFLD patients with diabetes, biliary insufficiency develops, the PLA2 and ET indices are significantly increased, which indicates the presence of inflammation and a high risk of cardiovascular complications, including coronary atherosclerosis, myocardial infarction and stroke. An increase in the content of inflammatory markers leads to a decrease in the activity of nuclear receptors for the synthesis and conjugation of BA.

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EP261

Self-Management Behavior of the Patients with Type 2 Diabetes: A Cross-Sectional Survey in the Eastern European population (Belarus)

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Background
The prevention of complications and improvement of metabolic control and state of health in diabetes cannot be effective only with medications. And now we need to develop different approaches – not only up to date pharmacological treatment of diabetes, but change the Self-Management Behavior among patients with Type 2 Diabetes.
Aims
To assess the current status of diabetic self-management behavior and the factors responsible for such knowledge among type 2 diabetes patients in Minsk, Belarus.
Methods
A correlational, exploratory, quantitative research design was utilized. We used the Diabetes Self-Management Questionnaire (DSMQ) and a questionnaire with free questions related to diabetes to investigate patients with T2DM from August to December 2020 in Minsk, Belarus.
Results
We enrolled a total of 206 patients in the present study. The median score of self-management behavior was 5.48 (10 maximum point), the interquartile range was 4.64–6.04 points. An analysis of subscale was: 'Glucose Management' was 7.33 (6.00; 8.00) (P-value: < 0.001); 'Dietary Control' 5.00 (3.33; 5.83) (P-value: < 0.001); 'Physical Activity' 4.44 (2.22; 5.56) (P-value: < 0.001); 'Health-Care Use' 5.56 (3.33; 6.67) (P-value: < 0.001). Answers for the 16 th item 'My diabetes self-care is poor' were: 'Applies to me very much' 27.20%; 'Applies to me to a consider-able degree' 4.76%; 'Applies to me to some degree' 33.80%; 'Does not apply to me' 34.27%. Further, a correlation was made between the onset of the disease, the patient's age, the degree of cognitive impairment, the average mean of hemoglobin A1c and DSMQ subscales.
Discussion
Self-Management Behavior in Patients with Type 2 Diabetes was negatively correlated with: the duration of the course of diabetes; the patient's age; the degree of cognitive impairment; the existing disorders of carbohydrate metabolism.
Conclusion
There are a number of reasons that could affect on changes in Self-Management behavior. It is likely that the maximum Self-Management behavior changes are available to the patient in the early stages of the onset of type 2 diabetes. Given the limited capacity of any national health care system, it is worth paying attention to the possibility of making maximum efforts to change Self-Management behavior among patients in whom the period of diagnosis of diabetes mellitus is from 1 to 2 years.
Keywords: type 2 diabetes mellitus; DSMQ; Self-Management; Behavior; Self-care management; Eastern Europe.

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AEP262

Retinol-binding protein in the diagnosis nafld and type 2 diabets

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Retinol binding protein (RBP) is an adipokine, related to insulin resistance (IR). Excess free fat acid reduces the binding of insulin by hepatocyte receptors and leads to hyperinsulinemia. RBP transport protein synthesized in hepatocytes and adipocytes. The level of RBP increases in patients with obesity, diabetes andnon-alcoholic fatty liver disease (NAFLD). It is positively correlated with the degree of severity of the inflammatory process and fibrosis. The RBP regulates the activity ofinsulin in tissues, skeletal muscles, and the liver.

Purpose of research

Determine RBP in patients with NAFLD and type 2 diabetes. Compare the results of RBP with markers of lipoprotein-associated inflammation phospholipase (FLA2) and nitrogen oxide (NO), which inhibits the proliferation of collagen and regulates hepatic blood flow.

Material and methods

208 patients with NAFLD and type 2 diabetes were examined. The average age is 57.3 ± 5.2. There were 76 patients with type 2 diabetes and 132 with impaired glucose tolerance (NTG). BMI more than 30 kg/m^2 (34.85 ± 1.79). Clinical, biochemical, and instrumental research methods were performed. RBP was determined in 89 patients with type 2 diabetes using the immunoassay method in blood serum. The control group consisted of 15 practically healthy person. FLA was determined by immunoenzyme method. NO metabolites were determined by Express method.

Research result

The RBP content in the control group was 26.15 ± 1.31 mg/l. The RBP content in patients with type 2 diabetes without NAFLD (group 1) was reduced by 12.8 % and amounted to 30.54 ± 0.87 mg/l. The RBP content in 49 patients with NAFLD and2 diabetes (group 2) wassignificantly increased by 48.9 % and amounted to 55.83 ± 2.92 mg/l. The FLA2 content wasincreased by 4.78 times in relation to the control in group 2. The content level stable nitric oxide metabolites wasincreased in parallel with liver activity enzymes. There is a direct positive correlation between FLA2 and NO. The correlation coefficient was $r = 0.625$ $P = 0.001$

Conclusion

The level of RBP was significantly increased in patients with type 2 diabetes and NAFLD compared with control and group 1. Increase in the content of inflammatory markers accompanied by an inflammatory process in the liver with increased activity liver enzymes and the severity of morphological changes.

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AEP263

Study on INS gene rs689 polymorphism in patients with diabetes mellitus genetic burden

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Testing for genetic markers is a promising approach in early diagnosis of type 1 diabetes mellitus (DM1). Of all DM1-associated genes and genetic loci, after HLA class II, insulin promoter gene confers the highest risk for the onset of disease with the burdened familial history for diabetes mellitus.

Materials and methods

Genealogical analysis was used to identify the hereditary nature of the disease. DNA samples from 94 Uzbek patients with DM1 with the burdened familial history and from 66 apparently healthy persons included into the control group were analyzed. Original designs for primers to perform standard polymerase chain reaction (PCR) were made by bioinformatics analysis of data from NCBI Genome Data Viewer (GDV) by means of BioEdit program. INS (rs689) gene polymorphic region was amplified by PCR using allele-specific PCR methods.

Results

The findings from the genotyping of rs689 polymorphism of INS gene demonstrated that the frequencies of INS gene wild A allele were 76.1% and 90.1% in patients and controls, respectively. In the population sample, the T deleterious allele could be seen less frequently than in the 1st group patients (9.9 and 23.9%, respectively). Among patients with DM1, the AT genotype was 2.3 times more frequent than in the non-diabetics (39.3 vs 16.7%, respectively). The findings from the study on association between INS gene polymorphism and DM1 risk demonstrated statistically significant association of the T allele (χ^2=9.4; P< 0.05; OR = 2.88; 95%CI 1.84–5.59) and the AT heterozygous genotype (χ^2=9.2; P< 0.05; OR = 3.42; 95%CI 1.58–7.42) with the increased DM1 risk. The differences with the control group by the A allele (OR = 0.34; 95% CI: 0.18–0.67; χ^2 = 9.4) of INS gene can be the evidence for its negative association with the disease, that is, the A allele carriership reduces DM1 onset risk being of a protective character. In other studies, next to significantly lower incidence of DM1 the Asian populations were established to have higher frequency of the A allele of INS gene rs689. Thus, the findings from genotyping of INS gene rs689 polymorphism in patients with the familial burden for diabetes mellitus demonstrated association of the T allele and the AT heterozygous genotype with the DM onset risk.

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EP264

Treatment recommendations for dapagliflozin across a cardio-renal and viscero metabolic (crv-m) continuum: an expert consensus delphi study

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Introduction

Dapagliflozin is sub-optimally utilised in the real world. There is a lack of a comprehensive collaborative guidance for a practical approach to manage patients with cardiometabolic, renometabolic and viscerometabolic disorders. Patients across the CRV-M continuum includes patients with varied clinical profiles.

Methods

Two round Delphi study was conducted using a virtual online-digital connect approach with 35 clinicians with cumulative clinical experience of 1050 man years of experience across different specialties. This was preceded by contemporary evidence-based discussion on therapeutic approaches, through multidisciplinary modules for six hours covering cardiometabolic, renometabolic and viscerometabolic disorders, with focus on dapagliflozin. A consensus was reached on the clinical aspects that were endorsed by 50% or more of the experts

Results

Of the total 33 questions, seven were unanimously (100%) rated with the same response and 12 received the same response by > 50% of the participants. The mean man years of experience of the respondents with unanimous response was 175.7 years (± 43.92, minimum 120, maximum 240, 95% CI 135.1 to 216.3) significantly higher as compared to respondents > 50% similar response 122.5 years (± 10.74, minimum 60, maximum 180, 95% CI 98.86 to 146.1) (P = 0.0118). The index weighted impact score based on the man years of experience was higher for the

unanimous responses group (1.43). There was a unanimous consensus, with absolute agreement for the cardiometabolic based chronic disease (CMBCD) approach, SGLT2 inhibitors as emerging approach to address the residual risk, and reduction of single-nephron glomerular filtration rate as a mechanism for renoprotection. 88% participants attributed insulin resistance as an important reason for autonomic dysfunction in patients with T2DM. The DAPA-CKD and DAPA-HF trials appears to have a potential scientific impact in the real-world utilisation of Dapagliflozin in patients with DKD and HFrEF.
Conclusion
The results of this study suggest that irrespective of presence of diabetes, dapagliflozin has a potential to optimise the management of patients. Dapagliflozin, beyond the ability to increase glycosuria, with relatively higher level of evidence, across the CRV-M continuum, appears to be a promising agent.

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AEP265

Acute fatty liver of pregnancy masquerading as diabetic ketoacidosis

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Acute fatty liver of pregnancy (AFLP) is a rare obstetric metabolic emergency (UK incidence 1/20.000 maternities) which typically presents in 3rd trimester or postpartum and has a high maternal and foetal mortality and morbidity (UK Maternal mortality 1.8%, perinatal mortality 104/1000 births). Diagnosis can be delayed due to lack of set diagnostic criteria, rarity and overlapping clinical presentation with many other obstetric metabolic pathologies. Urgent delivery and supportive care are the mainstay of treatment. We would like to present an interesting case of AFLP which was initially managed as diabetic ketoacidosis (DKA). A 20-year-old lady with a background of gestational diabetes on insulin presented at 32 weeks' gestation in her second pregnancy with general malaise, reduced foetal movements, and anorexia and was found to be icteric with hyperglycaemia, severe metabolic acidosis and ketosis and deranged liver functions. She was started on fixed rate intravenous insulin infusion (FRII) and IV fluids with a diagnosis of DKA. She was transferred to ITU due to lack of response to treatment where intravenous bicarbonate was given with only transient improvement in her acidosis. Liver ultrasound showed uncomplicated gallstones with normal liver. Rest of the non-invasive liver screen was unremarkable. Foetus was being regularly monitored through cardiotocography with no concerns. She was being managed with inputs from obstetrics, diabetologists, gastroenterologists and intensivists in ITU for five days but despite appropriate management of DKA, there was no resolution of her metabolic abnormalities, at which point, expert opinion was sorted from maternal medicine department of the tertiary care centre who suggested a diagnosis of AFLP and advised urgent delivery. She underwent emergency caesarean section at 33 weeks' gestation and all her biochemical abnormalities started to improve post-partum with complete resolution of acidosis in 48 hours and normalisation of LFTs in two weeks. The baby was admitted to NICU for two weeks and intubated and NG fed for first week and later on discharged with no complications. Both mother and baby are now healthy. AFLP is a rare obstetric emergency which requires a high index of suspicion for diagnosis. This case was especially challenging given the hyperglycaemia and ketosis at presentation; these are not widely recognized metabolic abnormalities in AFLP. Diabetologists would rarely be involved in the care of AFLP however this case shows the importance of suspecting an alternate diagnosis when a 'diabetic emergency' does not respond to otherwise highly effective treatment modalities.

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AEP266

To assess the glucose metabolism using the flash glucose monitoring system (FGMS) in patients with hormone replacement therapy for hypopituitarism

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Background
Hormone replacement therapy is often used for hypopituitarism, which leads to dysglycemia. This study is conducted to assess the glucose metabolism conditions using the flash glucose monitoring system (FGMS) in patients with hormone replacement therapy.
Method
Seven patients who were diagnosed as hypopituitarism and treated with glucocorticoids and L-Thyroxine were qualified to participate in this study. These patients' blood pressure, blood sugar, sodium ions and FT3, FT4 were normal after hormone replacement therapy. We also recruited five healthy volunteers responsible for normal controls. FGMS data were disposed from two perspectives. Firstly, parameters consist of 24-hour mean blood glucose (24 h MBG), standard deviation of blood glucose (SDBG), coefficient of variance (CV), mean of daily differences (MODD), time in range (TIR). Secondly, several time periods were analyzed specifically, including the whole day, nocturnal, fasting, and postprandial periods. All of these indexes were analyzed by a t-test or Mann-Whitney test.
Results
Compere with HCs, the indexes including 24hMBG (P = 0. 956), SDBG (P = 0. 056), CV (P = 0. 610), MODD (P = 0. 416) and TIR (P = 0. 59) had normal outcomes. There was no significantly different AUC was identified at the whole day (P = 0. 360); significantly different AUC was found at nocturnal period (3. 93 ± 0. 50vs4. 0 ± 0. 41, P = 0. 009), fasting period (4. 05 ± 0. 62vs4. 28 ± 0. 38, P = 0. 003), after breakfast (4. 77 ± 0. 64vs4. 80, 5. 95, P < 0. 001), after lunch (6. 11 ± 0. 93vs5. 86 ± 0. 42, P < 0. 001) and after dinner (5. 95 ± 0. 66vs4. 58, 6. 33, P = 0. 09).
Conclusion
Patients with hormone therapy had higher postprandial blood glucose than HCs. Because exogenous hormones cannot simulate the secretion rhythm of endogenous hormones. In addition, patient's nocturnal blood glucose was low. Exogenous hormones had a short acting time, which can not maintain nocturnal blood glucose. On the other hand, exogenous hormones inhibited adrenal glands' function, leading to the further lack of endogenous hormones and the low blood sugar level at night.

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AEP267

p63 induces the fibrosis in NASH

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p53 family controls several metabolic and cellular functions. The p63 member regulates lipid metabolism in hepatocytes and contributes to the development of liver steatosis. Here we show that p63 plays an important role in liver fibrosis. P63 is upregulated in patients with NASH, correlating positively with fibrosis score and collagen 1a1 expression. P63 expression is also increased in different animal models of diet-induced NASH and chemically induced liver fibrosis. Mice with hepatic downregulation of p63 fed a high fat diet or choline deficient and high fat diet (CDHFD) for 52 weeks display reduced collagen deposition, hydroxyproline levels and expression of collagen markers. Similar results were found when these mice were challenged to methionine and choline deficient diet. Consistent with this, the hepatic overexpression of TAp63α isoform accelerates the fibrosis induced by CDHFD. Our findings indicate an unexpected role of p63 in the metabolic and profibrotic action in liver disease.

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AEP268

Challenges in availability of insulin in Malwa region of Madhya Pradesh, INDIA during COVID-19 lockdown and its impact on perceived stress in patients

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Title:
Challenges in availability of insulin in Malwa region of Madhya Pradesh, INDIA during COVID-19 lockdown and its impact on perceived stress in patients
Introduction
There are large number of patients of diabetes who require insulin to control their blood sugar. During the covid 19 lockdown, many medicines were not easily available and insulin being a life-saving and necessary medicines requires smooth availability. Non availability of insulin causes sugar fluctuations and anxiety in minds of patients and attendants and can affect well-being.
Methods
We surveyed 140 patients on insulin for their insulin availability and stress level were recorded using perceived stress score questionnaire during the period of COVID-19 Lockdown-1 from 5th to 10th april 2020.
Result
There was a difficulty in procuring insulin in the region surveyed which was reported by 73 % of respondents. The difficulty was more with analogues 88% as compared with regular insulins. Was more in rural areas 53 % as compared to urban areas. Almost 88 % of respondents had higher perceived stress scores due to this reason.
Discussion
There is pressing need to establish supply chains in a proper manner so that a patient need not face difficulty in procuring a lifesaving drug such as insulin. The need is more in Rural areas, and more with analogues so that the stress associated with scarcity of insulin can be alleviated.
Keywords: Insulin, analogue, nonavailability, perceived- stress, lockdown, covid-19.

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AEP269

Factors predictive of glycemic control of pregnant diabetic women

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Introduction
Diabetic pregnancy is an at-risk pregnancy, hence the importance of perfect glycemic control. The objective of this study is to evaluate glycemic control of pregnant women and these intervening factors.
Materials and methods
Our study is prospective observational and analytical, including 300 patients with diabetic pregnancy followed in the obstetric gynecology department of Ibn Rochd hospital in Casablanca-morocco between November 2019 and November 2020.
Results
The study included 300 patients with an average age of 32.6 years (18–42). 45% had gestational diabetes and 55% had pre-gestational diabetes, of which 5% had planned their pregnancy. The mean pre-conceptional HbA1c was 8%. For treatment, 78% of the patients were on insulin and 22% were following hygienic and dietary rules. All patients were on a basal bolus regimen, 37% of whom were on analogues. Regular self-monitoring was ensured in 32% of patients. Physical activity was practiced in 27% of patients. 90% of the patients ate three meals a day and 66% of the patients ate one to two snacks a day. 40% abused slow sugars and 36% consumed fast sugars. Glycemic control was perfect in 64% of the patients and insufficient in 36%. A significant relationship was found between glycemic control and slow sugar abuse ($P < 0.05$) as well as type of diabetes ($P < 0.02$) (better control for pre-gestational diabetes).
Discussion
It is established that an optimized management, in particular a perfect glycemic balance, reduces the risks related to pregnancy. Several factors intervene as demonstrated in our study, namely: eating habits and type of diabetes.
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AEP270

Correlation between cystatin C and cardiovascular risk factor in patients with type 2 diabetes mellitus without kidney disease

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Introduction
Diabetes mellitus (DM) is considered as equivalent to cardiovascular disease (CVD), so the intensive control of all risk factors for CVD in patients with DM is recommended. Risk factors for CVD include: dyslipidemia, hypertension, smoking, family history of CVD and albuminuria. In addition to being a sensitive and reliable marker for evaluation of kidney function, research suggests that cystatin C may be a useful predictor for the detection and prediction of CVD. The aim of the study was to investigate the correlation between serum cystatin C and the risk factors for CVD in patients with type 2 DM without kidney disease.
Methods
The cross- sectional study included 90 patients with type 2 DM who were divided in two groups: group I 50 patients with type 2 diabetes mellitus without kidney disease and 40 patients with diabetes mellitus with kidney disease. Patients with DM did not have presence of CVD (ischemic heart disease, previous myocardial infarction and stroke). Patients without kidney disease were noralbuminuric and have normal glomerular filtration rate calculated using Chronic Kidney Disease Epidemiology Collaboration equation. We examined the correlation between serum cystatin C and risk factors for CVD dyslipidemia, hypertension, smoking, albuminuria, and a family history of CVD.
Results
The analysis showed that group II had more risk factors for CVD. Patients without kidney disease had LDL and triglycerids without reference range for DM, 15 were smokers and positive family history of CVD was found in 7 patients. The mean serum levels of LDL and triglycerides were higher in group II (LDL 3.34 ± 1.09 vs. 2.78 ± 1.15, $P < 0.05$, triglycerides 2.26 ± 1.22 vs. 2.11 ± 1.09, $P > 0.05$). In group I, cystatin C values showed a statistically significant direct correlation with serum triglycerides ($r = 0.42$, $P < 0.05$) and and systolic blood pressure ($r = 0.33$, $P < 0.05$) and inverse correlation with serum HDL cholesterol level. In group II cystatin C also showed significant correlation with triglycerides ($r = 0.36$, $P < 0.05$), inverse correlation with serum HDL ($r = –0.40$, $P < 0.05$).
Conclusion
The study showed correlation between cystatin C and CV risk factors as lipid parameters and systolic blood pressure in patients with type 2 DM without kidney disease.
Key words: diabetes mellitus, cystatin C, cardiovascular disease, kidney function

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AEP271

Role of diabetic autonomic neuropathy in development of diabetic cardiomyopathy in patients with diabetes

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Aim
Diabetic cardiomyopathy (DC) is congestive heart failure developed in diabetic patients, without coronary, hypertensive, valvular nor myocardial alcoholic disease. Aim of this stady was to confirm if presence of diabetic autonomic neuropathy (DAN) is correlating with development of DC in patients with diabetes.
Methods
We have evaluated 90 examinees: 30 of them with diabetes type 1(T1D), 30 with diabetes type 2 (T2D) and 30 healthy examinees that were in control group. With all examinees we have performed cardiovascular dynamic tests and echocardiography – one-dimensional, two-dimensional and doppler on Aloca 830 machine. Parasympathetic function was tested with 3 cardiovascular reflexes tests (Valsalve maneuver, deep breathing test, stand-up after lying position test), and sympathetic function with 2 tests (orthostatic hypotension test, and hand grip test).
Results
Results have showed that systolic function of left chamber (LC) in T1D patients with DAN was normal in 90.5%, and pathological in 9.5% ($P < 0.01$), and in T2D patients with DAN was normal in 76.7%, and

pathological in 23.3% ($P < 0.01$). LC diastolic function in T1D patients with DAN was normal in 46.7%, and pathological in 52.4% ($P > 0.05$). In T2D patients with DAN, diastolic function of LC was impaired in 83.3% ($P < 0.01$).
Conclusion
DAN is significantly increased in patients with T2D. Within those patients, diastolic function of LC was impaired significantly more frequent, until systolic function was non-affected in both of these diabetes types. Correlation between LC diastolic function impairment and DAN could signify its possible spot in diabetic cardiomyopathy etiopathogenesis.

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AEP272

Influence of nutritional status on clinical outcomes among hospitalized patients with covid-19

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Background and aims
Several factors that worsen the prognosis of the new coronavirus SARS-CoV-2 have been identified, such as obesity or diabetes. However, despite that nutrition may change in a lockdown situation, little is known about the influence of malnutrition among subjects hospitalized due to COVID-19. Our study aimed to assess whether the presence of malnutrition among patients admitted due to COVID-19 had any impact on clinical outcomes compared with patients with the same condition but well nourished.
Methods
75 patients admitted to hospital due to COVID-19 were analyzed cross-sectionally. Subjective Global Assessment (SGA) was completed by phone interview. Clinical parameters included were extracted from the electronic medical record.
Results
According to the SGA, 27 admitted due to a COVID-19 infection had malnutrition. Patients not well nourished were older than patients with a SGA grade A (65 ± 14.1 vs 49 ± 15.1 years; $P < 0.0001$). Length of hospital stay among poorly nourished patients was significantly higher (18.4 ± 15.6 vs 8.5 ± 7.7 days; $P = 0.001$). Mortality rates and admission to ICU were greater among subjects with any degree of malnutrition compared with well-nourished patients (7.4% vs 0%; $P = 0.05$ and 44.4% vs 6.3%; $P < 0.0001$). CRP (120.9 ± 106.2 vs 60.8 ± 62.9 mg/l; $P = 0.03$), D-dimer (1516.9 ± 1466.9 vs 461.1 ± 353.7 ng/ml; $P < 0.0001$) and ferritin (847.8 ± 741.1 vs 617.8 ± 598.7mg/l; $P = 0.03$) were higher in the group with malnutrition. Haemoglobin (11.6 ± 2.1 vs 13.6 ± 1.5 g/dl; $P < 0.0001$) and albumin 3.2 ± 0.7 vs 4.1 ± 0.5 g/dl; $P < 0.0001$) were lower in patients with any degree of malnutrition.
Conclusions
The presence of a poor nutritional status is related to a longer stay in hospital, a greater admission in the ICU and a higher mortality.

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AEP273

Acute hyperglycemic emergencies during lockdown: COVID-19 collateral damage

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Introduction
In march 2020, the COVID-19 pandemic registered its first cases in Portugal, leading the government to impose lockdown, in order to prevent the spread of cases. With social isolation and outpatient activity being ceased, there was an increase in mortality of non-COVID patients. The lockdown recommendations are in contradiction with comprehensive diabetes care and reflected in less regular patient-provider interactions, which in some cases contributed to the worsening of glycemic control and presentation with acute complications of diabetes.
Aim
To evaluate the impact of lockdown in the severity and characteristics of hyperglycemic emergencies (diabetic ketoacidosis [DKA] and hyperosmolar hyperglicemic state [HHS]).
Methods
Retrospective single center study. We included patients with a diagnosis of DKA or HHS admitted in the lockdown months (march to may 2020). The control group were patients admitted with DKA or HHS in the homologous period of 2019.
Results
18 patients were admitted in 2020 and 12 in 2019. The mean age was 48 (± 24) years in 2019 and 60 (± 26) in 2020 ($P = 0.192$). HHS represented 50% of cases in 2020 and 25% in 2019 ($P = 0.171$). In the lockdown period patients were more likely to have type 2 diabetes (55.6% vs 33.3%, $P = 0.232$), had a higher number of comorbidities (2.4 ± 1.4 vs 1 ± 0.9, $P = 0.009$), more microvascular complications (50% vs 8.3%, $P = 0.049$), and usual attendance at primary care services (61.1% vs 16.7%, $P = 0.008$). At admission, lockdown patients were more likely to present with dehydration (55.6 vs. 9.1%, $P = 0.009$) and altered mental status (61.1 vs 25%, $P = 0.048$). There were more cases of severe DKA in 2020 (45.5% vs 0%, $P = 0.038$). Although with statistically not significant difference, patients had tendentially higher urea (39.5 vs 30.5 mg/dl, $P = 0.391$), creatinine levels (1.85 vs 1.42 mg/dl, $P = 0.051$) and osmolarity (310 vs 293 mOsm/kg, $P = 0.172$); more complications during in-hospital stay (38.9 vs 8.3%, $P = 0.064$) and higher mortality (16.7 vs 0%, $P = 0.136$). The cases of initial presentation of diabetes did not differ between periods (16.7%).
Conclusion
During lockdown there were more admissions with acute hyperglycemic emergencies, those with more severe presentations, resulting in a higher fatality rate. Reduced access to primary care and hospital services for diabetes, combined with fear of exposure to the virus in these settings drive to delayed care-seeking. Telehealth or telephonic consultations should be encouraged to prevent complications and ensure access to therapy. Download of records from insulin pumps/CGM should be used whenever possible to optimize glucose control.

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AEP274

Sex-specific variations in lipid concentrations following a low-fat diet are mediated by vitamin D status: a 12-week prospective dietary intervention study among Christian Orthodox fasters

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Background
Orthodox religious fasting (OF) is a variation of the classical Mediterranean Diet during which meat and other animal products are restricted, whereas fish are occasionally and sea food are always allowed. The aim of this prospective study was to assess sex-specific differences in changes of lipid concentrations in a cohort of metabolically healthy adults following OF and investigate a potential role of vitamin D status in mediating these variations.
Methods
45 individuals (24 females, 53.3%) with mean age 48.3 ± 9.1 years and mean Body Mass Index 28.7 ± 5.8 kg/m^2 were followed for 12 weeks. Anthropometrical, dietary and biochemical data (serum lipids and vitamin D concentrations) were collected at baseline, 7 weeks after the implementation of OF and 5 weeks after participants returned to their standard eating habits (12 weeks from baseline). According to 25-hydroxy-vitamin D [25(OH) D] measurements, fasters were classified into two groups: those with concentrations above and below the median of values.
Results
Female participants with 25(OH)D concentrations below the median demonstrated a non-significant reduction by 15% in total and low-density

lipoprotein cholesterol during the fasting period, followed by a significant increase (170.74 vs. 197.50 and 99.63 vs. 121.06 mg/dl respectively, $P < 0.001$) 5 weeks after OF cessation. On the other hand, male participants with 25(OH)D levels below the median manifested an inverse, non-significant trend of increase in serum lipids during the entire study period.
Conclusions
Our findings indicate sex-specific variation in lipid concentrations following a low-fat dietary pattern, modulated by vitamin D status. Further studies are required in order to unravel the underlying mechanisms and evaluate the association of these inter-gender differences with cardiovascular risk and benefit of vitamin D supplementation.

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AEP275

Low-density lipoprotein cholesterol target achievement in patients with diabetes

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Background
Diabetes is often associated with other cardiovascular (CV) risk factors such as dyslipidemia, wich increases the risk of degenerative disease and contributes to elevate morbi-mortality in these patients. 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 100 diabetic. CV risk levels and low- density lipoprotein cholesterol (LDL-C) goal achievements were performed according to ESC's guidelines updated in 2019.
Results
The mean age was 50 ± 10.6 years with a predominance of females (52.8%). All patients had dyslipidemia associated with type 1 (72.8%) or type 2 (27.8%) diabetes. The most common type was mixed dyslipidemia (47.2%), followed by pure hypertriglyceridemia (38.9%) and only 13.9% had pure hypercholesterolemia. According to new guidelines, 37.8% and 62.2% were considered as very high and high CV risk, respectively. Most patients at very high cardiovascular risk (82%) had complicated diabetes. These complications were represented by diabetic retinopathy (65.4%) and diabetic kidney disease (34.6%). The other patients had cardiovascular disease established clinically or by imaging (18%), namely coronary artery disease (6%), stroke or transient ischemic attack (1.2%) and arterial occlusive disease of the lower limbs (10.8%). Less than half of the patients achieved their recommended LDL-c goals (38.3%). According to the CV risk level, only 12.1% and 26.2% met their goals for very high risk and high risk, respectively. Non-achievement of LDL-c goals was significantly associated with discontinuation of treatment ($P < 0.001$). In 2/3 of cases, it was explained by the non-availability of lipid-lowering treatment in dispensaries. Among the patients who did not reach their LDL-c goals, poorly adapted dosage and treatment were observed in 48.3% and 32.3% of cases respectively ($P = 0.04$).
Conclusions
Despite of high CV risk levels, most of patients didn't achieve recommended goals. This is likely to be due to either discontinuation of medications or therapeutic inertia.

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AEP276

Heterozygous familial hypercholesterolemia with intolerance to PCSK9 inhibitors

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Introduction
Heterozygous familial hypercholesterolemia is one of the most common genetic disorders and it is associated with an at least ten times higher risk of coronary heart disease. Frequently, it is necessary to medicate the patients with PCSK9 inhibitors (PCSK9i) so they can reach LDL-c target values. In Portugal, the only evolocumab is available and the most commonly reported adverse effects are local pruritus and upper airway symptoms.
Case report
A 42-year-old woman was referred to our department because of a poorly controlled hypercholesterolemia despite being on maximal doses of statin and ezetimibe. She had a family history of premature coronary disease and had a serum total cholesterol level of 415 mg/dl and an LDL-c level of 327 mg/dl. Her Dutch Lipid Clinical Network score was above 8 points. As so, she underwent genetic testing which revealed a pathogenic mutation in heterozygosity. She started evolocumab and responded well to the first dose (LDL-c reduction of 53%) but reported transient headaches, nausea and myalgia. After the second dose, she developed self-limited headaches, dizziness, myalgia and an acute confusional state with spatial disorientation and horizontal binocular diplopia. Both a brain CT scan and an MRI were performed and showed no relevant findings. The patient also underwent neurological, psychiatric and otorhinolaryngological assessments which excluded other etiologies. Thus, evolocumab was suspended. 6 months later, her cholesterol levels had risen to alarmingly high levels and the PCSK9i was reintroduced – the patient once again developed a worrisome confusional syndrome and evolocumab was permanently suspended. As an alternative, she started lipoprotein apheresis and responded well to this treatment (LDL-c reduced by 57%). Since then, she has an apheresis session every two weeks and no adverse effects have been reported.
Discussion
This case report demonstrates an association between evolocumab and the development of neurocognitive symptoms. Other potential explanations would be the induced hypocholesterolemia or the abrupt cholesterol reduction. However, it has already been proved that LDL-c reductions to values below 25 mg/dl due to the action of PCSK9i occur safely. Furthermore, a similar LDL-c reduction was achieved with the lipoprotein apheresis without any adverse effects. In fact, although extremely rare, the association between PCSK9i and neurocognitive symptoms has been described in some clinical trials. As so, the authors intend to raise awareness on the need to monitor neurocognitive symptoms in patients taking evolocumab.

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AEP277

Frequency of obesity among individuals with spondylarthritis

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Background
Spondylarthritis may be associated with substantial burden of comorbidities, which can increase the cardiovascular risk. Obesity if associated with spondylarthritis not only can rise the risk of a possible heart disease but it may also deteriorate their functional prognosis.
Objectives
The main target of this study was to evaluate the frequency of obesity in spondylarthritis patients.
Materials
We performed a cross-sectional study including 96 patients with spondylarthritis(SA) diagnosed according to ASAS criteria, the disease activity were assessed using ASDAS, for each patient we mesured height in meter and weight in kg and we calculated the body mass index(BMI) using the metric formula Weight(kg)/Height(m)^2.
Results
The mean average was 41.45 + 12.52 years, sex ratio was 3. Clinical phenotypes of SA were: ankylosing spondylarthritis (62.4%),psoriatic arthritis(20.8%), arthritis associated with inflammatory bowel disease (12%). The mean duration of the disease was 110.9 + 106.16 months. The mean C-reactive protein and erythrocyte sedimentation rate were 31.48 and 37.19 respectively. The mean ASDAS-CRP,BASMI and BASFI were 3.63 + 2.26 and 2.45 + 2.44, 4.61 + 2.67. The mean BMI was 25.38 + 4.61. Underweight percentage was 0.2%, patients in the normal range were 50%, patients with overweight percentage was 45.8%(33.33% were pre-obese and 14.58 % obese).54.34 % of patients with overweight have ankylosing spondylarthritis and 26% of them have psoriatic arthritis. There were no correlation between BMI and ASDAS-CRP, BASMI and BASFI.
Conclusion
Spondylarthritis with obesity may increase mortality in our population by increasing the cardiovascular risk, that is why a healthy eating and if possible a regular physical activity may improve the prognosis of the disease.

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AEP278

Response to direct antiviral agents in chronic hepatitis C in patients with metabolic syndrome

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Introduction
Direct antiviral agents (DAAs) are a real revolution in the treatment of chronic hepatitis c (CHC). It is a short-term treatment with few side effects. Insulin resistance in patients with metabolic syndrome, causes the onset of steatosis, contributes to the progression to cirrhosis and decreases the chances of a response to treatment. The aim of our study was to evaluate the response to DAAs in patients with metablic syndrome.
Methods
This is a retrospective study including all patients with hepatitis C treated with DAAs, between January 2018 and December 2020.
Results
Fifty paients were included in our study, divided into 31 women and 19 men, with an average age of 52 years (between 16 and 82 years). Twenty three patients (46%) had a metabolic syndrome. Thirteen patients had arterial hypertension and 7 patients were diabetic. HCC was discovered during screening in 40% of cases. The other circumstances of discovery were: blood donation (15%), asthenia (15%), arthralgia (15%), cytolysis (10%) and thrombocytopenia (5%). Genotype 1b was predominant (76%). The mean pretreatment viral load was 1.457.542 IU/ml. Abdominal ultrasound revealed hepatic steatosis in 8 cases. Twelve patients had F0-F1 Fibrosis measured by Fibroscan. The viral load at the end of anti-viral treatment and the viral load 6 months after the end of treatment were undetectable.
Conclusion
In our study, metabolic syndrome was present in 46% of patients. Sustained virological response was obtained in all patients. Thus the metabolic syndrome did not influence the response to DAAs.

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AEP279

The gut microbiota phylotypes in obese patients with arterial hypertension and pre-diabetes

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Gut microbiota, its phylotypes, the Firmicutes/Bacteroidetes ratio can play important role in the pathogenesis of arterial hypertension, obesity and metabolic disorders.
The aim of the study was to evaluate the content of the main phylotypes of the gut microbiota (Firmicutes, Bacteroidetes and Actinobacteria), the Firmicutes/Bacteroidetes ratio in patients with arterial hypertension, abdominal obesity and pre-diabetes.
Materials and methods
The study involved 46 patients with arterial hypertension 2–3 degrees and abdominal obesity (30 men and 16 women), mean age 54.9 ± 6.2 years old with pre-diabetes (main group, $n = 17$) or without disorders of carbohydrate metabolism (comparison group, $n = 29$). The main and the comparison groups were comparable in age, gender composition and duration of hypertension. The control group consisted of 20 healthy individuals without cardiovascular diseases, obesity and severe chronic diseases. The investigation included standard clinical, laboratory and instrumental methods. The content of the main gut microbiota phylotypes was determined by identifying the total bacterial DNA and DNA of Firmicutes, Bacteroidetes, and Actinobacteria using the method of quantitative real-time polymerase chain reaction. The Firmicutes/Bacteroidetes ratio was calculated additionally.
Results
In patients with arterial hypertension and abdominal obesity (total group) significant increasing of the relative content of Firmicutes compared with the control group was observed (45.42 [33.24; 55.07] % vs 29.18 [22.45; 38.14] %, $P < 0.01$), in the absence of a significant difference with the relative content of Bacteroidetes and Actinobacteria. The Firmicutes/Bacteroidetes ratio was significant higher in total group in comparison with control group (1.59 [1.04; 5.17] vs 0.92 [0.64; 2.37], $P < 0.01$). In patients with arterial hypertension and abdominal obesity with pre-diabetes in comparison with those without disorders of carbohydrate metabolism found significant increasing of the relative content of Firmicutes (51.12 [29.78; 68.51] % vs 40.73 [21.53; 57.14] %, $P < 0.01$) and the Firmicutes/Bacteroidetes ratio (1.84 [1.24; 5.68] vs 1.35 [0.96; 4.64], $P < 0.01$). The relative contents of Bacteroidetes and Actinobacteria were not significant differ in main and comparison groups ($P > 0.05$).
Conclusion.
The results of the study may indicate a significant role of the gut microbiota in the development of initial disorders of carbohydrate metabolism in patients with arterial hypertension and abdominal obesity. The relative content of the Firmicutes and the Firmicutes/Bacteroidetes ratio can be considered as important markers of pre-diabetes in indicated patients.

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AEP280

Effects of Glucagon-Like-Peptide-1 analogue treatment in genetic obesity

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Introduction
Obesity is highly prevalent, comes with serious health burden and is difficult to treat. In a minority, there is a genetic cause for the obesity. In these patients, therapy-resistant obesity is often observed despite intensive lifestyle treatment. Moreover, it is still unclear whether bariatric surgery is less successful in genetic obesity. Liraglutide is a Glucagon-Like-Peptide-1 (GLP-1) receptor agonist or GLP-1 analogue, showing positive effects on metabolic parameters, satiety and weight loss in lifestyle-induced obesity. We present our experiences of GLP-1 analogue treatment in patients with genetic obesity disorders.
Methods
Adults with overweight or severe obesity and a molecularly proven genetic cause were treated with liraglutide 3.0 mg daily, in addition to ongoing intensive supportive lifestyle treatment. Anthropometrics, metabolic parameters, resting energy expenditure (REE), side effects, and subjectively reported satiety and quality of life were assessed.
Results
Two patients with a heterozygous pathogenic melanocortin 4 recepter variant and two patients with 16p11.2 deletion syndrome, ranging in age between 21 and 32 years and in BMI between 28.1 and 55.7 kg/m^2 at baseline, were treated. At end of follow-up, ranging between 33 weeks and 12 years, a mean change in BMI and waist circumference was observed of –5.7 ± 3.8 kg/m^2 and –15.2 ± 21.1 cm, respectively. All patients reported better quality of life, three of them also reported improved satiety. Moreover, improvement of metabolic parameters was seen. No clear effect on REE was observed. Two patients experienced mild side effects, e.g. nausea and stomach pain, for a brief period.
Conclusion
We here show beneficial effects of GLP-1 analogues on weight, metabolic parameters, and quality of life in four patients with genetic obesity. Satiety improved in three of the four patients. All patient achieved at least the clinically relevant 5–10% weight loss. Our findings suggest that GLP-1 analogue treatment might be an effective treatment option, in addition to a healthy lifestyle, for patients with genetic obesity.

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AEP281

Effect of elevated hemoglobin A1c on complication rates after bariatric surgery: a retrospective cohort study

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Objective
The aim of this study is to evaluate whether an increased preoperative hemoglobin A1c (HbA1c) is a risk factor for postoperative complications.
Methods
We retrospectively reviewed a database of patients who underwent a laparoscopic sleeve gastrectomy or a laparoscopic gastric bypass. The database was split into two cohort according to the preoperative HbA1c (> or ≤ 7 mmol/l).
Results
We included 250 patients in both groups. There were 31 complications (12.4%) in the group with a preoperative HbA1c ≤ 7 mmol/l and 50 (20%) in the group with a preoperative HbA1c > 7 mmol/l (P = 0.057). The preoperative HbA1c is a predictive risk factor for patients younger than 52 (OR = 1.031, 95%CI (1.009–1.053)/P = 0.005) but not for those older than 52 (OR = 1.009, 95%CI (0.985–1.033)/P = 0.48).
Conclusions
In this study an increased preoperative HbA1c (> 7 mmol/l) was associated with a greater risk for postoperative complications in bariatric patients younger than 52 years old, although the magnitude of this risk may be clinically less relevant.

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AEP282

Role of sarcopenia in cognitive function in patients with morbid obesity before bariatric surgery

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Aim
Obesity was shown to be related to global cognitive decline, being especially altered the executive function and the information processing speed. Additionally, sarcopenic obesity (SO) was associated independently with a deterioration in global cognition, executive function, information processing speed, global memory and cerebral atrophy in patients > 65 years. However, at present there is no data regarding the role of sarcopenia in the cognitive function in patients with morbid obesity (MO) < 65 years.
Material and methods
Cross-sectional study. Forty-three patients that will undergo Y-de- Roux gastric by-pass were selected from those attended at the MO Unit of our hospital. Body composition by bioimpedance analysis (BIA) and Neurocognitive Test Battery (NTB) were assesed in all patients 1 month prior bariatric surgery (BS). For identifying subjects with SO by BIA, we used the skeletal muscle mass index (SMI) (SM/height^2). We set that obese subjects from the lowest tertile of SMI were sarcopenic whereas those from the two highest tertiles were not.
Results
Thirteen patients were allocated in the SO group and 26 in the non-SO group. All patients in the SO group were female (100% vs 58%), older (59 ± 5 vs 51 ± 8 years), with lower BMI (41 ± 1.3 vs 45 ± 5 kg/m^2), higher fat mass (%) (50 ± 4 vs 43 ± 8) and lower claw force by hand dynamometer (21 ± 4.5 vs 31.5 ± 10) (P < 0.005). SO group had worse performance (raw score) in inverse visual span [3(2–5) vs 4(3–7)], Trail Making Test A [47(32–99) vs 38(15–98)], Trail Making Test B [133(74–300) vs 86(36–300)] and Symbol Digit Test (31 ± 13 vs 42 ± 13) (P < 0.005). No differences were observed in educational level between both groups. The 4 cognitive tests correlated with age (P < 0.005). After regression analysis, age and the presence of SO significantly correlated with Trail Making Test B and Symbol Digit Test, but only was the inverse visual span test that correlated with SO (ń0.459, P < 0.05), losing the correlation with age.
Conclusions
Sarcopenia could play a role in impaired executive function and information processing speed in a cohort of patients with MO < 65 years. Larger series are needed in order to confirm this preliminary results.

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AEP283

Diabetic nephropathy in absence of diabetic retinopathy in type 2 diabetes mellitus patients

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Background
There is a well-recognized association between diabetic retinopathy (DN) and diabetic nephropathy (DN), in which nephropathy without retinopathy is rare but retinopathy without nephropathy is common.
Aim
To highlight the discordance between retinopathy and nephropathy and describe a series of patients with diabetic nephropathy who had no evidence of diabetic retinopathy.
Methods
110 type 2 diabetes patients with diabetic nephropathy were studied retrospectively. Patients with clinical suspicion of non diabetic nephropathy were excluded. The patient's age, gender, body mass index, duration of diabetes, glycosylated hemoglobin (HbA1c), low density lipoprotein cholesterol and presence of diabetic peripheral neuropathy were determined.
Results
Of the study population, 31 patients (28.18%) had no evidence of diabetic retinopathy. 51.61% were male. Median age was 56 ± 15 years. The mean duration of diabetes was 12 ± 5 years, mean body mass index was 28.72 ± 4.3 kg/m^2 (overweight), mean low density lipoprotein cholesterol was 1.25 ± 0.3 g/l. All patients had poor glycemic control with a mean HbA1c of 10.3%, 51.61% had treated hypertension, 32.26% had diabetic peripheral neuropathy. 58.06% had albuminuria without renal failure, 41.92% had renal failure without albuminuria: mean estimated glomerular filtration rate (eGFR) was 50 lm/min/1.73 m^2.
Conclusion
We have identified a subset of patients with diabetic nephropathy but who are protected from retinopathy. It is possible that there is an extreme phenotype of diabetic patients with unaffected eyes who carry genes protecting against DR.

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EP284

Management of emphysematous pyelonephritis: Report of Two Cases

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Introduction
Emphysematous pyelonephritis (EPN) is a necrotizing infection of the renal parenchyma which occurs preferentially in diabetics and is fraught with heavy mortality. Adequate therapeutic management is controversial: medical or surgical, conservative or radical. We report two observations of emphysematous pyelonephritis in two female diabetic patients, aged 58 and 50 years old, respectively.
Observation
The symptoms were similar for both patients: fever, lower back pain, renal angle tenderness, dysuria, hyperglycemia and ketonuria. Blood tests indicated an inflammatory syndrome, acute renal failure and diabetic ketoacidosis. The urinalysis revealed pyuria, leukocyturia and a varied bacterial flora. The urine's culture of the first patient yielded a growth of Candida whereas E.coli was isolated in the second patient. In both cases, renal ultrasound showed uretero-pelvic dilation upstream of a stone embedded in the meatus and CT-scan confirmed the diagnosis of EPN. The outcome of conservative management was different for both patients. The first patient was successfully treated with conservative management using broad-spectrum antibiotic and percutaneous drainage. However, despite percutaneous drainage and antibiotic therapy, subsequent nephrectomy was required for the second patient as she presented a septic shock. The outcome was favorable in both cases after conservative management in the first case and radical management in the second case.
Conclusion
EPN is a life-threatening infection that should be suspected in any diabetic with severe acute pyelonephritis resistant to medical treatment. In case of failure of conservative treatment, nephrectomy should be considered.

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AEP285

Association of metabolic syndrome and hepatic steatosis in type 2 diabetics

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Introduction
Metabolic steatopathy or non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2DM) are common diseases that regularly coexist and can act in synergy by increasing the risk of metabolic complications and cardiovascular events. NAFLD seems to be frequently associated with metabolic risk factors reflecting the metabolic syndrome. The aim of this study is to analyse the characteristics of this association in type 2 diabetics.
Materials and methods
This is a retrospective and descriptive study, including 190 type 2 diabetic patients, hospitalised in an Endocrinology-Diabetology department over a period of 6 years. All the patients benefited from an abdominal ultrasound with NAFLD search, and were monitored by our centre's hepato-gastroenterology department as part of a multidisciplinary care programme. The data were exploited by SPSS-V21.
Results
Among the 190 participants in the study, NAFLD was found in 51% patients. The mean age of our patients was 59.7 ± 11.6 years, with a female predominance of 73.2%. The mean initial HbA1c was 10.1 ± 2.1%, with a mean duration of diabetes of 9.8 ± 7.9 years. Patients had hypertension (57.7%), obesity (55%), abdominal obesity (78%) and metabolic syndrome in 88.7% of cases. 89.6% had dyslipidemia, hypertriglyceridemia in 45.4% and hypoHDLemia in 75.8%. Macroangiopathic complications were present in 25.8% of patients and microangiopathic complications in 36.1%. The management of NAFLD consisted of optimal glycemic control through lifestyle modification alone (56.7%), with metformin (16.5%). 5.2% of patients were treated with liraglutide.
Discussion-conclusion
NAFLD is a common comorbidity during diabetes type 2. It is frequently associated with the metabolic syndrome. Thus, early screnning of NAFLD in type 2 diabetes is recommended, with multidisciplinary management by reducing the modifiable metabolic risk, optimal glycemic control and optimisation of weight loss to limit the progression of the disease.

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AEP286

Brain perfusion in patients with type 1 diabetes and cognitive dysfunction

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Purpose of the study
Evaluation of cerebral microcirculation using contrast and non-contrast magnetic resonance perfusion in patients with type 1 diabetes and cognitive dysfunction.
Material and methods
The study complied with generally accepted ethical rules. The study included 45 patients with type 1 diabetes mellitus with cognitive dysfunction and 20 patients without. All patients were continuously monitored glycemia. Magnetic resonance imaging was performed on a Signa Creator 'E' magnetic resonance imaging machine, GE Healthcare, 1.5 Tesla, China: the techniques were dynamic contrast ('Gadovist', IV, bolus, 5 ml) and arterial spin labels.
Results
We found decreased blood flow velocity in patients with type 1 diabetes and cognitive dysfunction in the white and gray matter areas of the frontal, occipital and temporal lobes $P \leq 0.05$). Hyperglycemia and the following glycemic variability indices - index of long-term glycemic increase, risk of hyperglycemia and hypoglycemia, rate of glycemic change, indicator of glycemic control quality - have the greatest effect on cortical structures according to perfusion data, and in case of uncontrasted glycemic control quality and rate of change, risks of hypo and hyperglycemia. The main factors of cerebral microcirculatory changes are history of severe hypoglycemia episodes, duration of disease, arterial hypertension and elevated cholesterol levels.
Conclusion
The level of glycated hemoglobin and glycemic variability, as well as acute complications, duration of DM, and associated conditions (arterial hypertension and hypercholesterolemia) underlie microcirculatory impairment of the brain in type 1 diabetes. The most significant data were obtained with contrast perfusion.

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AEP287

Predictive factors associated with diabetic kidney disease in adult-onset Type 1 Diabetes

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Introduction
Uncontrolled hyperglycemia of diabetes is a common cause of renal failure and diabetic nephropathy, which is also called diabetic kidney disease (DKD). Despite improvements in the management of type 1 diabetes (T1D), progression of diabetic nephropathy remains unpredictable and associated with high morbidity and mortality. The objective of this study is to assess the prevalence and risk factors for diabetic kidney disease among adults-onset T1D.
Patients and methods
A retrospective study, from 2010 to 2019, including 166 patients diagnosed with T1D, occurred after the age of 20, with positive anti-pancreatic antibodies (Anti GAD,Anti ICA and /or Anti IA2). The incidence of DKD and its potential predictive factors were analyzed.
Results
Our study includes 71 women and 95 men, with mean diabetes duration of 7.34 ± 6.73 years (2 months-44.5 years).The mean age was 31.81 years. DKD was observed in 6% of patients after a mean diabetes duration of 23 ± 8.3 years.By the time of diagnosis of DKD, mean age was 41.7 ± 7.2 years. Approximately 80% of patients who had been diagnosed with DKD were hypertensive. The mean systolic and diastolic BP were 139.01 ± 24.55 mm Hg and 77 ± 11.6mmHg,respectively. The mean urea and creatinine levels were 16 ± 9.12 mmol/l and 241.6 ± 160.2 umol/l,respectively. Seven patients underwent hemodialysis for end-stage renal disease. Diabetes duration was a significant predictor of incident DKD ($P < 0.05$). T1D adults with diabetic nephropathy were older than those with normal renal function (41.7 ± 7.92 vs 31.18 ± 31.18 years; $P < 0.05$). Significant linear trends were observed for hig systolic and diastolic blood with increasing creatinine level ($P < 0.05$). Adults with diabetic retinopathy have a significant high prevalence of DKD (90%) ($P < 0.05$). DKD is significantly more prevalent among T1D adults who have been diagnosed with macrovascular compared to those without macrovascular damage (90% vs 2.6%; $P < 0.05$). High triglycerides and total cholesterol levels have also been associated with a heightened risk of DKD ($P < 0.05$).
Conclusion
Identification of predictive factors of DKD is a crucial step in the management of patients diagnosed with T1D during adulthood. Linear relationship of diabetic nephropathy was found with diabetes duration, age, macrovascular complications and perturbed lipid profile. Then, further studies are needed to better identify these factors and facilitate monitoring of T1D patients.

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AEP288

The impact of printed educational materials on knowledge in women with gestational diabetes mellitus

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Aim
To evaluate the impact of printed educational materials on knowledge in women with gestational diabetes mellitus (GDM).
Materials and methods
A randomized controlled trial was performed among women with GDM. A total of 135 pregnant women with GDM who attended antenatal clinic were randomly assigned to either an intervention (45 pregnant women) or a control group (90 pregnant women). The women from intervention group received additional printed educational materials about GDM management, while patients from control group received standard care. A self-administrated questionnaire was used for evaluation of women's knowledge about GDM management. Data was statistically processed using SPSS ver. 17.
Results
Demographic and maternal characteristics were similar in both groups. The overall mean age was 32.3±4.9 years ranging from 24 to 45. The correct

answers about knowledge of diabetes complications were reported in more than 50% of women in both groups. There was a significant difference in knowledge about the risk factors for GDM (85% in intervention group vs 44% in control group, $P < 0.01$). The number of correct answers were higher in the intervention group in regard of GDM treatment (92% compared with 79% in control group, $P < 0.01$), self-monitoring of blood glucose and outcomes of GDM ($P < 0.01$). The differences in nutritional knowledge were not statistically significant.
Conclusion:
The results from the study show that printed educational materials can improve patients' knowedge about GDM management as well as their health literacy and motivation.

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AEP289

The effect of empagliflozin on main cardiovascular risk factors in patients with type 2 diabetes with normal and excessive body weight

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Aim
Study the efficacy of empagliflozin effects on main cardiovascular risk factors in non-insulin-dependent diabetic patients with normal and excessive body weight.
Objectives
60 patients with type 2 diabetes who have been taking metformin for at least 6 months but haven't reached the target level of glycated haemoglobin (HbA1c), as well as 10 healthy individuals were examined. Depending on the prescribed treatment patients with type 2 diabetes were randomly split into 4 groups: IA and IIA – patients with normal body weight, IB and IIB – overweight patients. IA and IIA patients took individual doses of metformin, IB and IIB patients took empagliflozin at a dose of 10 mg/day in addition to metformin.
Results
After a 6-month course of treatment, the dynamics of blood pressure (BP) has become more pronounced due to the complex treatment as compared with basic therapy. Systolic BP has decreased by 11.82% ($P < 0.05$) in IB group and by 12.4% ($P < 0.05$) – in IIB group, diastolic BP has decreased by 8.15% ($P < 0.05$) and 8.3% ($P < 0.05$) respectively. The treatment has resulted in a positive dynamics of carbohydrate metabolism, which was statistically more significant in patients of IB and IIB groups than in IA and IIA groups: fasting glycaemia in patients of IB group has decreased by 27.19% ($P < 0.05$), the level of HbA1c – by 10.13% ($P < 0.05$), in patients of IIB group – by 16.28% ($P < 0.05$) and 11.1% ($P < 0.05$), respectively. In our opinion, a statistically significant ($P < 0.05$) decrease of HOMA IR index by 41.9% in patients of IIB group is of great importance, in other groups no statistically significant changes have been found. During treatment no statistically significant decrease in body mass index (BMI) was observed in patients of IA, IIA and IB groups, while in patients of IIB group this index has decreased significantly ($P < 0.05$) from 27.82 ± 0.35 up to 25.1 ± 0.50 kg/m^2. Statistically significant effect of empagliflozin on leptin levels has been revealed. It has decreased by 29% ($P < 0.05$) in patients with normal BMI in IB group, and by 39.5% ($P < 0.05$) – in the group of overweight patients (IIB). Patients not taking empagliflozin haven't presented any statistically significant dynamics of leptin levels.
Conclusions
Empagliflozin has a significant effect on the main cardiovascular risk factors: it helps to reduce body weight, waist circumference, BP, leptin levels, carbohydrate metabolism and insulin resistance.

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AEP290

Gestational diabetes:predicting factors for switch to insulin

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Introduction
Insulin therapy in gestational diabetes (GD) is the second line of therapy after failure of diet rules (DR). The aim of our study was to determine the predictive factors for switching to insulin in gestational diabetes.
Method
This is a descriptive cross-sectional retrospective study, including 82 patient files followed at the gestational diabetes unit of the National nutrition institute.
We analysed
Age, term of pregnancy at first consult, initial blood sugar level, family history of diabetes cases, pre-conceptional Body Mass Index (BMI), weight gain during pregnancy and obstetric history.
Results
The average age of our population was 33.5 years (19–44 years). The average pre-conceptional BMI was 29 kg/m^2 (18–47.2 kg/m^2).The average GD discovery term was 28 weeks. A family history of diabetes cases was found in 46.3% of the cases. The average gestity was 3 and the average parity was 2. The history of GD was found in 13.4% of cases, a fetal death was found in 11% of cases and fetal macrosomia in 12.2% of cases. The diet rule lead to achieve glycemic targets in 77.5% of patients and a switch to insulin therapy was imperative in 22.5% of cases. The average of HBa1c was 5.2%. No significant relationship was found between age, preconceptionl BMI, weight gain during pregnancy, and use of insulin therapy during GD. The use of insulin was more frequent when there is a history of foetal macrosomia ($P = 0.022$), when the term of discovery of GD is early (less than 24 weeks) ($P = 0.045$), when initial blood sugar level > 1 g/l ($P = 0.045$) and increased pregnancy ($P = 0.042$).
Conclusion
In our study, history of macrosomia, early discovery term of GD, baseline blood glucose > 1 g/l and numerous pregnancies are predictors of insulin use during GD. In the presence of these factors, an intensification of DR and closer monitoring should be implemented for better management.

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AEP291

Clinical research out of insulin glargine u300 in type 1 diabetes mellitus patients with frequent hypoglycemia: a real world experience

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Aims/Introduction
We aimed to see whether Insulin Glargine U300 can provide better blood glucose control while reducing hypoglycemia in a more homogeneous population compared to previous studies.
Materials and methods
For evaluation of FBG, HbA1c and weight at 6 months and all variables final, observation windows of 120–240 days (4–8 months) and 240–480 days (9–16 months) after Insulin Glargine U300 initiation, respectively, were permitted. Hypoglycemia was defined as blood glucose level < 70 mg/dl, either symptomatic or asymptomatic, or measured in hospital or at home.
Results
The 35 patients comprised, 20 (57.1%) female and 15 (42.9%) men with a mean age of 24.1 ± 6.6 years. Mean BMI was 24.4 ± 7.4 kg/m^2. Pre-study treatment regimens were given Table 1. A significant decrease was not found between baseline and HbA1C values in 6 month ($P = 0.199$) but in follow-up period (between 9–16 month) significant decrease was found ($P = 0.025$) (Table 2.). Hypoglycemic events occurred in all patients (100%) before using Insulin Glargine U300, while the incidence of hypoglycemic events gradually decreased to 74.3%, 68.6% and 68.6% between months 1–3, 3–6 and 6–9 respectively. Of the 26 patients that declared their satisfaction, 23 (88.5%) of them were satisfied, 2 (7.7%) of them indicated that there was no significant difference, and 1 (3.8%) patient was unsatisfied.
Conclusions
Over 9 – 16 month follow up period, Insulin Glargine U300 led to a significant reduction not only in HbA1c levels but also in the frequency of hypoglycemia, and also yielded high satisfaction rates.

Table 1. Pre-study treatment regimens

Treatment	n (%)
Basal insulin + bolus insulin	35 (100)
IGlar U100	28 (80)
Insulin Detemir	7 (20)
Insulin Aspart	23 (65.7)
Insulin Lispro	8 (22.2)
Insulin Glulisin	4 (11.1)

Table 2. Comparison of baseline and final body weight, FBG, and HbA1C values

	Means	*P***
Fasting blood glucose (mg/dl)†		
Baseline – 6 month	191.2 ± 114.3–180.8 ± 97.9	0.678
Baseline – Final	191.2 ± 114.3–149.5.3 ± 62.4	0.043
6 month – Final	180.8 ± 97.9–149.5.3 ± 62.4	0.054
HbA1c (%)†[mmol/mol] †		
Baseline – 6 month	9 ± 2[74.9 ± 21.9]–8.9 ± 2[73.8 ± 21.9]	0.199
Baseline – Final	9 ± 2[74.9 ± 21.9]–8.7 ± 1.6[71.6 ± 17.5]	0.025
6 month – Final	8.9 ± 2[73.8 ± 21.9]–8.7 ± 1.6[71.6 ± 17.5]	0.179
Weight (kg) †		
Baseline – 6 month	66.3 ± 11.6–66.4 ± 12.1	0.835
Baseline – Final	66.3 ± 11.6–66.5 ± 12.8	0.796
6 month – Final	66.4 ± 12.1–66.5 ± 12.8	0.811

†: mean ± SD, **Paired t-test

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AEP292

A survey of nutritional issues in type 2 diabetes among patients in khorezm region of uzbekistan

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Purpose of the study
In Uzbekistan, more than 80% of patients with type 2 diabetes mellitus have uncompensated diabetes, including those receiving adequate free drug therapy. This is mainly due to the neglect of non-drug measures and unhealthy diets. The purpose of the study was to establish the reasons for patients' non-compliance with nutritional rationalization prescriptions, on the example of the Diabetes School at Khorezm Regional Endocrinology Center.
Methodology
An examination of 54 patients with type 2 diabetes mellitus, including a comparison of fasting and prandial blood sugar levels, of HbA1c, combined with an adherence survey. The survey had a question on digital literacy (capacity to use IT for remote consultations).
Results
Only 3 patients in the sample registered target levels of carbohydrate metabolism (HbA1c less than 7%, fasting sugar less than 7 mmol/l, prandial glycemia less than 10 mmol/l). Based on levels of compliance with nutritional rationalization, patients were divided into three categories: 22 (40.7%) patients with a negative attitude to any dietary restrictions, 26 (48.2%) patients wishing but lacking knowledge about correct nutrition, and 6 (11.1%) patients who were compliant and knowledgeable about nutritional rationalization. But only 3 of them had compensated diabetes. The respondents believed that the reasons for the ineffectiveness of the diet therapy are outdated nutritional traditions, the impact of food advertising, aggressive advertising of dietary supplements and the consumption of excessive amounts of processed foods, as well as the high salt, sugar and fat content in locally popular foods (e.g. bread and biscuits). Of 54 patients, only 6 (9.3%) were capable to use IT for remote consultation.
Conclusions
Regular workshops at the Diabetes Schools are not effective since they don't offer tailored approach sensitive to the stage of the disease, its complications, age, gender, diabetes treatment, dietary habits, marital status, financial security and employment. Remote observation will not work for the elderly and digitally illiterate patients and will be limited to better educated patients active in the workforce. For sufficient glycemic control, the efforts of the endocrinologist and patients is to be combined with relevant policies at the level of the medical practice and research communities, the food industry and government agencies.

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AEP293

Effectiveness of semaglutide in obese patients with type 2 diabetes. a six-month clinical experience

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Introduction
Semaglutide is a glucagon-like peptide-1 receptor agonist which has shown important benefits in patients with type 2 diabetes mellitus (T2DM) in randomized clinical trials. Its commercialization in Spain began in May of 2019. The main purpose of this study was to analyze the effectiveness of this drug into routine clinical practice in patients with T2DM with a body-mass index above 30 kg/m^2.
Matherial and methods
Retrospective observational study including demographic, analytical and clinical features of 27 patients in whom semaglutide was started. The beginning dose was 0.25 mg once-weekly during the first month, and after this period of time it was increased to 0.5 mg once-weekly. A second follow-up visit was performed 6 months after the drug was started, with the aim of evaluating the impact of its use.
Results
Data of 27 patients (14 men and 13 women) with TD2M were analyzed. The overall mean age was 60.1 ± 11 years, with a mean time of evolution of the disease of 8.7 ± 6.5 years. The 18.5% of them had established cardiovascular disease (coronary heart disease). Basal characteristics of the population at the beginning: BMI 42.3 ± 8.3 kg/m^2; weight 116.8 ± 30.3 kg; HbAa1c 8.2 ± 1.6%; fasting blood glucose 166.7 ± 55.6 mg/dl; blood pressure 149.5 ± 22.2/84.8 ± 12.6 mm Hg. The number of antidiabetic drugs was 1.44 ± 0.75 before starting semgalutide (85% of the patients were receiving metformin, 26% SGLT-2 inhibitors, 26% GLP-1 RA, 11% sulfonylurea and 7% DPP-4 inhibitors). 37% of the patients were treated with insulin therapy. At six-months follow-up visit, significant mean reductions of BMI (39.9 ± 7.1 kg/m^2), weight (110.7 ± 25.9 kg), HbA1c (6.6 ± 1.1%) and fasting blood glucose (116.4 ± 24.9 mg/dl) were obtained. After this, 85% of the patients treated with metformine and 48% with SGLT-2 inhibitors. Sulfonilureas were discontinued in all patients. The DPP4 inhibitors were discontinued when semaglutide was started. The percentage of patients with insulin therapy did not change.
Conclusions
Semaglutide is an effective pharmacologic agent for the treatment of T2DM in terms of metabolic control (HbA1c reduction) and weight reduction.

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AEP294

Serum ferritin levels correlate with ultrasonography-determined liver steatosis severity in type 2 diabetes patients with NAFLD

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Introduction
Non-alcoholic fatty liver disease (NAFLD) is a component of metabolic syndrome (MetS). Hence, it is frequently associated with type 2 diabetes mellitus (T2DM). The low-grade inflammation associated with NAFLD usually explained the changes in serum iron metabolism. This study aims to assess the link between liver steatosis severity and serum iron, ferritin, and transferrin levels.
Material and methods
A case-control study involved 30 non-obese subjects (BMI 18.5–30 kg/m^2), who suffered from T2DM for less than 5 years. Such subjects are regularly under treatment by metformin (M) and sulphonylurea (SU) derivates. Liver steatosis severity is determined by ultrasonography and presented as grades 1, 2, and 3 (initial, moderate, and advanced liver steatosis), respectively, according to Singh *et al*. criteria (Singh *et al*. Indian J Endocr Metab 2013;17: 990–5).
Results
In the observed population, 14 (47%), 11 (36%), and 5 (17%) subjects are determined to grade 1, 2, and 3 liver steatosis severity groups, respectively. The mean values of iron homeostasis markers have not differed from normal values. Liver steatosis severity grades positively correlated with serum ferritin levels, and this correlation is not revealed in the cases with serum iron and transferrin levels.
Conclusion
The low grade of liver steatosis has predominated in non-obese T2DM subjects under treatment with M and SU, irrespective of glycemic control quality. An increase in liver steatosis severity follows the ascending trend of ferritin levels. Further studies are needed to elucidate the impact of the quality of T2DM control on liver steatosis severity and iron metabolism markers.
Keywords: Non-alcoholic fatty liver disease, type 2 diabetes mellitus, ferritin
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AEP295

Risk factors for diabetes mellitus in a high-risk population: About 500 cases

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Introduction
The prevalence of diabetes and pre-diabetes is steadily increasing. It affects 3 new cases every 10 seconds and more than 6 million per year. Objective: to determine the risk factors associated with diabetes in an Algiers population not known to be diabetic but at high risk.
Methods
500 patients aged 40 and over consulting at the level of primary care structures, volunteers but at high risk of diabetes, are subjected to a questionnaire, then to screening by carrying out an OGTT, an HbA1c (HPLC), an SNSF. The sensitivity and specificity of HbA1c at different thresholds for the diagnosis of diabetes and pre-diabetes were studied by ROC curve. The diagnostic performance of HbA1c was assessed by the areas under the ROC curve (AUC) estimated by the DeLong method.
Result
Among the 500 patients studied 69% are women and 31% are men with a sex ratio of 2.22. Of which half of the cases aged between 45–54 years. 53.2% of patients present with dysglycemia: including 29.4% pre-diabetes: (6.8% moderate fasting hyperglycemia (HMJ), 22.6% (Glucose intolerance) and 23.8% diabetes mellitus. The risk factors associated with diabetes in our population in descending order are:
• Excess weight (BMI ≥ 25 kg/m^2) (P < 0.001).
• Male sex. (p: 0.025).
• Age ≥ 45 years (p: 0.033).
• Maternal family history of diabetes mellitus. (P: 0.042)
• waist/hip ratio ≥ 0.85 (android type) in women (P: 0.043)
• high blood pressure (P: 0.045).
Conclusion
Diabetes mellitus is a major public health problem around the world. It is unfortunately associated with the development of serious complications, which have a significant impact on morbidity and mortality. Early diagnosis could reduce and delay these complications, so it is important to identify pre-diabetic conditions early so that prevention efforts can be implemented by targeting these populations, and thus help prevent or slow down. the progression of this condition to overt diabetes.
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AEP296

Newly diagnosed diabetes in pregnancy among bulgarian pregnant women - national screening in 2019

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According to the FIGO (2015) and later WHO (2019) classifications, hyperglycaemia detected for the first time during pregnancy may be associated with Diabetes In Pregnancy (DIP) or Gestational Diabetes mellitus (GDM).
Aim
To specify the frequency and type of newly diagnosed diabetes during pregnancy in the Bulgarian population of women.
Material
We studied 547 pregnant women with a mean age of 30 ± 5 years, through a cross-sectional multicenter population-based study in 84 settlements in Bulgaria.
Methods
A two-hour, 75 g oral glucose tolerance test (OGTT) was performed in one Central laboratory on the day of the blood sampling. The statistical analysis was performed using standard SPSS 13.0 for Windows.
Results
Hyperglycaemia was observed in 14.4% (79/547) pregnant women after fasting state or in the course of classic OGTT, according to the criteria of WHO'2019, FIGO'2015, NICE'2015. It turned out that the number and frequency of pregnant women with Hyperglycemia in the period up to 24 gestational week (g.w.) is 7.5% (29/386) and increases in the period after 24 g.w. reaching 31% (50/161), P < 0.01. Only 8.9% (7/79) of the pregnant women were newly diagnosed with Diabetes mellitus according to the criteria for the general non-pregnant population, ie. Diabetes in Pregnancy (DIP), while the remaining cases met the criteria for GDM - 91.1%.
Conclusion
As soon as pregnancy occurs, it is necessary to perform OGTT to detect undiagnosed Diabetes mellitus (DIP). In the case of a negative result, OGTT is repeated in 24–28 g.w, when the risk of GDM increases.
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AEP297

Effect of yog nidra on the self-estimated levels of stress and epworth sleep score in t2dm patient.

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Introduction
Stress and anxiety have become major killers in our developed and devloping countries both. Literature has shown reluction in stress results in better owerall well being. lack of sleep is also a contibutor to stress.In T2DM patients this becomes even more important as the have higher oxidative stress, Yoga Nidra is already prescribed by scholars in several countries because of its potential to activate the parasympathetic nervous system and positively influence stress-related parameters such as skin conductivity and cortisol level, which is beneficial for reducing stress related illness and further complications.
Aim
Effect of Yog Nidra on the self-estimated levels of stress and Epworth Sleep Score in T2DM Patient.

Method
The meditation was provided as audio file and carried out during a period of 30 days by the participants of the meditation group.
Method
This study is the first to examine the effects of of Yoga Nidra that was independently conducted by each of the participants using an audio file. Instructions and data collections were carried out via online Survey; the audio file with the Yoga Nidra meditation was provided via download link. No eligibility or exclusion criteria for selection of participants. All subjects participated anonymously and voluntarily. The study was conducted in a pre-post-follow-up design with two measurement points. The intervention period between pre-test and post-test was 30 days;To measure the self-estimated levels of stress and any changes in the course of the study Percieved Stress Score was used.
Result
The meditation group (N = 41) showed Reduction in percieved stress score, Better Epworth Sleep Score (ESS) after the intervention compared with a control group (N = 43).
Discussion
The present study showed the effectiveness of Yoga Nidra and seated meditation in reducing anxiety and stress levels of T2DM Patients when compared to the control group.Yoga nidra is easy to administer, relatively safe and does improve sleep.The model developed for yoga nidra intervention can be used in chronic insomnia patients as an adjunct in management of chronic insomnia. However, more studies, with different groups of all ages and occupations, are necessary to better elucidate the mechanisms through which Yoga Nidra works.

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AEP298

ABSTRACT WITHDRAWN

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AEP299

Microbiota disorders in type 2 diabetes and obese patients

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Aim
To assess the effect of Zakofalk in complex therapy in patients with type 2 diabetes and obesity.
Materials and methods
We examined 68 patients with type 2 diabetes and 28 with obesity (body mass index over 30 kg/m^2). The control group consisted of 20 people. The groups were comparable in terms of age, sex, and antihyperglycemic therapy. In addition to a thorough clinical examination of all study participants, the content of short-chain fatty acids (SCFA)took place. SCFA before and after four weeks of Zakofalk therapy. In 45 patients with type 2 diabetes during examination, including capsule endoscopy, endoscopic and histological changes in the lining of the colon were diagnosed, their own previously not diagnosed microischemic colitis. Some patients with type 2 diabetes and obesity have a concomitant disease with irritable bowel syndrome. The results of the study of the SCFA content are presented below. According to the structure of aspen bacterial metabolites of the colon in the study groups, P < 0.05: Butyrate: type 2 diabetes + NAFLD at 19%, the norm at 16% Propionate: type 2 diabetes + NAFLD at 23%, the norm at 20% Acetate: Type 2 DM + NAFLD at 58%, normal at 64% The total concentration of SCFA in patients with type 2 diabetes, P < 0.02: Obesity group: 11.4 ± 4.1 mg/g Type 2 diabetes group: 4.9 ± 1.0 mg/g Norm: 10.6 ± 3.1 mg/g
Conclusions
Thus, the appointment of butyrate seems to be a promising approach to improve the effectiveness of treatment of patients with type 2 diabetes and obesity. The use of butyrate (Zakofalk) in complex therapy leads to a decrease in systemic and local inflammation, regulation of the production of glucagon-like peptide-1 and glucagon-like peptide-2, PYY, reprofiling of the microbiota from lactate to butyrate, a decrease in insulin resistance, an improvement in the glycemic profile, restoration of the visceral barrier intestine, stimulation of its own butyrate-producing microbiota. In the treatment of microischemic colitis, the drug helps to reduce flatulence, abdominal pain, normalize stool, and modify eating behavior.

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AEP300

Evaluation of international experience in the management of patients with diabetes mellitus after liver transplantation

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Aim
Analyze a number of foreign sources to assess the risks of developing post-transplant diabetes mellitus (PTSD).
Materials and methods
In total, we analyzed more than 70 sources from Western Europe, East Asia and South Africa. Pancreatic ńcell dysfunction, impaired insulin secretion associated with the use of calcineurin inhibitors and inhibitors of the mammalian target of rapamycin complex 1 (mTORC1), postoperative weight gain, and hepatitis C associated with insulin resistance. According to Lv C., Zhang Y and all; Song J.L., Gao W and all; Xue M., Lv C. and all - a quarter of patients without diabetes mellitus developed PTSD at the time of liver transplantation, which corresponded to the previously presented data - from 19 to 35% However, studies by Liu F.C., Lin J.R. and all; Abe T., Onoe T and all reported lower incidence rates of 6 to 8%. According to Aravinthan A.D., Fateen W., Doyle A.C. *et al*., the incidence of PTDM was significantly higher in the early post-transplant period. According to the results of a retrospective study by E.J. Carey *et al*., A 2-fold increase in the risk of developing PTSD is associated with an excess of plasma glucose for every 10 mg/dl before liver transplantation. It has been suggested that a wide range of factors in the recipient and donor, the causes and severity of liver disease, as well as the characteristics and duration of surgery and treatment in the post-transplant period play an important role in the development of PTSD. A meta-analysis of 19 retrospective studies of over 4.500 patients by D.W. Li *et al*., Identified independent risk factors for PTSD. These included male sex, body mass index, etiology of hepatitis C, impaired fasting plasma glucose levels before liver transplantation, and tacrolimus use.
Conclusions
General approaches to the treatment of PTSD have not yet been developed. Patients require individual drug correction under the supervision of an endocrinologist and hepatologist. Of course, it will be more difficult for liver cells burdened with pathologically altered metabolism in diabetes mellitus to cope with toxic effects, because this organ is characterized by a reduced functional reserve. Therefore, when prescribing therapy, preference should be given to drugs that are least metabolized in the liver. In patients with diabetes after liver transplantation, it is necessary to carry out not only adequate immunosuppressive therapy, but also hypoglycemic therapy. Insulin is currently the drug of choice.

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AEP301

Nutritional status of Tunisian women followed for gestational diabetes

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Introduction
The respect of dietetic rules constitutes the cornerstone of the management of gestational diabetes (GD). The aim of our study was to describe the spontaneous food intake in Tunisian women followed for GD.
Methods
This is a descriptive and retrospective study, including 82 patients followed at the gestational diabetes unit of the National Institute of Nutrition. We analyzed: age, pre-conceptional body mass index (BMI), weight gain during pregnancy and food survey.
Results
The average age of our population was 33.5 years (19–44 years). The average preconception BMI was 29 kg/m^2(18–47.2 kg/m^2). The average weight gain during pregnancy was 6 kg (–14 to + 37 kg) Pregnant women followed for gestational diabetes were investigated at the average term of

28 weeks. The food survey had found an average intake of carbohydrates, proteins and lipids respectively of 52.5%, 32% and 15.7%. Regarding the food survey, 39.7% of the women had an excessive intake of carbohydrates, 46% had an excessive intake of lipids and 30.2% had a reduced intake of proteins. Daily fiber intake was decreased in 55.6% of women participating in the survey. An iron deficiency was found in the daily food intake in 92% of women. Vitamin D intake was decreased in 96.8% of the population surveyed with calcium intake decreased in 52.4% of cases. The w6/w3 ratio was increased in 79.4% of the women and 84% of the participants had a decreased zinc intake.
Conclusion
Nutritional education targeting the general population should be established in order to limit the consequences of these multiple nutritional deficiencies.

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AEP302

The role of diabetes in the clinical presentation and prognosis of bell palsy

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Objective
to analyze the clinical presentation and prognosis of Bell's palsy in diabetic patients.
Materiel and methods
This retrospective study included 76 diabetic patients with Bell 's palsy in the ENT department of Tahar Sfar Mahdia; Tunisia from January 1988 to December 2018. The system of House-Brackmann was used for assessing the severity of nerve damage.
Results
a total of 76 diabetic patients with Bell's palsy were included in this study. The average age was 46 years (range: 26 and 82 years). In terms of their sex distribution, we found a male dominance (41 men, 35 women). According to the House-Brackmann (H-B) grading system, four patients were diagnosed with grade III, 41 with grade IV, 15 with grade V and 16 with grade VI. All 76 patients received the same therapeutic protocol, which included intravenous administration of prednisolone and acyclovir 500 mg intravenous thrice daily. Serum glucose was monitored thrice daily with finger prick testing and appropriatr treatement was administered according to the instructions of their physician. After a 6-months follow-up, complete recovery was achieved in 60 patients. Three patients presented a grade IV, five patients a grade III and 10 patients a grade II paresis. Recurrence episodes were noted in four patients.
Conclusion
a relationship between the severity of Bell palsy and diabetes seems to be demonstrated. We highlight the importance of glycemic control for prevention as well as the treatment of Bell palsy in diabetic patients.

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AEP303

Poor glycemic control in type 2 diabetes: From eating behavior to therapeutic inertia

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Introduction
Adherence to therapy is a common problem, predominating mainly in patients with chronic diseases like diabetes, and it is often associated with inappropriate eating behavior, both of these factors can lead to a poor glycemic control, and of cause a high levels glycated hemoglobin.
Objectives
Evaluate the impact of various parameters (age, gender, duration of diabetes, socio-economic status, polymedication, analphabetism, family situation, etc.) on therapeutic adherence, dietetics and physical activity in poor glycemic control in type two diabetic patients.
Methods
This is a transversal study of one hundred twenty-seven patients that they have poorly controlled diabetes, who were hospitalized in the Endocrinology Department between two thousand sixteen and two thousand nineteen for management.
Results
Our study included one hundred twenty-seven patients, hospitalized for poorly controlled diabetes. Seventy percent of patients are female, the average age is sixty-four years, the average glycohemoglobin is ten and a half pourcent. The average duration of diabetes is eleven years, fifty-nine pourcent of cases have a poor socio-economic level, forty-eight pourcent live in rural areas, sixty-six pourcent are illiterate, ninety-nine pourcent lives with family and thirty-four pourcent are in polymedication. sixty-two pourcent of these patients report poor adherence to treatment, and the dietary assessement found inappropriate eating behavior in eighty-three pourcent of patients, and that thirteen pourcent of these patients practice regular physical activity.
Conclusion
Treatment adherence, diet and physical activity are important parameters in the management of type two diabetes, which explains the poor glycemic control in many patients despite an adapted antidiabetic treatment.

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AEP304

Impact of diabetes mellitus on survival in upper aerodigestive tract squamous cell carcinoma

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Introduction
Association between diabetes mellitus and cancer outcomes has been demonstrated in several cancer sites. Data for upper aerodigestive tract carcinoma are limited. Our aim is to study the impact of diabetes mellitus on survival in 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 < 00.05 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 59.8 years. The tumour 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 was not significantly poorer overall or disease-free survival in type 2 diabetes mellitus patients. This may provide guidance for the multidisciplinary team that treats diabetic patients with head and neck cancer.

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AEP305

Comparing impact of SGLT2 inhibitors and GLP-1 agonists on lipid profile among the patients with diabetes mellitus Type 2. Results of a prospective 18-week observational study

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Background
In Georgia, significantly huge number of patients with Diabetes Mellitus Type 2 (DMT2) suffer from cardiovascular diseases (CVD) and obesity. Since, dyslipidemia is one of major factors, leading to cardiovascular

(CV) mortality, it is crucial to investigate the effects of relatively novel hypoglycemic agents- Sodium Glucose Cotransporter 2 (SGLT2) inhibitors (Dapagliflozin) or Glucagon like peptide 1 (GLP-1) agonists (Liraglutide) on lipid profile.
Aim
The aim of our short-term observational study was to assess and compare impact of SGLT2 inhibitor and GLP-1 agonist on lipid profile in patients with DMT2 and dyslipidemia.
Methods
A total of 48 patients with DMT2, (Mean age 51.8 yrs. ± 6.1. Mean duration of DMT2 ± 8.3 yrs., n = 30 male, n = 28 female) were recruited in the observational study. All of them had been treated with GLP1 agonists or SGLT2 inhibitors, (25 patients treated with SGLT2 inhibitors, 23 patients treated with GLP1 agonists) as add-on therapy to Metformin, at least for 6 months. On based of that, we divided the patients respectively into two groups and compared the effects of GLP-1 agonists and SGLT2 inhibitors on lipid profile at baseline and on 18th week of the study. All the patients were instructed to keep healthy diet and physical activity
Results
42 patients completed the follow-up. After 18 weeks of the treatment, the study showed the upward trend of HDL-Cholesterol (HDL-C) and downward trends of Total Cholesterol (TC) and LDL-Cholesterol (LDL-C) among patients treated with SGLT2 inhibitors (mean LDL-C –0.2 mmol/l, mean TC –0.2 mmol/l and mean HDL-C + 0.3 mmol/l). Mean reduction in LDL-C by 0.4 mmol/l was seen among the patients treated with GLP-1 agonists. However, there was no significant effect shown on mean HDL-C or TC values. Mean levels of Triglycerides (TG) remained unchanged in both groups.
Discussion
We think, that different impacts of hypoglycemic medications on lipid profile seen in our patients should be taken into concern. Mean LDL-C was reduced in both groups, but more effectively in GLP-1 treated patients, On the other hand mean HDL-C was increased only in SGLT-2 inhibitor-treated patients. Thus, these hypoglycemic agents have mildly different beneficial effects on dyslipidemia, However these are the 18-week study results and we do hope to investigate accurately the whole lipid profile among our patients for following months.

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AEP306

Nutritional impact of tobacco in diabetic patients

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Background
It's well known that smoking and diabetes are direct causes for serious health problems such as cancer, and atherosclerosis. It is suggested that smoking indirectly leads to atherosclerosis by influencing nutrient intakes as smokers tend to eat more fat and carbohydrates and less mono unsaturated fats and fiber than non-smokers. But no studies assessed the impact of tobacco on nutrition in diabetic patients.
Aim
The aim of this study was to compare the nutrient intake in smokers and non-smokers in people suffering from diabetes.
Methods
We compared the food survey of smokers and non-smokers in diabetic patients. Sixty male diabetic patients were divided in two groups, 30 of whom were current-smokers and 30 were non-smokers.
Results
The main age of the participants was 51 years old. The average tobacco consumption among smokers was 26.41 pack-year. The average BMI was 26.74 and 23 kg/m^2 in non-smoking and smoking diabetics respectively. Loss of appetite was reported in two smoking diabetics. The average caloric intake in non-smoking diabetic patients was 2670 kcal versus 2984 kcal in smoking patients (P = 0.189). The average fat intake in smokers was 111 g versus 108 g in non-smokers (P = 0.533).The average consumption of saturated fats was 10.16 in non-smokers and 7.6 in smokers (P = 0.300). The average consumption of polyunsaturated fats was 17.4 g and 10.4 g in non-smokers and smokers respectively (P = 0.329). Monounsaturated fat were 21 g in non-smokers versus 15 g in smokers (P = 0.240). The average intake of carbohydrates in non-smokers was 353 g versus 409 g in smokers (P = 0.098). Fiber intake was 20.7 g and 17.2 for non smokers and smokers respectively (P = 0.371).
Conclusion
Unlike data in literature, no significant difference was found regarding carbohydrate, proteins, fat and fiber intake, as well as the intake of mono and polyunsaturated fats between smokers and non-smokers.

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AEP307

Characteristics and Prevalence of diagnosed type 1 diabetes among Tunisian adults

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Introduction
Diabetes mellitus is a serious metabolic disease, described by the World Health Organization as a global epidemic. An alarming increase in its prevalence among adults is observed in Tunisia as everywhere else in the world. Because type 2 diabetes preponderates among adults, few epidemiological studies focused on type 1 diabetes (T1D) that occurs during the adulthood. The aim of this study is to determine the prevalence of DT1 among Tunisian adults and identify their clinical and biological features.
Patients and methods
This study was carried out on adults who had diabetes diagnosed after the age of 20 years (n = 280), in Sfax (the south west of Tunisia) during the period from January 2011 to December 2019. Various clinical and biochemical parameters were evaluated.
Results
Among the 280 included adults, 166 (59%) were diagnosed with type 1 diabetes. An average of 9 patients per year was newly diagnosed with T1D after the age of 20 years. In our study, 22.9% of patients were ethylic and 44% were smokers. The mean age at onset was 31.81 years old ± 9.39 (range, 20–64 years) with significant male predominance (P = 0.01) and a sex ratio of 1.34. Approximately 71% of patients had a family history of diabetes. High blood pressure (56%), obesity (26.5%) and ischemic heart disease (12.7%) were the most common family histories. Only 46 patients (27.7%) had an autoimmune disease besides diabetes. The association of another autoimmune disease with diabetes was significantly more common in women (P < 0.05).Furthermore, adults presenting with another autoimmune disease were significantly older than those without (P < 0.05). The mean of basal metabolic index (BMI) was 21.05 kg/m^2. Underweight was found in 23.5% of cases and 63.9% of patients had normal BMI. Overweight and obesity were observed in 9% and 3.6% of patients, respectively. Ketosis were observed in 50.6% of cases, with beta cell decline ranging from 1 week to 24 months, preceded by oral therapy in 24.1% of cases. Mean blood glucose was 21.01 ± 7 mmol/l and mean glycated hemoglobin (HbA1c) was 11.88 ± 2.51% Glutamic acid decarboxylase (GAD) autoantibodies were positive in 97.6% of cases with a mean average of 485.31 ± 431.5 UI. Protein tyrosine phosphate (IA2) and islet cell (ICA) autoantibodies were positive in 13.3 and 17.4% of cases,respectively.
Conclusion
This study provided an estimate of incidence of diagnosed T1D among Tunisian adults and highlights the importance of its screening even during adulthood.

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AEP308

Screening for dyslipidemia in diabetic patients in a town in the Moroccan desert: the town of Es-Smara. Screening for dyslipidemia in diabetic patients in a town in the Moroccan desert: The town of Es-Smara

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Introduction
In diabetes, lipid abnormalities are frequent and pronounced and are an important factor in increased cardiovascular risk, especially in type 2 diabetics, mostly in combination with other risk factors. The aim of this work is to highlight the prevalence of dyslipidemia in a considerable population of diabetics in Es-Smara.

Patients and methods
As part of a multidisciplinary medical caravan carried out in the Moroccan desert, a diabetology consultation was conducted for the benefit of diabetic patients in the Es-Smara region. The biological analyzes were carried out in the same laboratory; they included the determination of triglycerides and cholesterol with its HDL and LDL fractions, serum creatinine and glycated hemoglobin.
Outcomes
During 3 days of consultation, we have identified 116 patients with type 2 diabetes, the average age of the patients was 57 years, with a female predominance. Hypertension was noted in 26% of patients. Waist circumference was high in 113 patients (97%) with an estimated mean of 92.7 cm and a female predominance of 77%. Sedentary lifestyle was found in 111 patients (95%). The mean duration of diabetes was 6.4 years, poor glycemic control was observed in 54 patients (46.5%) with an average HbA1c of 8.67%. In our study, 87 patients presented with dyslipidemia (75%). It was dominated by hypertriglyceridemia in 47.4% of cases, LDL hypercholesterolemia represented 31%, HDL hypocholesterolemia 17% and mixed dyslipidemia 39%. Dyslipidemia was more common in women (65%) than in men. We noted a considerable consumption of fenofibrates in 35% of cases.
Discussion/Conclusion
These dyslipidemic diabetics are patients at very high cardiovascular risk with potential damage to target organs. It is therefore incumbent on them to significantly improve their care through an adequate health policy, the aim of which is to improve access to care and extend social coverage. Earlier screening, appropriate and vigorous treatment of the associated cardiovascular risk factors is also required in order to control this dyslipidemia.

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AEP309

Achieving target values for measures for peripheral arterial disease, nephropathy and dyslipidemia in type 2 diabetes- two year assessment

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Objective
T2DM is a major risk factor of peripheral artery disease, leading to increased morbidity and mortality as well as an accelerated disease course. Microalbuminuria is an indicator for overt nephropathy and early cardiovascular disease
Methods
We analysed data from outpatients attending a comprehensive diabetes care centre (n = 202), from 2019 till 2020, who had any of values beyond normal targets, for either of HbA1c, LDL-C, Ankle Brachial Index (ABI), Toe Brachial Index (TBI) or Albumin Creatinine Ratio (ACR). Percentage of patients achieving target values were classified as ATV (Achievers for the Target Value)
Results
Total of 202 patients (95 males, 107 females) were evaluated for glycemic and non – glycemic parameters (lipid profile, ABI, TBI, UACR). Mean age was 53 (± 13 years (95% CI 51 to 55). Mean duration of diabetes was 7.7 (± 6.5 minimum 1, maximum 36, 95% CI 6.8 to 8.6). The mean HbA1c was 8.5% (± 2 minimum 5.3, maximum 15, 95% CI 8.2 to 8.8). 4 patients reported macroalbuminuria (ACR > 300) and 49 patients had microalbuminuria (ACR 30–300). HbA1c and non glycemic measures as a marker for comprehensive diabetes care (table)

Table 1. HbA1c and Non Glycemic Measures as a Marker for Comprehensive Diabetes Care

	Mean	± SD	95% CI	n (%) within target
HbA1c (< 7%)	8.7	2.1	8.3 to 9.1	54 (26.7)
LDL-C (target < 100 mg/dl) (n = 102)	73	18	69 to 76	102 (50.4)
ABI- Right (target 1–1.29)	1.2	0.07	1.2 to 1.2	146 (72.2)
ABI- Left (target 1–1.29)	1.2	0.08	1.2 to 1.2	141 (69.8)
TBI- Right (target 0.5–0.75)	0.65	0.066	0.62 to 0.68	25 (12.3)
TBI- Left (target 0.5–0.75)	0.63	0.077	0.60 to 0.67	22 (10.8)
Albumin Creatinine Ratio (ACR) (Normal < 30)	12	6.7	11 to 14	92 (45.5)

Discussion/Conclusion
Achievement of TBI (left side) was most compromised with just 10.8% of the patients demonstrating desired values, followed by TBI (right side) within normal values in 12.3% of patients and HbA1c of < 7 was not achieved by 73.3% of patients. Highest proportion of ATV were for the ABI value-right (72.2%). Results from our study provide indicators for formulation of patient outcome improvement plan. Evidence from our comprehensive care approach complements the clinical decision-making tool to allocate resources to intervene early to minimise the complications of diabetes and improve outcome

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AEP310

Vitamin D levels in a cohort of patients with SARS-CoV-2 infection and relationship with disease outcome

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Infection with the new SARS-CoV-2 or Covid-19 virus has a variable course. It may run as a mild disease or may cause severe pneumonia necessitating hospitalization. Vitamin D has immunostimulatory action and causes the release of substances necessary for combating an infection. Therefore, the relationship of vitamin D with the SARS-CoV-2 virus is under scientific evaluation. The aim was to measure vitamin D levels in a cohort of patients hospitalized with SARS-CoV-2 infection. In a cohort of 43 patients, 20 male and 23 female, hospitalized with the SARS-CoV-2 infection 25(OH)D_3 levels were measured. 25(OH)D_3 levels were also measured in a group of control subjects. The patients were classified in 4 groups, a group with uncompromised respiratory function (n = 17 patients), a group with mild respiratory insufficiency (n = 12), a group with severe respiratory insufficiency (n = 5) and a group with severe respiratory insufficiency requiring intubation (n = 8). For the evaluation of the results of the present study 25(OH)D_3 levels were classified as deficiency (0–10 ng/ml), insufficiency (10–20 ng/ml) and sufficiency > 20 ng/ml. 25(OH)D_3 levels in the SARS-CoV-2 patients were 16.16 ± 1.55 ng/ml (mean ± SEM) as compared to those in the control group, 27.28 ± 1.94 ng/ml (P < 0.001, Student's t test). Within the group 37 patients finally survived the infection while 6 died either during hospitalization or immediately thereafter. The outcome of the infection, i.e. respiratory insufficiency or need for intubation was found to be related to the levels of 25(OH)D_3 (P = 0.003, chi-square test). It appears that vitamin D deficiency as assessed by the measurement of 25(OH)D_3 levels is prevalent in patients with severe SARS-CoV-2 infection requiring hospitalization. Vitamin D levels appear also to be related to the outcome of the infection. This result is in accordance with the immunostimulatory action of vitamin D, an action known since the very early years of its discovery.

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AEP311

Impact of the COVID pandemic and lockdown in the glycemic and weight control of patients with type 1 and type 2 diabetes – data from a Portuguese hospital

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Introduction
Due to the COVID pandemic, Portugal was forced to start lockdown on March 18 th that lasted until June 1st. Lockdown caused a lot of changes in the daily activities of the Portuguese people, such as eating habits, exercise, time spent at home and stress management. After the lockdown people noticed difficult access to healthcare.
Objective
Our aim was to evaluate if these changes had an impact in the glycemic and weight control of patients with diabetes.

Material and methods
We performed a retrospective study and included patients with type 1 and type 2 diabetes followed in our hospital. We checked hemoglobin A1c (%) between December 2020-February 2021 (before lockdown), between June-August 2021 (during lockdown) and after September 2021 (after lockdown), and we evaluated weight (Kg) before and after lockdown. In the group of type 1 diabetes we also analyzed TIR (time in range (%)) and TBR (time below range (%)) before lockdown (January-February), during lockdown (April-June) and after lockdown (July-September).
Results
We included data from 233 patients, 119 with type 1 diabetes, (43.9 ± 1.2 years; 51% women and 49% men) and 114 with type 2 diabetes (65.4 ± 1.2 years; 52% men and 48% women). Our analysis showed no significant changes in any of these variables, but showed a trend for improvement in the glycemic control in type 2 diabetes (A1c before lockdown 8.1 ± 0.14 vs during 7.8 ± 0.18 vs after 7.8 ± 0.2; $P = 0.323$). In patients with type 1 diabetes we noticed a trend for glycemic improvement during lockdown but not after (A1c 8 ± 0.1 vs 7.7 ± 0.1 vs 8 ± 0.2; $P = 0.2$), and also better TIR during lockdown (45.5 ± 1.8 vs 51.7 ± 2.1 vs 48.2 ± 1.8; $P = 0.08$). However, our analysis showed an elevation of the time spent in hypoglycemia after lockdown (TBR 5.2 ± 0.6 vs 5.3 ± 0.7 vs 6.5 ± 0.6; $P = 0.3$). There was a trend for reduction in weight in type 2 diabetes after lockdown (82.47 ± 2.4 vs 80.44 ± 2.7; $P = 0.576$).
Conclusion
Glycemic control can improve during lockdown maybe because people can more easily manage diabetes at home. At the long term, the pandemic can worsen the glycemic control, because of the lack or difficult access to healthcare and increased stress. The new diabetes technologies can help us managing these patients, especially during the pandemic.

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AEP312

An unusual case of hypoglycaemia

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We report a 77 year old male who presented to the respiratory clinic with episodes of periodic sweating. These episodes were associated nausea. They came on with exercise and always occurred before meals. The resolving factor noted by the patient was food intake and no features suggestive of reactive hypoglycaemia were noted. His past medical history was significant for hypertension, mild bronchiectasis, mild to moderate obstructive sleep apnea requiring CPAP therapy and ischemic heart disease. He was previously taking Ramipril for his blood pressure control but was switched to Losartan two months back due to cough. He was not known to have diabetes. The patient was reviewed in the cardiology clinic as well and the possibility of a cardiac arrhythmia was ruled out. Blood insulin and C-peptide levels were sent off which came back raised. On the basis of this the patient was referred to the Endocrinology clinic to rule out the possibility of an Insulinoma and for further workup. The patient was provided with a glucometer and was checking his blood glucose levels when he was symptomatic and three times a day. Blood glucose readings as low as 2.5 mmol coinciding with symptoms of sweating and nausea were recorded. Physical examination was unremarkable with the exception of some mild respiratory crackles at the right base which were stable from previous examination. He had a BMI of 32. A 72 hour fasting test and short Synacthen test was done, both of which were normal, and the possibility of insulinoma was ruled out. The patient's Losartan was stopped and the hypoglycaemic episodes were resolved. ACE inhibitors and ARBs are the first line treatment for hypertension as recommended by NICE. Several studies have reported ACE inhibitors and ARBs improve insulin sensitivity and is favoured in patients with impaired glucose tolerance. Due to this, ACE inhibitors can lead to approximately three to four fold increase in hypoglycaemic episodes in in diabetics and rarely in non-diabetics. However no cases of hypoglycaemia in non-diabetics have been reported with ARBs so far.

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AEP313

Features of the course of metabolic syndrome in latent autoimmune diabetes in adults

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Introduction
Latent autoimmune diabetes in adults (LADA) is a specific type of diabetes mellitus (DM), the prevalence of which varies from 4% to 14%. Although LADA combines the pathogenetic and clinical features of both type 1 (T1DM) and type 2 diabetes mellitus (T2DM), the latest recommendations of the American Diabetes Association refer it to T1DM (ADA, 2021). Given that this variant of diabetes is also similar to T2DM, the risk of metabolic syndrome (MS) in this category of patients is particularly relevant. At the same time, the existing results of research in this area are quite contradictory. The aim of this study was to determine the prevalence of metabolic syndrome and its components in LADA depending on the phenotype of the underlying disease.
Materials and methods
54 patients with LADA were examined, the comparison group consisted of patients with T1DM (30 patients) and T2DM (45 patients). The average age was 54.7 years. Patients with LADA according to the main phenotypes were divided into 2 groups: LADA 1 (28 individuals) with high antibody titres (□180 U/ml) to glutamic acid decarboxylase (antiGAD) and LADA 2 (26 individuals) with low antibody titres (18 -180 U/ml). The phenotypic features of the prevalence of MS and its components in LADA were studied in accordance with the criteria of the International Diabetes Federation (IDF, 2009). In establishing LADA, we were guided by the recommendations of the Immunology of Diabetes Society (IDS, 2005).
Results
The prevalence of MS in LADA was 55.6% and exceeded that in T1DM (19%), but was lower compared with T2DM (71.4%). In addition to hyperglycemia, abdominal obesity (62.2% of patients), hypertension (77.8%), and dyslipidemia (55.6%) were the most common components of MS in LADA. The highest prevalence of MS was found in patients with LADA 2 phenotype (69.2%), which was close to that in T2DM. At the same time, it was lower (40.9%) in LADA 1, but twice as high as in T1DM. Negative correlations were found between body mass index, waist circumference and antiGAD titers in patients with LADA ($P < 0.05$).
Conclusion
Metabolic syndrome was found in 55.6% of patients with LADA. The prevalence of metabolic syndrome depends on the phenotype of the disease and was highest in LADA 2 (69.2%), which indicates that patients with this phenotype belong to the group of high cardiovascular risk.

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AEP314

Evolution of the parameters of liver function after sleeve gastrectomy

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Introduction
Obesity is an undeniable global health problem that has taken on epidemic proportions in both developed and developing countries. Bariatric surgery offers a promising therapeutic option mostly in the face of frequent failures of dietary management of obesity. Our study aimed to describe the evolution of parameters of liver function after sleeve gastrectomy.
Methods
It was a retrospective study including 40 obese patients who were followed up at the Research Unit on Obesity at the National Institute of Nutrition and Food Technology in Tunis up to 12 months after sleeve gastrectomy. In preoperative, all patients underwent an abdominal ultrasound and a liver bioassessment. The preoperative clinical and biological data and those checked at six and 12 months after surgery were collected from the patients' medical records.
Results
The mean patients' age was 34.65 ± 8.17 years and the sex-ratio was 0.21. The mean body mass index (BMI) was 50.23 ± 8.3 kg/m^2. Fifteen percent of our patients had hepatic cytolysis and 12% had anicteric cholestasis. Fatty liver disease was noted in 62% of patients. After sleeve gastrectomy, blood levels in transaminases decreased significantly ($P < 0.01$). No patients had hepatic cytolysis one year after the intervention. Also, blood levels of gamma-glutamyl transferase decreased significantly ($P < 0.05$). Only one patient retained anicteric cholestasis one year after surgery. Of the 25 patients with hepatic steatosis initially, four had had an abdominal ultrasound control which confirmed the absence of this abnormality. The mean excess weight loss was 40.2 ± 14% [4.1–74.6] at six months and 55.8 ± 20.5% [7.3–90.1] at one year. More than half of our patients lost more than 50% of their excess weight one year after sleeve gastrectomy.

Conclusion
Results of our study testify to the effectiveness of sleeve gastrectomy in improving parameters of liver function. This would be explained not only by the significant weight loss induced by this surgical technique but also by the metabolic changes such as increased levels of incretin thus improving insulin sensibility of patients and their metabolic parameters.

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AEP315

Diabetic peripheral neuropathy: Predictive factors and management

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Introduction
Diabetic peripheral neuropathy is a common degenerative complication of diabetes. The aim of our work is to focus on the prevalence of this complication in relation to the imbalance of diabetes in type 2 diabetics (T2DM).
Materials and methods
This is a retrospective study, including 202 type 2 diabetic patients hospitalized in an Endocrinology-Diabetology department, over a 6-year time period. All patients have benefited for a neurological examination with calculating of the DN4 score, the data were exploited by SPSS-V21.
Results
The mean age of our patients was 57.1 ± 13.1 years, with a sex ratio M/F of 0.25. The prevalence of diabetic neuropathy was 22.27% with an average duration of diabetes of 14.37 ± 8.85 years and an average HbA1c of 10.7 ± 1.6%. The DN4 score is positively correlated with the level of HbA1C (P = 0.04). Other microangiopathies were present in 53.33%, including nephropathy (24.44%) and retinopathy (35.55%). Macrovascular complications were present in 62.22%, including coronaropathy (42.22%), ischemic stroke (20%), peripheral arteriopathy (6.66%). The therapeutic management consisted of an optimal glycemic control, leading to an HbA1c level of 8.2 ± 2.2% on average after 3 months. 4.4% of patients were treated for neuropathic pain with an antidepressant.
Conclusion
The prevalence of diabetic neuropathy is high in T2DM, uncontrolled diabetes is the most common factor which is frequently associated with other degenerative complications. The preventive and curative treatment consists of an optimal glycemic control.

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AEP316

Chronic diabetic kidney disease, senescenceand cardiovascular disease

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Cardiovascular disease (CVD) is more prevalent in patients with chronic kidney disease (CKD) and *Diabetes mellitus (DM)* than in the general population. Microparticles (MPs) released during cell activation and/or apoptosis could be biomarkers of CVD. These MPs, which show vascular damage, are named according to the injured cell, as endothelial (EMPs) or platelet (PMPs).
Aim
Assess the MPs plasma concentration in diabetic patients with or without nephropathy, and evaluate its correlation with the occurrence of CVD.
Patients and methods
A prospective, observational, transversal study in 46 diabetic patients from Infanta Leonor University Hospital. Total MPs, endothelial and platelet, were measured in all cases. The Chi-square test was used to compare qualitative variables, and a linear regression analysis with the MPs as a dependent variable. A $P < 0.05$ was considered significant.
Results
Out of the 46 patients, 27 (58.7%) were men, and 23 (50%) were on hemodialysis (HD). The average age was 64.9 (11.7) years old, patients on HD being older ($P < 0.01$). They also had a higher frequency of atrial fibrillation ($P < 0.035$), retinopathy, neuropathy, heart failure, peripheral artery disease and high blood pressure (HBP) ($P < 0.01$for all), than patients with normal glomerular filtration rate. They showed, as well, a higher number of total MPs ($P < 0.01$) and endothelial MPs ($P < 0.01$), with no difference of PMPs. The linear regression analysis to establish if the difference was a consequence of age or HD, showed that only HD was a determining factor for total MPs, but not for EMPs.
Conclusions
The increase in total MPs and EMPs observed in patients on HD with a higher number of CVD non-thrombogenic episodes in the diabetic population studied, could be related to the lack of MPs difference observed.

	Diabetic patients on HD (n = 23)	Diabetic patients with normal RR (n = 20)	Total DS o%	P
Sex ♂	16(61.5%)	11(55%)	27(58.7%)	ns
Atrial fibrillation	5(21%)	0	5(11.6%)	0.035
Ischemic cardiopathology	5(21.7%)	4(20%)	9(20.9%)	ns
Retinopathy	20(76.9%)	2(10%)	22(51.2)	< 0.01
Neuropathy	17(73.9)	1(5%)	18(41.9)	< 0.01
Heart Failure	12(46.2%)	0	12(27.9)	< 0.01
Cerebral Vascular Stroke	4(17.4%)	0	4(9.3)	ns
Peripheral Artery Disease	11(42.3%)	1(5%)	12(27.9)	< 0.01
HBP	23(100%)	12(60%)	35(81.4)	< 0.01
Dislipemia	23(100%)	15(75%)	31(72.1)	ns
Smokers	4(17.4%)	5(25%)	9(20.9)	ns
Left ventricular hypertrophy	19(82.6%)	0	19(44.2)	< 0.01
Diastolic dysfunction	5(21.7%)	0	8(18.6)	< 0.01
Left ventricular dysfunction	6(26.1%)	3(15%)	9(20.9)	< 0.01
MP in total xµl	33004(7272)	24745(5791)		< 0.01
ME xµl	191.2(218)	62.8(1.9)		< 0.01
MP xµl	701(639)	441(310)		ns

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AEP317

Peculiarities of type 2 diabetes in men with androgenic deficiency

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Relevance
Androgenic deficiency is an important pathogenetic element in the development of metabolic syndrome and cardiovascular diseases in men. It has been proven that in male patients with type 2 diabetes, hypogonadism develops much more often.
Objective
To study the features of the course of type 2 diabetes mellitus (T2DM) in men with androgen deficiency. Research objectives: 1. To estimate the incidence of hypogonadism in men 35–65 years old with type 2 diabetes. 2. To compare the incidence of non-fatal myocardial infarction and history of stroke in the group of patients with T2DM and hypogonadism with the group of patients with T2DM without hypogonadism. 3. To study the spectrum of late complications of T2DM in these groups. 4. Compare the parameters of carbohydrate and lipid metabolism, the degree of insulin resistance in these groups.
Materials and methods of the research
The study included 84 men with type 2 diabetes. To diagnose hypogonadism, the levels of total testosterone (T), sex hormone binding globulin (SHBG), albumin and luteinizing hormone (LH) were measured. Free testosterone (free T) levels were calculated using a calculator from Ghent University Hospital, Belgium. 43 patients underwent a retrospective analysis of case histories (spectrum of late complications, the presence of heart attacks and strokes, laboratory data – total cholesterol (CS), triglycerides (TG), fasting blood plasma glucose, basal insulin level, glycated hemoglobin (HbA1c)). The HOMA-IR index was used to determine the degree of insulin resistance.
Research results
The average age of men was 56.21 ± 6.26 years. The incidence of laboratory-confirmed hypogonadism is 42.9%. An average positive

correlation was found between androgen deficiency and the incidence of non-fatal cardiovascular events ($r = 0.45$ $P < 0.05$). There was no statistically significant relationship between the presence of hypogonadism and the incidence and degree of late complications of T2DM. Patients with low T levels tended to have higher HOMA-IR values compared to patients with normal T levels ($P < 0.05$). At the same time, the indicators of carbohydrate and lipid metabolism did not differ significantly in these groups ($P > 0.05$).
Conclusions
The revealed incidence of hypogonadism in men with T2DM corresponds to the data of international studies. The presence of a significant correlation between low testosterone levels and cardiovascular events in patients with T2DM suggests that hypogonadism can be used as an additional criterion for cardiovascular risk. Testosterone deficiency exacerbates insulin resistance, which can lead to weight gain and impair carbohydrate metabolism.

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AEP318

Influence of depression on glycemic control in patients with typ1 diabetes

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Aim
Depression in diabetic patients is related to low quality of life, inadequate abiding by diabetes diet, physical activity and drug therapy.Aim of the stady is determine the presence of depression and its impact on the level of metabolic control of the disease; impact of structured education on the level of knowledge and HbA1c in patient with diabetes type 1 (T1D)
Methods
The study included 38 patients with T1D, median age of 32.7 years, 27 women and 11 men. For assessment of the level of depression the Zung Self-Rating Depression Scale was used, as well as questionnaire on socio-demographic information. Interactive education program-structured therapy and study program 'Düsseldorf model' of 5 day duration was applied. All patients had HbA1c measured in the beginning of the education and at 3, 6, 9 and 12 month follow-ups.
Results
Based on the Zung Self-Rating Depression Scale 52.6% patients had clinically significant level of depression, 42.1%showed mild symptoms of depression and5,.2% patients showed no symptoms of depression. In the group of depressive diabetics 65% had unsatisfactory level of glycoregulation. After structured education program HbA1c levels decreased by 1.8% after 6 months and 1.2% after 12 months compared to initial levels ($P < 0.005$).
Conclusion
It could be concluded that the presence of depression has a tendency to predict poor metabolic control of diabetes. Structured education program is efficient in improving glycaemic control in patients with type 1 diabetes. It motivates patients in achieving better glycaemia control.

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AEP319

Angiotensin-converting enzyme gene (i/d) polymorphism in association with the diabetic nephropathy

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Polymorphisms in the Angiotensin-converting enzyme (ACE) gene have been associated with development of diabetic nephropathy (DN), a major microvascular complication of the type 2 diabetes mellitus (T2DM). Since the genetic predisposition plays an important role in development of DN in patients with T2DM, genetic testing might largely contribute to better assessment of the risk of DN in such patients. The aim of this study is to investigate the association of the ACE gene I/D polymorphism with DN in T2DM patients. The study is designed as a case-control genetic association study. The samples from 88 patients with T2DM were analyzed, including 57 patients with DN and 31 without DN. The study includes also 26 healthy controls. The demographic, clinical and laboratory data are analyzed in addition to the genetic profiling of the patients for the ACE gene. Genotyping of the ACE gene I/D polymorphism resulted in determination of the patient's genotype: D/D, I/D or I/I. The results revealed a statistically significant association of genotypes D/D and I/D with the occurrence of nephropathy compared to the I/I genotype. In the group of patients with T2DM, the carriers of the D/D or I/D genotypes have 6.46 folds higher odds and 1.7 folds higher relative risk for developing nephropathy than the carriers of I/I genotype. The results confirmed the correlation of the genetic polymorphism and the development of the DN in patients with T2DM indicating its potential predictive use in terms of the clinical follow-up, treatment selection and prognosis of DN.

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AEP320

Bruns–garland syndrome as the first presentation of type 2 diabetes – a report of two cases from Sri Lanka

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Introduction
Diabetes mellitus (DM) is a global health issue. Sri Lanka has the second highest diabetes prevalence at 20–79 years in South-East-Asia (1). Diabetic-radiculoplexus-neuropathy is a rare entity causing significant disability, also known as diabetic amyotrophy and Bruns-Garland syndrome, occurring due to immune mediated microvasculitis (2). Although Diabetic-lumbo-sacral-radiculoplexes-neuropathy (DLRPN) is well described, Diabetic-cervical-radiculoplexus-neuropathy (DCRPN) is rare. We report two cases of DLRPN and DCRPN as the first presentation of DM.
Case-description
Case-1: A previously healthy 49-year-old Sri Lankan hotel chef presented with painful weakness and wasting of left arm for 3 months with weight loss. Left shoulder-girdle muscles were wasted with diminished power and reflexes. He had high Erythrocyte-sedimentation-rate (ESR) at 60 mm/hr, with normal C-Reactive protein (CRP). His cerebrospinal fluid (CSF) showed albumino-cytological-dissociation with high CSF protein at 70 mg/dl and unremarkable high volume cytospin. His magnetic resonance imaging (MRI) of cervico-thoracic spine with brachial plexus was normal. His Fasting blood glucose (FBG) was198 mg/dl, and HbA1C was 9%, confirming newly diagnosed DM. Nerve conduction study (NCS) showed comparative amplitude reduction. Electromyogram revealed positive sharp waves, frequent fibrillations and high amplitude polyphasic motor unit potentials with reduced recruitment in proximal muscles of left upper limb. Case-2: A previously healthy 47-year-old carpenter presented with asymmetrical painful weakness of thighs for 5 months with weight loss and fatigue. Lower limb proximal muscles were asymmetrically wasted with reduced power and knee jerks. He had high ESR of 72 mm/hr with normal CRP and CSF showing albumino-cytological-dissociation with unremarkable high volume cytospin. He was diagnosed with DM on admission, with FBG of 208 mg/dl and HbA1C of 9.4%. MRI and NCS were normal. Electromyogram showed similar changes in both quadratus femoris, more on left side. Both had no trauma history, infection or osmotic symptoms. Screening for an alternative aetiology was unremarkable. Patient1 was diagnosed with DCRPN while patient2 with DLRPN. Both showed significant improvement following optimization of glycemic control, with symptomatic treatment and physiotherapy.
Conclusion
DCRPN and DLRPN were never reported as the first presentation of diabetes in Sri Lanka. DCRPN is rare and can lead to misdiagnosis. This is an eye opener to consider a new diagnosis of diabetes mellitus even in previously healthy patients presenting with radiculo-plexus neuropathies to the Neurology department.
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AEP321

Immune thrombocytopenia presenting with celiac disease and Hashimoto's Thyroiditis in type 2 diabetes patient: A case report

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Introduction
The combination of at least three autoimmune diseases in the same patient is defined as multiple autoimmune syndrome. Recent studies demonstrated a higher prevalence of celiac disease in patients with immune thrombocytopenia when compared to the general population. Here we report the occurrence of celiac disease, Hashimoto's disease and immune thrombocytopenia in type 2 diabetes patient.
Case report
A 64 years old man was referred for a recently diagnosed corticosteroid induced type 2 diabetes mellitus treated by oral anti diabetic drugs (metformin 2000 mg/j + glimepiride 2 mg/j). Past medical history was significant: immune thrombocytopenia diagnosed at the age of 30 years old treated by corticotherapy in 1986, 2017 and 2019, celiac disease diagnosed at the age of 44 years old treated by gluten free diet, benign stenosis of the common bile duct, hypertension controlled by two antihypertensive drugs (bisoprolol 5 mg/j + loop diuretics 40 mg/j) and atrial fibrillation anticoagulated with Vitamin K antagonists. The physical examination was strictly normal. The biochemical report was: Hb1Ac = 10.3%, triglycerides = 2.45 mmol/l, total cholesterol = 4.03 mmol/l, HDL = 1.05 mmol/l, LDL = 1.86 mmol/l, ASAT = 25 UI/l, ALAT = 54 UI/l, eGE = 116.3 ml/min/1.73 m^2, white blood cell count = 8000/mm3, hemoglobi *n* = 14 g/dl and a platelet count = 24 0000/mm^{33}. The corticosteroid tapering protocol has been started. The patient refused insulintherapy. Medical decision was to intensify the treatment: glimepiride 4 mg/j + metformin 2000 mg/j. Four months later, the biochemical report was HbA1c = 6.5%, fasting blood glucose = 8 mmol/l, elevated TSH (38µUI/ml) and decreased FT4 (8.57 pmol/l). Primary hypothyroidism was diagnosed on routine screening. The patient did not report any hypothyroidism symptoms. Since the main etiology is autoimmune, an access protocol was complemented with antibodies, highlighting the elevation of antiperoxidase antibodies (455.9 UI/ml) concluding diagnosis of Hashimoto's Thyroiditis. Interconsultation with the cardiology service was initiated, starting treatment with Levothyroxine 12.5 µg/day. Appropriate adjustment of the Levothyroxine therapy is needed to determine the proper dosage.
Conclusion
Patients with autoimmune history should be screened regularly in order to detect the outbreak of new autoimmune diseases, since they have common mechanisms and a shared genetic background.

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AEP322

A retrospective analysis of clinical manifestations of patients with acute intermittent porphyria: three case reports and literature review

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Background
Acute intermittent porphyria (AIP), a rare autosomal-dominant inherited disorder, caused by pathogenic mutations in the gene encoding porphobilinogen deaminase (PBGD). To explore its clinical characteristics, we investigated three patients with AIP admitted to our hospital.
Methods
In this study, patients successfully diagnosed with AIP and treated at the First Hospital of Shanxi Medical University since January 1, 2016, were enrolled. Information regarding the medical history, symptoms, treatments, prognoses, and gene mutations of these patients was collected and analysed.
Results
Three patients, all young women, were included in the study. Their main symptoms were abdominal pain, accompanied by abdominal distension, nausea, vomiting, hypertension, tachycardia, etc. Laboratory results from all three subjects showed severe hyponatremia and hyperuricemia. At the same time, patients A and B suffered from epileptic seizures when their serum sodium levels sharply decreased. After carbohydrate loading therapy, the symptoms of all three patients were alleviated. And the earlier carbohydrate loading was administered, the faster the symptoms were relieved and the better the prognosis would be. However, high-doses of glucose intravenously administered may exacerbate hyponatremia. During the treatment, their uric acid levels firstly dropped and then rose again as their conditions improved. There were different mutations in the PBGD gene that had been detected in the three patients: Patient A with the heterozygous deletion frameshift mutation (c.730_731del), Patient B with c.1078_1132del, Patient C with the intronic mutation c.160 + 5G > C.
Conclusion
The clinical manifestations of AIP are complex and variable. In patients with unexplained abdominal pain, hyponatraemia, and neuropsychiatric symptoms, acute episodes of AIP should be considered. Our study indicated that seizures in patients with AIP might be associated with hyponatremia. Gene sequencing can identify possible pathogenic mutations and improve the accuracy of diagnosis. Carbohydrate loading is the main treatment to alleviate the symptoms of AIP. Meanwhile, patients' serum sodium levels should be monitored and corrected in time during glucose therapy.

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AEP323

Identification of a novel mutation of the abcc8 gene in a greek subject with mody12

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Introduction
'Maturity-onset diabetes of the young' (MODY) constitutes a group of clinically and genetically heterogeneous monogenic forms of diabetes, characterized by beta-cell dysfunction. It describes an autosomal dominantly inherited disorder, caused by mutations in different genes, characterized by noninsulin-dependent diabetes commonly diagnosed at a young age. Fourteen MODY subtypes have been reported, often misdiagnosed as type 1 or 2 diabetes.
Aim
To present a male suspected for MODY, who was tested molecularly using the Next Generation Sequencing (NGS) for 7 MODY genes (GCK, HNF1A, HNF4A, HNF1B, INS, ABCC8 and KCNJ11).
Case description
A 17-year-old male presented after laboratory investigation indicating hyperglycemia (glucose: 281 mg/dl). He complained for polyuria, polydipsia and weight loss (~ 4 kg) in the last month. On admission, he had glucose: 391 mg/dl without acidosis, HbA1c: 10.4%, normal BMI (18.7 kg/m^2) and negative pancreatic auto-antibodies. Urinary protein excretion was elevated (205 mg/day). There was no family history of diabetes. He was initially treated with insulin, which was gradually decreased and finally discontinued within a month. Three months later his HbA1c was 7.2% and insulin treatment was implemented again due to poor glycemic control. Genetic analysis revealed that he was heterozygous for a novel p.V21F variant of the ABCC8 gene (exon 1, c.61G > T, of paternal origin) and for the p.A98V variant of the HNF1A gene (exon 1, c.293C > T, of maternal origin). p.V21F variant is reported for the first time and is classified as likely pathogenic, while p.A98V is classified as likely benign. Once the mutation was identified, the patient switched to gliclazide, which was eventually replaced by insulin as hyperglycemia was not successfully controlled with sulfonylurea alone (HbA1c after 3 months of treatment increased to 7.6%). Genetic investigation in both parents revealed that the father was heterozygous for the same ABCC8 p.V21F likely pathogenic variant, but asymptomatic. The HNF1A variant was inherited from the mother.
Conclusions
Given the different therapeutic approach and the complications risk depending on the diabetes form, a correct diagnosis and optimal treatment is essential for a good prognosis and appropriate genetic counseling. This case emphasizes the need of considering molecular analysis, even in the absence of a family history of diabetes if clinical suspicion for MODY is high. A novel likely pathogenic variant of the ABCC8 gene is described, which refers to subtype MODY 12 and cannot be successfully treated with sulfonylurea monotherapy, as generally suggested (1).
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AEP324

Diabetes, a harbinger of pancreatic tumor

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Introduction
Pancreatic cancer is one of the cancers of the digestive tract for which the prognosis has not been improved in terms of early diagnosis. Recent diabetes can be indicative of this pathology.
Observation
A 56-year-old man with no notable pathological history who has presented for 04 months a deterioration in general condition with weight loss. On clinical examination: BMI: 17 kg/m^2. In biology: Venous glycemia: 32 mmol/l/l, HbA1c: 8.9%. Transaminases: normal, total bilirubin: 317 mmol/l (60N). GGT: 92 IU/l (5N), PAL: 537 IU/l, albuminemia normal, serum calcium. No degenerative complications of diabetes have been noted. An abdominal ultrasound revealed dilation of the intra and extra hepatic bile ducts without any detectable obstacle. Bili-MRI showed a poorly limited 17 × 18 mm pancreatic head mass responsible for dilation of the Wirsung's duct with upstream parenchyma. The patient was put on insulin therapy and underwent a corporeal-caudal pancretectomy surgery followed by hormone therapy. The evolution was marked by glycemic instability with severe hypoglycaemia despite a drop in insulin-like doses of 0.1 u/kg. Is this an improvement in his diabetic pathology?
Conclusion
Diabetes can be concomitant with the diagnosis of pancreatic cancer in 40% or during the two years preceding the diagnosis of this neoplasia in 16% of cases. Diabetes can get better 57–89% of the time. Experimental studies have well established the diabetogenic effect of pancreatic neoplastic cells which are metabolically active. They alter carbohydrate metabolism, lowering the release of insulin.

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AEP325

Association of glucocorticoid receptor gene polymorphism A3669G (9β) with lower glucose concentration 2 hours after OGTT in patients during chronic glucocorticoid treatment

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Background
2–3% of the general population is chronically treated with glucocorticoids (GCs). Modification of the structure and/or function of the glucocorticoid receptor (GR) due to its polymorphisms may result in increased (GC – S – bclI, N363S) or decreased (GC – I – A3669G, ER22/23EK) sensitivity to GCs. To date, whether such modulation of cell's response to GCs can be associated with presence or absence of the side effects of GCs treatment has not been studied.
Objective
The aim of the study was to investigate the association between GR polymorphisms (bclI, N363S, A3669G and ER22/23EK) and adverse events of GC treatment in patients diagnosed with rheumatic disease during chronic glucocorticoid treatment.
Material and methods
150 patients were enrolled into the study. Based on five-point (0'–120') oral glucose tolerance test (OGTT) glucose and insulin areas under the curve (AUC) as well as indicators of insulin resistance were calculated. Data regarding BMI and waist circumference were gathered and body composition was measured using dual energy X-ray absorptiometry. High Resolution Melting method was used for genotyping.
Results
OGTT was performed in 125 females and 25 males of mean age of 56.8 years. Mean current dose of GCs was 7 mg. 21 carriers of GC – I variants (excluding GC – S carriers) had lower glucose concentrations 2 h after OGTT compared to 55 carriers of the 'wild type' of all four polymorphisms (98.9 mg/dl vs 128.4 mg/dl, $P = 0.01$). There was also a trend towards higher cumulative dose of GCs (31.9 g vs 12.55 g, $P = 0.06$) and longer treatment duration in GC – I carriers (139.1 months vs 80 months, $P = 0.09$). There was no difference between groups in age, current dose of GCs, cholesterol concentrations, BMI, waist circumference, body or trunk fat percentage, HOMA-IR, HbA1c, Matsuda Index, AUCs, glucose or insulin concentrations in other time points of OGTT. 53 carriers of N363S and/or heterozygous bclI variants (excluding GC – I carriers) were compared to 50 'wild type' carriers. There was no difference between groups in age, current, cumulative dose of GCs, treatment duration, cholesterol concentrations, BMI, waist circumference, body or trunk fat percentage, HOMA-IR, HbA1c, Matsuda Index, AUCs, glucose or insulin concentrations in OGTT.
Conclusion
Polymorphisms of GR that decrease sensitivity to GCs (A3669G and ER22/23EK) are associated with lower glucose concentrations after 2 h of OGTT. Whether this could lead to decrease risk of diabetes in carriers is open for future studies.

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AEP326

A case of hypertriglyceridemia after the use of tamoxifen

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Introduction
Tamoxifen is a selective estrogen receptor modulator used in the treatment of estrogen/progesterone receptor-positive breast cancer. Due to the increased frequency of breast cancer in the premenopausal period, the use of tamoxifen is quite common in patients with hormone receptor positivity. Although it is a commonly-used drug, the number of cases with elevated triglyceride levels is very few. Here, we present a case with severe hypertriglyceridemia due to the use of tamoxifen admitting with the acute pancreatitis-like clinic.
The Case
A 44-year-old female patient diagnosed with breast cancer two years ago had undergone neoadjuvant chemotherapy. Tamoxifen treatment was started 1.5 years ago when a positive estrogen receptor has detected a result of pathology. The patient, who presented with complaints of abdominal pain and nausea, was hospitalized with the diagnosis of severe hypertriglyceridemia when the triglyceride level measured was 1560 mg/dl (N 50–150). There was no other disease in the patient's history that could be the cause of secondary hypertriglyceridemia (diabetes, family history, alcohol use…). Body Mass Index was 26 kg/m^2. She did not have sensitivity, defense, and rebound in the abdomen in physical examination. Amylase, lipase values, and thyroid function tests were normal in the biochemical examinations of the patient. Since the amylase-lipase values may be normal in pancreatitis with hypertriglyceridemia, abdominal tomography was performed to rule-out possible diagnosis of pancreatitis in the etiology of abdominal pain. In the tomography, the gall bladder, biliary tracts, and pancreas were reported to be normal. Gemfibrozil 1200 mg/day and Omega-3 capsule 3000 mg/day treatment was initiated for the patient. The intravenous fluid replacement was also performed. It was considered that the elevated triglyceride levels of the patient might be due to the use of tamoxifen. After consultation with medical oncology, the patient's tamoxifen treatment was changed to anastrozole. In the follow-up of the patient, here complaints regressed. The patient, who had triglyceride levels of 480 mg/dl, was discharged.
Conclusion
Clinicians must be careful in terms of hypertriglyceridemia that may be associated with tamoxifen and pancreatitis that may develop in this respect. Screening for dyslipidemia before starting tamoxifen is recommended, especially in people with a family history. Patients' lipid levels should be followed. In the presence of symptoms, the drug should be discontinued and not retried because of the risk of inducing acute pancreatitis. Even if the amylase and lipase values are normal, caution should be exercised in patients with high triglyceride levels.

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AEP327

The impact of violated production of vascular endothelial growth factor expression on thyroid hormones metabolism in obese patients

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Introduction
Obesity is an important medical and social problem of our time, because its prevalence is growing rapidly and affects about 30% of the adult population of the planet. Obesity is characterized by an increase in the expression of cytokines that cause endothelial damage. It is known that prohormone thyroxine (T_4) is converted into 5 times more active triiodothyronine (T_3) in peripheral organs (such as liver kidneys) and tissues with the help of deiodinases. Hyperproduction of cytokines by adipose tissue impairs this conversion of thyroid hormones with the development of 'low T_3' syndrome. Besides adequate blood supply is important in the process of deiodination of T_4. Therefore, it is important to study the relationship between endothelial function and thyroid hormones metabolism.
The aim of the study
To study the dependence of thyroid hormones metabolism on the level of vascular endothelial growth factor in the serum of venous blood in obese patients.
Materials and methods
52 obese patients and 20 practically healthy persons were enrolled into the study. Obesity was established in the case of an increase in body mass index above 30 kg/m^2. Free triiodothyronine (fT_3) and free thyroxine (fT_4) levels were determined. To assess the violation of peripheral conversion of thyroid hormones, the ratio of fT_3/fT_4 was calculated. The level of vascular endothelial growth factor (VEGF) was determined.
Results
In obese persons, a decrease in fT_3 by 31.4%, an increase in fT_4 by 22.6% and decrease in fT_3/fT_4 ratio by 39.1% ($P < 0.05$) were found. An increase in VEGF expression by 37.3% on the background of obesity compared with control ($P < 0.05$) were revealed. Negative correlations between VEGF expression and fT_3 ($r = –0.438$, $P < 0.05$), fT_3/fT_4 ($r = –0.522$, $P < 0.05$) were obtained.
Conclusions
1. Metabolism of thyroid hormones is decreased with the development of the syndrome of 'low triiodothyronine syndrome' in obese patients. 2. Endothelial function is impaired with increasing expression of vascular endothelial growth factor against the background of obesity, 3. Indicators of thyroid hormone metabolism depend on the level of vascular endothelial growth factor.

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AEP328

Non alcoholic steatohepatitis related cirrhosis and hepatocellulair carcinoma: A ten years rerospective study

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Introduction
Currently, the incidence of metabolic steatopathies is clearly increasing. Unlike simple fatty liver disease, non-alcoholic steatohepatitis (NASH) can progress to cirrhosis and hepatocellular carcinoma (HCC). The aim of our study was to determine the factors associated with these complications in patients with NASH.
Methods
This is a retrospective study including all cirrhotic patients followed between January 2011 and December 2020. The severity of the cirrhosis was assessed by the CHILD-Pugh score. Six-monthly abdominal ultrasound monitoring was performed in all patients for the detection of HCC.
Results
One hundred and sixty six patients; 92 women (55.4%) and 74 men (44.6%) were included. The average age was 57.2 years (between 17 and 88 years). NASH was retained in 27 patients (16.3%) as the etiology of the cirrhosis. Cirrhosis was classified as CHILD A in 8 cases (29.6%), CHILD B in 13 cases (48.2%) and CHILD C in 6 cases (22.2%). Twenty two patients presented with edemato-ascitic decompensation (81.5%). Four patients (14.8%) developed hepatic encephalopathy. Esophageal varices were present on upper gastrointestinal fibroscopy in 26 patients (96.2%): grade 1 (11 cases), grade 2 (12 cases) and grade 3 (3 cases). Two patients (7.4%) developed hepatocellular carcinoma after 5 years and 6 years of progression respectively. Death occurred in 4 patients (14.8%) with a mean delay of 37 months.
Conclusion
In our study, non-alcoholic steatohepatitis related cirrhosis was found in 16.3% of all cirrhotic patients, of which 7.4% developed HCC.

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AEP329

The role of obesity management in the reversal of type 2 diabetes mellitus

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The prevalence of Type 2 Diabetes Mellitus (T2DM) is drastically rising globally. It is projected to rise to close to 600 million in 2 decades. This rise parallels the increased prevalence of obesity which is estimated to rise to over 1 billion obese individuals by the year 2025. The association between the Body Mass Index (BMI) and type 2 Diabetes is well recognised. Raised BMI is a major predictor of the risk of T2DM. T2DM is associated with multiple complications and it wields huge negative impact on the economy due to its financial burden. Preventing Type 2 Diabetes, therefore, has become a public health priority. Many published randomized controlled trials (RCTs) have demonstrated that implementing lifestyle measures in terms of dietary modifications and/or increasing the level of physical activity can successfully prevent or delay the onset of T2DM. This integrative review utilises evidence from different randomised trials obtained through a literature search on the database of PubMed and Google Scholar to examine the evidence behind the idea that T2DM is preventable by lifestyle modification. 12 RCTs carried out on individuals with impaired glucose tolerance and reviewed the effect of lifestyle interventions on the onset of type 2 Diabetes were identified and analysed. Most of the studies yielded consistent results in keeping with those of other diabetes prevention trials. There is clear evidence in literature that T2DM can be prevented or its onset delayed by intensive lifestyle changes including dietary measures and increased level of physical activity. There is, however, limited evidence that implementing lifestyle changes might alter the overall macro or microvascular outcome. There is wide variability in the applied lifestyle changes in these trials. Future research should focus on establishing standardised dietary and physical activity recommendations that are tailored to the needs of different ages and ethnic subgroups in the community as per NICE guidance.

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AEP330

Study on oxidative stress parameters in obesity associated insulin resistance and diabetes mellitus

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Obesity of varying severities can be seen in the vast majority of patients with type 2 diabetes mellitus (DM2). Oxidative stress is considered as a key pathogenetic link in the formation of metabolic disorders in obesity. The work was initiated to assess intensity of oxidative stress in obese patients with DM2.
Materials and methods
The patients were divided into 3 groups. Patients with DM2 and BMI > 30 kg/m^2 were included into the 1st group. The 2nd group consisted of obese non-diabetic persons with BMI > 30 kg/m^2. Apparently healthy persons with BMI < 30 kg/m^2 were included into the 3rd group. Concentrations of malondialdehyde (MDA), a lipid peroxidation (LPO) end product, were

used to assess LPO in blood of patients with diabetes mellitus. Activity of catalase, an antioxidant system (AOS) enzyme, was used to assess AOS. Serum concentrations of TNF-α, a proinflammatory cytokine, were measured by EIA with the test systems (Vector-Best, Russian Federation).
Results
As compared to apparently healthy persons, HOMA-IR index was found higher in obese non-diabetics by 1.8 times ($P < 0.05$) and in obese patients with DM2 by 2.6 times ($P < 0.01$). Lipid profile parameters typical of atherogenic disorders, to name elevated triglycerides, as well as LDL, VLDL and cholesterol, were found in obese patients in these two groups. Our study on blood LPO and AOS demonstrated significant impairments in peroxidation and weakening of antioxidant mechanisms both in obese diabetics and non-diabetics. As compared to apparently healthy persons, serum concentrations of MDA, a toxic product of lipid peroxidation, were observed higher in obese diabetics (by 40.3%, $P < 0.01$) and obese non-diabetics (by 14.3%, $P < 0.05$). In these patients, blood catalase activity was found declined to be the evidence for reduction of AOS activity. Of interest, as compared to apparently healthy persons, serum TNF-α levels were found significantly higher by 5 times ($P < 0.01$) in obese diabetics and by 4.5 times ($P < 0.05$) in obese non-diabetics, demonstrating direct correlation to HOMA-IR index.
Conclusion
Associated with obesity, insulin resistance and diabetes mellitus facilitate intensification of oxidative stress in the organism. Significant elevations in serum TNF-α concentrations is the risk factor for insulin resistance and DM2.

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AEP331

Do metabolic syndrome and diabetes affect skin autofluorescence in patients with morbid obesity?

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Purpose
Obesity, diabetes mellitus, and metabolic syndrome (MetS) have been known to be associated with increased skin autofluorescence (SAF). In patients with MetS, higher SAF measurements were found to be associated with an increased number of the components of MetS. In this cross-sectional study, we aimed to evaluate the association of MetS and its' components with skin autofluorescence in severely obese patients and to examine whether diabetes or metabolic syndrome contributed to the increase in skin AGE in obese patients.
Methods
We included 801 patients with morbid obesity who were followed up at Marmara University Medical School Endocrinology and Metabolism Department outpatient clinic between 2017 and 2020. Cross-sectionally, advanced glycation end products (AGEs) were measured using SAF in the forearm approximately 10 cm below the elbow fold, with an AGE Reader (DiagnOptics Technologies, Groningen, The Netherlands). Laboratory data [fasting plasma glucose, HbA1c, LDL-c, HDL-c, triglyceride, total cholesterol] were obtained retrospectively from the medical records.
Results
In this cross-sectional study, the prevalence of MetS in morbidly obese patients was 65.5% (n = 525). Diabetes mellitus and hypertension were present in 40.9% (n = 328) and 43.7% (n = 357) of the patients. Morbid obese patients and patients with MetS had higher SAF measurements compared to the control group, 1.85 ± 0.44 AU and 1.86 ± 0.43 AU versus 1.72 ± 0.30 AU, respectively ($P = 0.016$). SAF measurements of MetS negative patients were not statistically different from the control group ($P = 0.076$). Patients with five MetS criteria had higher SAF measurements compared to patients with less number of the MetS components ($P = 0.019$). There was no difference between SAF levels between diabetic patients, patients with impaired glucose metabolism and patients with normal glucose metabolism ($P = 0.513$). In multiple regression analysis, HDL level was found to be an independently associated parameter with SAF (R2 = 6.06%, $P = 0.033$).
Conclusion
We found that obesity itself rather than concurrent diabetes and metabolic syndrome contribute to an increase in SAF. Although MetS, diabetes mellitus are known as factors related to increased SAF, obesity can cause elevated SAF measurements in different ways independently of concomitant comorbid diseases, larger studies with longer follow-up are needed to enlighten the underlying mechanism.

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AEP332

Prevalence of obesity and its association with metabolic diseases in women from low-and-middle income countries (LMICs): A systematic review and meta-analysis

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Introduction
Obesity is a global health challenge, with more than 50% of the world´s obese population residing in LMICs. Although adiposity is a well-known major risk factor for noncommunicable diseases (NCDs) such as hypertension, and diabetes mellitus, the delivery of effective NCDs interventions is still a challenge to health systems. About 85% of the NCDs premature deaths occur in LMICs. Obesity is more prevalent in women than men, however the burden of obesity and its association with NCDs in women from LMICs is unknown. We performed a systematic review and meta-analysis to assess the prevalence of obesity and metabolic complications in adult women from LMICs.
Methods
MEDLINE, EMBASE and Cochrane were searched from inception to February 2020. Cross-sectional and cohort studies that reported prevalence of obesity from LMICs were included. Prevalence (95%CI) of obesity and metabolic outcomes were assessed and stratified according to World Bank Region, country´s income status, setting, and year of the study. Meta-regression was performed for the association between the risk of obesity, hypertension, and T2 diabetes and age.
Results
From the 11.189 citations identified, 218 studies were eligible for analysis (376.405 women in 63 countries). Overall prevalence of obesity, hypertension, and type 2 diabetes in women were 22% (95% CI 20–24%), 26% (95% CI 23–30%), and 7% (95% CI 6–9%), respectively. Prevalence varied according to World Bank Region ($P < 0.001$), country´s income status ($P < 0.001$) and setting ($P < 0.001$). Higher rates of obesity, hypertension, and type 2 diabetes were found in upper-middle countries and urban setting. Obesity increased the risk of hypertension [OR: 2.43 (95% CI 2.19–2.80)] and type 2 diabetes [OR: 2.84 (95% CI 2.16–3.74)] in women. Overall, women presented almost a 3-fold increase of the risk of obesity [OR: 2.75 (95% CI 2.50–3.02)] as compared to men. Meta-regression suggests a positive association between women´s age and the prevalence of obesity [1.045 (95% CI:1.03–1.06, $P < 0.001$)], hypertension [1.085 (95% CI:1.07–1.10, $P < 0.001$)] and T2 diabetes [1.076 (95% CI:1.03–1.12, $P < 0.001$)]. Same association was found for the risk of obesity in women, irrespective of age difference between women and men [1.019 (95% CI:0.99–1.05, $P < 0.232$)].
Conclusion
Women are disproportionately affected with obesity compared to men in LMICs. It is therefore essential for decision-makers to develop appropriate strategies to tackle obesity and its complications in the female population in LMICs.

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AEP333

Adherence to the mediterranean diet and metabolic syndrome: Potential relationship in patients candidates for bariatric surgery

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Objective
To study the possible relationship between adherence to the Mediterranean diet and the metabolic syndrome.
Material and methods:
Retrospective observational study of patients evaluated in a prebariatric surgery consultation between November 2017 and November 2019,

who were given a questionnaire of adherence to a Mediterranean diet. Anthropometric and analytical parameters related to the metabolic syndrome are evaluated. The statistical study was carried out with the SPSS15 program
Results
Total of 135 patients (60% women) with a mean age of 44.53 ± 13.03 years. Average weight of 124.00 ± 25.84 kg and BMI of 43.68 ± 7.28 kg/m^2. When carrying out the adherence questionnaire to the Mediterranean diet, 61% obtained a score of less than 7 points (low adherence). Analytically, mean basal glycemia of 100.98 ± 25.59 mg/dl, HbA1c of 5.99 ± 0.99%, HOMA index of 5.99 ± 4.63, insulinemia of 25.97 ± 15.85 mg/dl. dl, total cholesterol 187.84 ± 36.58 mg/dl, HDL 47.78 ± 9.79 mg/dl, LDL 114.6 ± 30.15 mg/dl and triglycerides 164.88 ± 128.09 mg/dl. They had 25-hydroxyvitamin D levels of 18.4 ± 7.15 and C-reactive protein of 12.56 ± 23.05. When performing the Student's T test for independent samples, we found that the group with low adherence presented statistically significant differences (–10.16 ± 4.42 mg/dl, P = 0.02) in the levels of insulinemia; without differences in the rest of the variables analyzed.
Conclusion
Good adherence to the Mediterranean diet can contribute to a lower situation of hyperinsulinism, which in turn would lead to a lower risk of developing type 2 diabetes mellitus, which as we know is a fundamental element of the metabolic syndrome.

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AEP334

Antipsychotic induced obesity in schizophrenia and GLP-1 analog treatment? – A case-report

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Introduction
Schizophrenia is one of the seven most disabling diseases according to World Health Organization. The most potent antipsychotic drugs clozapine and olanzapine are associated with excessive weight gain. Premature deaths in schizophrenia and shorter life expectancy are mainly caused by obesity-related cardiovascular diseases. Obesity itself is associated with brain deterioration, cognitive decline and overall worse quality of life. GLP-1 receptor analogs may be a potent drugs in schizophrenia addressing metabolic disturbances with potential central effects through GLP-1 receptors leading to neuroprotection, plasticity and learning. Studies in this specific field are scarce, so I present here a case-report.
Case-report
A 49 years-old male was referred to our obesity clinic. He has suffered from schizophrenia since the age of 24, type 2 diabetes since the age 34. The weight gain caused by psychiatric disease was poteantiated by psychiatric medication, currently a long term treatment by risperidone 4 mg daily and olanzapine 5 mg daily. At the initial visit, the patient was very passive in communication, but he filled all questionnaires including 10 days dietary monitoring, where the food was stated precisely with timing, location and in grams. After nutritionist consultation (diet 150 g saccharides, 50 g lipids, 80 g protein, 6000kJ) and physicians´ recommendations done emphasizing the need for physical activity -walking instructions, buying watch for daily step monitoring etc the patient lost 9 kilos in 3 months. He felt generally better, was surprisingly quite talkative, reached every day walk of about 8000 steps. The diabetes control improved from 70 mmol/mol to 57 mmol/l also due to newly prescribed weight-lowering GLP-1 analog semaglutide after 2 months of usage currently on dose 0.5 mg weekly, plus from previous metformin 2 g/day. After 3 months the BMI decreased from 37.6 kg/m^2 to 34.8 kg/m^2 and waist circumference from 125 cm to 120 cm, respectively.
Conclusion
From my clinical point of view I was a bit sceptic to the adherence of this schizophrenic patient to the weight-reducing programme. On the other hand the primary and secondary obesity prevention in psychiatric patients must be addressed. These patients need deeper clinical focus from all specialists and obesity centers shall meet the needs. Many schizophrenic patients are underestimated in obesity interventions and most of them never get a chance. GLP-1 analogs build new effective perspectives in the treatment of obese schizophrenic patients including potential neuroprotective effects.

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AEP335

Trends in dietary food groups and DASH score among adults: A longitudinal study from tehran lipid and glucose study, 2006–2017

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Background
To examine the secular trends of dietary food groups and diet quality among adults, overall and by sex, education, and occupation status.
Methods
This study was conducted within the framework of the Tehran Lipid and Glucose Study (TLGS). Demographic and anthropometric measurements were gathered using standard questionnaires. In terms of socioeconomic information, participants were divided into two groups according to their education and occupation levels. Regular dietary intakes of participants were gathered by a validated and reliable food frequency questionnaire over the previous year and the DASH scores were computed to evaluate the diet quality. Generalized Estimating Equations were used to assess secular trends in food groups within the four phases.
Results
From 2006 to 2017, the intakes of whole grains, legumes, and nuts and seeds increased, and the intakes of refined grains, dairy products, and solid fats decreased significantly (P for trend < 0.001). Dietary fruits, vegetables, meats, and soft drinks intakes did not change significantly. According to socioeconomic groups, meats intake decreased significantly among men, non-educated, and non-occupied participants, and fruits intake increased in both women and educated participants. Based on a 40-point scale, the DASH score increased from 18.1 ± 0.0 in phase1 to 22.7 ± 0.1 in phase 4 of the TLGS (P for trend < 0.001).
Conclusions
Over a decade, in addition to improvements in intakes of a number of dietary food groups, the estimated overall diet quality of the study population showed a modest improvement. These findings may determine areas for more attention to improve the overall dietary intake of the population.
Keywords: Food groups; DASH score; Trend; socioeconomic status; Adults; TLGS

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AEP336

A case of post-partum diabetic ketoacidosis in a patient with gestational diabetes mellitus

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Background
There is ample data linking GDM to risk of type 2 diabetes mellitus postpartum, however, development of type 1 diabetes mellitus and presentation with DKA is rare especially few weeks postpartum.
Case
A 28 year old female 4 month postpartum was admitted to hospital with rapid weight loss and osmotic symptoms. She did not have any past medical history of note, with history of T2DM in both mother and father. She had gestational diabetes during her pregnancy which required insulin to control. Her weight dropped from 72 kg post-natally to 55 kg on presentation with significant weight loss in the 2 weeks prior to admission. Her HbA1c in her third trimester was 42 which jumped to 98 mmol/mol. She was admitted with a glucose 20.5 mmol/l, H + 63 nmol/l, HCO3 10 mmol/l and was started on treatment for DKA at that point. Because of the history of Hb D Punjabi trait, fructosamine was checked which was also elevated at 600 umol/l. Her c-peptide was 0.11 nmol/l and GAD antibodies were negative. The patient was discharged 2 days later on Levemir and novorapid and followed up by the diabetes team.
Discussion
Previous case reports have shown that T1DM either presents early on in the first few days after delivery or few months afterwards, while our patient presented with DKA 4 months postpartum with DKA. The case presented here highlights that patients treated for GDM can present with T1DM postpartum and this should be considered.

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AEP337

A challenging presentation of Catamenial DKA

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A 34-year-old T1DM nurse was admitted with a history of recurrent episodes of DKA. In the current admission at our hospital, on detailed history she reported of getting DKA almost every month when her menses would start. She would be following the sick day rules of DKA but it wouldn't help prevent her going into DKA. No other precipitating factors were found. She was diagnosed as a case of Catamenial DKA and was started on OCP's to see how what effect it would have on her DKA the next month. She unfortunately was re admitted with DKA warranting ITU admission around the time of withdrawal bleeding of OCP's. A joint Endocrine- Gynaecology MDT was dine and she evaluated by Gynaecology team to rule out endometriosis with USS Pelvis and CT-TAP. She was then started on GnRH analogue to cease her menses and started on HRT with all the risks and benefits explained of the same. She has been regularly followed up at Diabetic and Gynaecology clinics and hasn't had an episode of DKA in the past 6 months now with excellent BM control. Points for discussion with the audience: 1. Catamenial DKA and its management. Your experience? 2. Guidelines for managing this rare type of DKA? 3. OCP vs GnRH + HRT ; your experience and alternatives?

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AEP338

Management of cervicofacial odontogenic cellulitis in diabetics

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Objective
To summarize the characteristics and treatment experience of cervicofacial odontogenic cellulitis in diabetic patients and to provide clinical basis for the diagnosis and treatment.
Material and method
Retrospectively analysed 50 cases of cervicofacial cellulitis in diabetics in the ENT department of Taher Sfar Mahdia, Tunisia from from january 2015 to december 2018.
Results
A total of 50 diabetic patients were included in this study. The average age was 40 years (Range: 7 and 71 years). In terms of their sex distribution, we found a male dominance. The level of hygiene of the patients was poor: 80% did not brush their teeth. 15 patients were cigarette smokers and 3 were alcohol consumers. The waiting period before consultation varied between 1 and 30 days. 30% of patients said they had taken a no steroidal anti-inflammatory drug. 50% of patients were under antibiotic treatment the time of the consultation. The clinical sign was mainly an exo-buccal tumefaction in 40 patients. The results showed that 35 of cases were located under the chin. As for the clinical form, 60% of the patients presented a serous acute cellulitis, 30% a suppurative acute cellulitis and 10% a chronic cellulitis. The main etiology was in 90% dental pulp necrosis. The treatment consisted in prescription of antibiotic and intensified insulin therapy in all of cases, a surgical drainage in 30% of cases and an extraction of the affected tooth in 70% of the cases. The treatment allowed to achieve a favorable evolution in 98% of the cases. One patient died due to mediastinitis.
Conclusion
the inadequate treatment or chronic dental infection, associated with immunodepression and some cofactors (tobacco, alcohol.) can lead to severe case of cellulitis. Medical and surgical management should be carried out as soon as possible to prevent serious complications.

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AEP339

Predictors of masked hypertension in type 2 diabetics

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Introduction
Masked arterial hypertension (HTAM) is a relatively recently described entity which gives patients with it the same cardiovascular risk as permanent hypertension. In this context, we report a prospective study including 53 patients in order to determine the prevalence and predictive factors of HTAM in diabetics.
Methods
Descriptive prospective study of 53 patients treated in the endocrinology Diabetology departement of hedi ckeker university hospital sfax, Tunisia. These patients had no history of hypertension and did not take any treatment for high blood pressure. Medical follow up showed normal blood pressure (lower than 140/90) for the last 2 years.
Results
The average age of our patients was 55.3 years (range 35–75 years) with a sex ratio (M/F) equal to 0.89. The duration of diabetes was on average 8.7 years (range 2–17 years). The prevalence of HTAM was 64%, occurring in predominantly non-dipper subjects (58.5%) Regarding the predective factors of HTAM, we were able to collect in univariate analysis the following factors: duration of diabetes, fasting blood sugar, weight and microalbuminuria. In multivariate analysis, the predictive factors that emerged in our study are poor glycemic control (HbA1c > 7%), high body mass index (BMI) and duration of diabetes with an OR of (15.8; $P = 0.04$) (1.2; $P = 0.02$) and (1.3; $P = 0.009$). Our results are consistent with those of the literature which shows that diabetes imbalance, BMI and duration of diabetes are predictive factors of AMTH. Other risk situations for HTAM, not isolated in our work, have been found and mentioned by some authors: advanced age, male sex, metabolic syndrome as well as normal high blood pressure in the office.
Conclusion
It seems essential to carry out ambulatory screening for HTAM in diabetic patients. The induced morbidity and mortality and the cardiovascular risk would be significant and fully justify it.

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AEP340

Management of carpal tunnel syndrome in diabetic patients

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Introduction
Carpal tunnel syndrome (CTS) is the most common compressive neuropathy in upper limb. Although most causes are idiopathic, CTS may be associated with some systemic conditions such as diabetes mellitus (DM). The aim of this study was to describe conservative procedures used in physical medicine and rehabilitation in the management of CTS.
Patients and methods
We carried out a descriptive retrospective study of cases of diabetic carpal tunnel syndrome treated in PMR department over a period of 1 year.
Results
Thirty-five cases of CTS were included in the study, 27 women and 8 men. The mean age was 46.68 ± 10.69 years. CTS was bilateral in 88% of cases. Acroparesthesias was the major symptom described in 56% of cases. An electro neuromyography (ENMG) was performed in 80% of patients revealing moderate impairment in 52% of cases. Rehabilitation techniques included transcutaneous electrical nerve stimulation (TENS) and therapeutic ultrasound (US) as well as manual therapy for the median nerve and its surrounding structures were prescribed to 62% of the patients. Half of the patients received vitamin therapy and 35.5% pregabalin. Theses therapeutic measures were efficient in 67.5% of the cases and local corticosteroid infiltration was required in 42.5% of the cases. Surgery was required in 12% of cases for whom conservative treatment wasn't efficient.
Conclusion
Conservative treatment including physiotherapy modalities and manual therapy occupies an important place in the management of CTS in PMR.

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AEP341

Prevention of cardiovascular risk in the elderly with diabetes

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Introduction
Cardiovascular disease is the leading cause of death ahead of infectious diseases and cancers. The frequency of morbidity and mortality associated with cardiovascular diseases increases in the elderly and their management becomes more difficult. Hence an early and adequate management of cardiovascular risk factors is needed. The objective of this work was to determine the cardiovascular risk factors in elderly diabetics and to assess the quality of cardiovascular risk management in these patients.
Patients and methods
Retrospective study of 94 diabetic patients aged over 65 years who were hospitalized in the endocrinology department of Mahdia or followed up at the outpatient clinic between November and December 2020.
Results
The mean age was 71 ± 5 years with extremes of 65 and 90. The female predominance was remarkable. Almost all of our patients had type 2 diabetes. The mean duration of diabetes was 12 ± 8 years. Cardiovascular disease was present in 26.6% of patients. The level of cardiovascular risk was high in 39.4% of patients and very high in 41.5% of patients. The cardiovascular risk factors observed were: hypertension (73.4%), android distribution of fat (7.44%), dyslipidemia (55.3%), microalbiminuria (7.44%), obesity (29.8%), smoking (7.4%) and a family history of cardiovascular disease at an early age (3.2%). The prevention of cardiovascular risk was primary for 37.2% of our patients and secondary for 30.9% of cases. Antiplatelet drugs were prescribed in 33% of patients. The subjects who required statin treatment as recommended represented 57% of patients, of whom 92.6% were treated.
Conclusion
Our study confirmed that the management of the cardiovascular risk in the elderly diabetic patients was satisfactory and in accordance with the recommendations of 'learned societies'.

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AEP342

The effects of COVID-19 pandemic lockdown on metabolic control of people with diabetes

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Aims
During April and May 2020 in Turkey, changing priorities in the health system and some restrictions on daily life in order to prevent the spread of SARS-CoV-2 infection may worsen metabolic control of people with diabetes. We aimed to investigate whether glycemic dysregulation or disturbance of lipid metabolism occur in people with diabetes during the lockdown period.
Methods
This retrospective study included 132 participants with type 2 diabetes mellitus and 6 participants with type 1 diabetes mellitus. We compared some metabolic parameters [HbA1c (Glycated haemoglobin), LDL (Low density lipoprotein), HDL (High density lipoprotein), Triglyceride, Body weight] of these people in pre-lockdown and post-lockdownperiod.
Results
HbA1c levels of the participants were higher in post-lockdown period when compared with pre-lockdown period (mean HbA1c 8.1% (65 mmol/mol) and 7.7% (60.7 mmol/mol) respectively, $P = 0.001$). In people with uncontrolled diabetes whose HbA1c > 7% (53 mmol/mol) in pre-lockdown period, higher triglyceride levels were detected in post-lockdown period ($P = 0.036$). There was no significant change in LDL, HDL levels and bodyweight.
Discussion
There are few studies analyzing real-life data specific to the metabolic control of people with diabetes during the pandemic period. In a Chinese study of 135 participants aged older than 65, HbA1c change between January and March in 2020 was statistically significant compared with the same period last year. In a study from India with 52 people with type 1 diabetes, it was observed that the average HbA1c values, which were 72.7 mmol/mol (8.8%) before COVID-19 lockdown period, increased to 85.8 mmol/mol (10%) after lockdown period. Our findings replicated the main outcomes of these two studies. In contrast with the Indian study, the majority of our sample was diagnosed with type 2 diabetes. Our study showed that triglyceride levels increased statistically significant in individuals with uncontrolled diabetes. The lockdown period may cause metabolic dysregulation due to physical inactivity, increased carbohydrate intake, weight gain, sarcopenia, and emotional stress.
Conclusion
Our results reflect the real-world experience of metabolic dysregulation of people with diabetes during lockdown. Considering these results; special measures like home exercise programs, telemedicine consultations, and the spread of technologies for diabetes should be taken for follow-up of individuals with diabetes during the pandemic lockdown.
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AEP343

The effect of Covid-19 pandemic lockdown on the blood glucose regulation of diabetic patients; one center experience

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Aim
The COVID-19 pandemic has affected the whole world, reducing hospital admissions of patients with chronic diseases. This study aims to evaluate the effects of difficulties experienced by diabetic patients in diabetes management on blood glucose regulation during the COVID-19 pandemic lockdown.
Methods
This study included 93 diabetic patients followed up in Endocrinology and Metabolic Diseases Clinic of Karadeniz Technical University. Biochemical parameters (glucose, HbA1c, lipid profile), diet and exercise status were compared between patients' first admission to the hospital after June 2020, the date that pandemic course started to slow down and their last admission before 11 March 2020, the date of the first case seen in Turkey. The frequency of blood glucose monitoring, compliance to diabetic treatment, hypoglycemia and hyperglycemia frequency, hospital admission requirements of patients and whether they had any infection were questioned.
Findings
89.2% of the participants were Type 2 Diabetes Mellitus (DM) and 10.8% were Type 1 DM. We found that 78.5% of them had dietary compliance, 41.9% did exercise at home, 53.8% used their medicines regularly, and 43.0% monitored their blood glucose every day. More than one hypoglycemia per week was observed in 15.1% of the patients, while hyperglycemia was observed more than once a week in 4.9%. When biochemical values before and after the lockdown were compared, a statistically significant decrease was found in fasting glucose level ($P = 0.026$) and body mass index ($P = 0.008$). No statistically significant difference was observed in terms of HbA1c and lipid levels before and after the lockdown. When the HbA1c change was evaluated; it was observed that the frequency of HbA1c increase was higher in those who did not comply to their diet and who did their blood glucose follow-up 'less than once a week or not at all' ($P = 0.001$; $P = 0.015$, respectively). When non-HDL-K change was evaluated; it was observed that non-HDL-C increase was higher in those who did not comply to diet regularly and did not exercise at home ($P = 0.047$; $P = 0.037$, respectively).
Discussion
This study has shown that patients who did not have COVID infection and did not apply to the hospital for treatment and follow-up of diabetes during the COVID-19 pandemic lockdown, can continue their diabetes management, compliance and follow-up on their own. It once again pointed out the importance of diabetes education, diet, exercise, frequency of blood sugar monitoring and compliance to the treatment.

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AEP344

Hypoglycemia in non-diabetic patients

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Keywords: Hypoglycemia- non-diabetic patients

Introduction

Hypoglycemia in non-diabetic patients is a rare entity, diagnosed by the presence of Whipple's triad (plasma glucose concentration less than 50 mg/dl, neuroglycopenic-symptoms, and resolution of symptoms after the correction of hypoglycemia). It may be secondary to several etiologies, including tumors that may be malignant. Prolonged supervised fasting is frequently used to diagnose and orientate the etiological investigations. The aim of our study is to describe the initial symptoms, the evaluation and management of hypoglycemia in patients without diabetes mellitus.

Patients-methods

This is a retrospective and descriptive study including non-diabetic patients admitted in the Endocrinology-Diabetology and Nutrition Department of the Mohammed-VI University-Hospital-Center of Oujda-Morrocco, for the exploration and management of hypoglycemia. All patients have benefited from a clinical examination, biological and radiological exploration.

Results

We have collected 07patients admitted to our department for hypoglycemia. No history of diabetes was noted in these patients. The mean age at admission was 29.8 ± 22.2 years, ranging from 17 months to 54 years. The sex-ratio (M/F) was 4/3. All patients showed neuroglycopenic signs. A prolonged supervised fast was performed in 5 patients, confirmed the presence of hypoglycemia. Eiologies were various: the diagnosis of adrenal insufficiency was established in 2 patients (17-month-old infant and 4-year-old child). A benign insulinoma was noted in one patient and a malignant insulinoma with extensive liver metastases in one patient with persistent hypoglycemia after surgery, motivating the use of everolimus at a dose of 10 mg/day. The diagnosis of functional hypoglycemia was concluded in 3 patients, secondary to somatostatin-analogues treatment in one acromegalic patient, one case of prediabetes, and in one patient an abnormal-regulation of carbohydrate metabolism was observed.

Discussion and conclusion

Recently, Non-diabetic hypoglycemia are classified according to the clinical condition of the patient: well or ill appearing individual. Biological exploration should be done at the time of spontaneous development of symptoms. If this is not possible, it can be done during a prolonged supervised fast test (up to 72 hours), which constitute the gold standard for diagnosis and etiological orientation. The etiological investigation includes searching for an insulinoma, the most frequent tumor responsible for hypoglycemia in adults, which requires an echo-endoscopy and pancreatic CT-scan.The treatment is initially based on the correction of acute hypoglycemia according to the patient's state of consciousness. Either by 15 to 20 g of glucose orally if patient is conscious or by intravenous administration of glucose serum if patient is unconscious. after correction, the treatment is etiologic.

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AEP345

The functional status of the thyroid gland in pregnant women with gestational diabetes mellitus

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Background and aims

Gestational diabetes mellitus (GDM) is a disease manifested by hyperglycemia, first diagnosed during pregnancy, which usually resolves after delivery. In GDM, there is a risk of adverse effects in both a mother and a fetus. Thyroid hormones (TG) play a huge role in the proper development of the child. Given the high prevalence of thyroid pathology and disorders of carbohydrate metabolism during pregnancy, the study of the relationship between these diseases and the prevalence of hypothyroidism in this group of pregnant women is relevant to improve the effectiveness of treatment and prevent complications.

Materials and methods

Retrospective analysis of individual pregnancy cards for 2019 based on the antenatal clinics of the Moscow Department of Health V.P. Demikhov Hospital. All women underwent a study of fasting blood plasma glucose, TSH, free T3, free T4, antibodies to thyroid peroxidase (TPO), an oral glucose tolerance test was performed at 24–28 weeks of gestation.

Results

Outpatient records of 779 pregnant women aged 19 to 46 years were evaluated, of which 599 patients were diagnosed with GDM. The average age of pregnant women with GDM was 33 years. Diet therapy was prescribed in 100% of cases. 349 (58.26%) pregnant women with GDM had no concomitant pathology. In 114 (19.03%) cases of GDM manifest hypothyroidism was revealed; in 19 (3.17%) cases, there was subclinical hypothyroidism as a result of autoimmune thyroiditis (AIT); 46 patients showed carriage of antibodies to TPO with a normal TSH level. The average values of hormonal parameters in the study group were: FT3 – 3.44 (0.36–15.8) pmol/l, FT4 – 2.33 (0.099–19.4) pmol/l, TSH – 3.15 (0.02–8.72) mIU/l. 74% of pregnant women with GDM had a BMI of 25 to 30 kg/m^2, with a mean of 27.3 kg/m^2. In 92 (15.35%) pregnant women, GDM developed against the background of obesity (BMI over 30 kg/m^2); 19 (3.17%) patients with GDM had hypothyroidism and obesity.

Conclusions

According to the conducted statistical analysis, it follows that GDM occurs more often in women with overweight at the time of gestation. GDM in this group of pregnant women is often combined with hypothyroidism and the carriage of antibodies to TPO. In this connection, further study of the relationship between these pathologies is required.

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AEP346

Use and effectiveness of dapagliflozin in type 1 diabetes: Clinical experience data of six months

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Introduction

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are a new class of oral antidiabetic drugs used for the treatment of type 2 diabetes mellitus. Recently, the SGLT2i dapagliflozin was approved for use in type 1 diabetes (T1DM) as an add-on to insulin therapy.

Material and methods

We conducted a retrospective observational study which included demographic and clinical-analytical data from 16 patients with T1DM that started dapagliflozin at a dosage of 10 mg/day. Our purpose was to assess the effect of dapagliflozin six months after its initiation.

Resultados

Data were analyzed from 16 patients with T1DM, 10 women and 6 men, 41.2 ± 14.8 years old, 22.7 ± 14.7 years of diabetes duration. 3 of the participants presented high blood pressure. With regard to diabetic complications, 4 patients had retinopathy, 1 nephropathy, 1 neuropathy, 1 ischemic cardiomyopathy. Basal characteristics of the participants: BMI 32.4 ± 6 kg/m^2; weight 91.1 ± 16.7 kg; HbA1c 8.1 ± 0.8%; blood pressure 129.8 ± 23.1/77.8 ± 11.12 mm Hg; basal insulin dose 46.7 ± 24.2 IU, prandrial insulin dose 34.8 ± 16 IU. 5 of the participants were on treatment with metformin. Six months after the initiation of dapagliflozin, significant reductions in BMI (30.7 ± 6.4 kg/m^2), weight (86.9 ± 18.2 kg), HbA1c (7.5 ± 0.7%), basal insulin requirements (44.3 ± 25 IU) and prandrial insulin requirements ((29.6 ± 15.2 IU) were observed. There were no significant differences with respect to blood pressure. Two patients discontinued dapagliflozin because of recurrent urinary tract infections.

Conclusion

The use of dapagliflozin in patients with T1DM was associated with an improvement of metabolic control, weight loss and reduction of insulin requirements, without severe side effects.

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AEP347

Growth factors in trophic disorders in diabetics

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Introduction

Epidermal growth factors accelerate healing in lesions of trophic disorders.

Methods

This is a prospective study carried out between February and June 2019 in the endocrinology and metabolic diseases department, involving 6 patients admitted for diabetic foot progressing for more than 3 months without

healing after conventional treatment. Having received the injections of growth factors of the EGF type.
Results
the sex ratio is 2, with an average age of 53 years (39–73), T2D is more representative at 67% with an average seniority of 16.5 years, all patients were unbalanced with an average HbA1c at 8.45%, degenerative complications are found in all our patients with an IRCT patient on dialysis. Foot lesions are mainly located on the sole of the foot with a type of plantar perforating disease complicated in 3 cases by osteitis, with an evolution ranging from 3 months to 2 years, on arteriopathic feet, classified stage IIIB and IIIC of the 'UT. The pre-treatment management consisted of a discharge and dressing adapted for each patient, a sorting of antibiotics and glycemic control. The patients received an average of 6 injections of EGF at the rate of 2 sessions per week, the average length of stay in hospital is 21 days. There was a case of over granulation causing treatment to be stopped. Complete granulation was obtained in 4 patients, with a mean total healing time of 80 days.
Conclusion
Growth factor injections considerably improved the healing and healing time of foot lesions in our patients and thus appears to be an asset in the management of diabetic foot.

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AEP348

The impact of functional insulin therapy on the psychological aspect of type 1 diabetics

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Introduction
Functional insulin therapy is an educational method that is part of a strategy to intensify type 1 diabetes in order to optimize the balance of diabetes while improving the psychological aspect of the patient. The aim of this study is to assess the impact of functional insulin therapy on the psychological aspect of type 1 diabetics.
Patients and method
This is a retrospective and analytical descriptive study, conducted from March 2019 to August 2019, we included 20 type 1 diabetic patients who benefited from a functional insulin therapy education program and an evaluation of the psychological impact made by a questionnaire and a psychological interview.
Results
The average age of the patients was 20 years, with a sex M/F ratio of 4/16, and the duration of diabetes was on average 8 years. Functional insulin therapy is used exclusively in all patients. The psychological evaluation shows an improvement in the perception of the impact of diabetes in (66%), there is a decrease in anxiety in (75%), With (80%) of the patients declared a satisfaction with the method, (60%) declared acceptance of the treatment, 14 patients (70%) reported more autonomy and self-management and only (40%) reported an improvement in their socio-professional relationships, The doctor-patient relationship improved in (90%) patients. According to the open questions, functional insulin therapy provides better diabetes control and food freedom. The difficulties mainly felt are the calculation of the quantities of carbohydrates, the economic constraint and the multiple injections for treatment and monitoring.
Conclusion
The results suggest that learning functional insulin therapy improves the psychological aspect of type 1 diabetics through better control of the disease.

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AEP349

Implementation of flash glucose monitoring system in a regional hospital in the province of Cordoba

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Introduction
The development of flash glucose monitoring system (FGM) has led to a change in the paradigm of diabetes control, beyond the evaluation of glycosylated hemoglobin (HbA1c). FGM allows to improve control of type 1 diabetes mellitus (T1DM) and the quality of life of patients.
Objective
Describe the baseline characteristics of patients with T1DM in a regional hospital in the southern area of the province of Cordoba and study changes after the start of FGM.
Design and methods
A retrospective observational study of patients we implant FGM, from the opening of the consultation (June 2020) to the present. Statistical analysis was performed using the SPSS program (SPSS, inc, v21.0) (Student's t-test for related samples).
Results
We evaluated 36 patients, a mean age of 36 ± 14.11 years, 58.3% women, BMI 26.46 ± 4.77 kg/m^2, 13.9% with thyroid pathology. Cardiovascular risk factors: 6.9% smokers, 11.1% hypertensive, 19.4% dyslipidemic. Previous follow-up of T1DM: 88.9% Endocrinology, 8.3% Internal Medicine and 2.8% Primary Care.
Baseline characteristics
20.83 ± 12.11 years of evolution, 38.9% performed between 4–6 daily blood capillary glucose, 30.6% diet by rations, basal insulin: 80.6% insulin Glargine U300; prandial insulin: 55.6% insulin Aspart; total daily insulin dose 0.70 ± 0.22IU/kg/day, 8.3% treatment with metformin. Microvascular complications: 19.44% (retinopathy); Macrovascular complications: 2.78% (ischemic heart disease). 5.6% of the patients required recycling of diabetes education. 94.4% had not used FGM and were referred to start it (86.1% in the first visit, 5.9% in the second). Biochemical and ambulatory glucosa profile (AGP) comparison from FGM implantation to successive revisions (first vs second, both with FGM): HbA1c 7.51 ± 0.72% vs 7.65 ± 0.65%, glucose 142.50 ± 36.65 vs 183.08 ± 63.88 mg/dl, P = NS both; no positive microalbuminuria data at follow-up. Coefficient of variation (CV) 38.54 ± 8.26 vs 36.55 ± 6.09%, GMI 7.06 ± 0.94 vs 7.36 ± 1.19%, time in hyperglycemia 31.09 ± 21.9 vs 35.18 ± 24.54%, time in hypoglycemia 6.73 ± 4.92 vs 9.91 ± 15.04%, time in range 62.18 ± 20.82 vs 5 4.91 ± 28.13%, P = NS in all. Average glucose 154.55 ± 35.64 vs 164.27 ± 45.83 mg/dl, P = 0.039.
Conclusions
In this cohort, the use of FGM has allowed a decrease in CV (although not significantly). However, the biochemical control and the glucometric data don't show an improvement trend, despite the increase in progressive use, possibly due to the low availability of data at present (more than half of patients have not yet undergone review after start FGM). In this regard, adequate diabetes education is essential, which we must emphasize more in our patients, increasing the rate of referral to nursing.

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AEP350

Dietary beliefs and behavior of pregnant women with diabetes

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Introduction
Pregnant women with diabetes are prone to overeating and decreased physical activity, both sources of glycemic disorder. The objective of our study is to evaluate these dietary beliefs in order to improve the management of diabetes.
Materials and methods
Prospective observational study, including 100 patients with diabetic pregnancy followed in the department of gynecology and obstetrics of the ibn rochd university hospital center in Casablanca between January 2020 and November 2020.
Results
The study included 100 patients with an average age of 30 years, 40.5% had gestational diabetes and 59.5% had pre-gestational diabetes. 78.9% of the patients were on insulin and 21.1% were undergoing hygienic and dietary rules. Glycemic control was perfect in 56.4% of patients. For eating behavior: an abuse of slow sugars was found in 64% of patients with fat abuse in 64.6% and a consumption of fast sugars in 24.6%. 70.8% ate at fixed times while 18% skipped at least one meal. Regarding dietary beliefs, 70% of the patients thought they should eat less to be healthy, 39% thought

they could eat the food they wanted, 40% thought they should eat for two and 35% thought that weight gain should not be limite. As for physical activity, it is practiced by 28% of patients, 72% think it helps glycemic control while 20% think it can harm their pregnancy.
Conclusion
Our study shows the dietary beliefs and behavior of pregnant diabetic patients and highlights the need for better information and improved dietary education of these patients.

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AEP351

Seasonal changes of 25(OH) vitamin D among elderly patients

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Introduction
Vitamin D plays an important role in human physiology. It is synthesis mainly by the skin during sun exposure. Elderly population are at risk to develop vitamin D deficiency caused by many factors (reduced sunlight exposure, impaired skin synthesis and hydroxylation in the liver and kidney as well as decreased dietary intake and impaired intestinal absorption).
Aim
The purpose of the study was to assess the status of vitamin D across the different seasons among elderly population.
Material and methods
The study group comprised 152 patients above 60 years, hospitalized in the geriatric department. The samples was collected between 2013–2015. Each individual provided consent before included to the study. Blood samples were collected after overnight fasting. The serum level of 25-hydroxyvitamin D (ng/ml) was measured by enzyme-linked immunosorbent assay (ELISA). The study group was divided into four seasons (spring, summer, autumn, winter).
Results
Mean age of participant were 76.24 ± 7.47 years. The mean 25(OH)D level among study group was 14.61 ± 5.96 ng/ml. The mean serum of vitamin D during particular seasons was: 15.54 ± 5.31 ng/ml (spring), 16.33 ± 7.40 ng/ml (summer), 14.14 ± 5.08 ng/ml (autumn) and 14.03 ± 4.28 ng/ml (winter). There was no statistically differences (P = 0.3450). Most of the patients had vitamin D deficiency – 83.20%. 16.80% study group had suboptimal vitamin D level. In the spring, autumn and winter, vitamin D deficiency was observed among 87.50%, 86.40% and 86.70% group. The proportion of suboptimal vitamin D level was higher in the summer (25.0%) as compared with the other seasons. We observed also that the mean serum of 25(OH)D level among respective months was not statistically significant differences (P = 0.2655).
Conclusion
Vitamin D deficiency was observed in examined study group, in spite of the seasons. There is no significant differences in mean serum vitamin D concentration among patients across the seasons. Anyway, a proper vitamin D supplementation should be recommended and implemented alongside any elderly person's daily diet.

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AEP352

Bullosis diabeticorum

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Introduction
Skin damage is common in diabetes. They can be classified into three groups: dermatoses associated with diabetes, acute and chronic skin complications of diabetes and dermatoses associated with antidiabetic treatments. Bullosis in diabetics, also called Bullosis diabeticorum, is one of the cutaneous complications of diabetes. It is a rare bullous dermatosis particular by its exclusive occurrence in diabetics.
Observation
We report the case of a 73-year-old patient. In his history, there was high blood pressure and type 2 diabetes for 26 years complicated by peripheral neuropathy. He had complained of tense blisters which had started suddenly and spontaneously for 05 days. These lesions were non-painful and non-itchy. There was no history of photosensitivity and the patient could not recall any new drug intake. Clinical examination revealed multiple tense bubbles of serous content on a nonerythematous base was ween on the anterior surface of both legs. Complete blood count and electrolyte test were within normal limits. Serum creatinine was 71 µmol/l, CRP 9 mg/l, and HbA1c 7.1%. Histopathology of the lesional skin showed a subepidermal bulla without any inflammatory infiltrate. A direct immunofluorescence test was negative. Local care after removal of bubbles was indicated. The bubbles healed spontaneously after three weeks, without recurrence with a follow-up of 11 months.
Discussion-conclusion
Diabetic bullosis is characterized by the sudden onset of large, tight bubbles with clear or hemorrhagic content, in healthy skin, without pain, pruritus, inflammation or mucosal damage. It predominates on the soles and the toes. The pathophysiology is poorly understood and would involve vascular alterations, mechanical and /or trophic abnormalities related to the underlying neuropathy. The main differential diagnosis is bullous pemphigoid. The treatment is symptomatic with a spontaneously favorable outcome over a few weeks. This evolution constitutes a key element for the diagnosis.

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AEP353

Screening for obstructive sleep apnoea in type 2 diabetes subjects using STOP-BANG questionnaire

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Introduction
The association between Obstructive sleep apnoea (OSA) and type 2 diabetes mellitus (T2DM) is well known and this combination imposes a higher risk of complications in the affected indvidual. Polysomnography which is a gold standard for diagnosing OSA is not universally available, so many of the patients with OSA remain undiagnosed. A questionnaire-based OSA screening for risk stratification can help early detection of OSA in T2DM.
Methods
This was a cross-sectional study done in an endocrine speciality hospital in the Indian state of Punjab. The participants were 486 adult subjects with T2DM who all underwent clinical evaluation, anthropometry, investigations and were administered STOP-BANG questionnaire, which is an eight items tool with four symptoms and four signs to stratify the OSA risk. The scoring scale is categorized into three risk groups; low risk (0–2), intermediate risk (3–4) and high risk (5–8) respectively.
Results
Out of all the participants 57.3% were males. Mean age of the participants was 56.7 ± 12.8 years. STOP-BANG score of ≥ 3 was present in 43.6% of the participants with moderate risk score (3–4) in 26.2% and high risk score (5–8) in 17.4% of the participants. The score showed positive correlation with age, male sex, duration of diabetes, BMI, hypertension and CAD. It was not correlated with Hba1c, use of insulin.
Discussion and conclusions
Various studies have shown high prevalence of OSA in subjects with T2DM and the presence of OSA being associated with an increased likelihood of hypertension, cardiovascular disease, diminished quality of life and increased mortality justifies the importance of screening for OSA in diabetic patients. In the present study by using a clinical tool STOP-BANG questionnaire we have found high prevalence (43.6%) of OSA in T2DM subjects and its significant correlation with age, duration of diabetes, BMI, H/T and CAD. STOP-BANG is a simple screening tool having high sensitivity and can be conveniently used in primary care setting to identify the subjects at risk of OSA. These sub-set of patients can be then subjected to polysomnography for confirmation and appropriate timely management, so as to reduce the morbidity and mortality associated with untreated OSA.

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AEP354

Predictors of the development of androgen deficiency in men with type 2 diabetes mellitus

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The aim of the study is the search of predictors of the development of androgen deficiency in men with 1 diabetes mellitus type 2. The study included 243 men with type 2 diabetes mellitus aged 35–55 years. The median age of men was 39.00 [30.00; 45.00] years, the median duration of diabetes mellitus type 2 was 12.00 [7.00; 22.00] years. As a result of the research, it was found that an increase in the patient's age significantly increased the risk of developing androgen deficiency (b = 0.07, Exp (b) = 1.08 (1.00 ÷ 1.16), P < 0.05). The age of smoking experience also had a significant effect on the risk of developing androgen deficiency (b = 0.06; Exp (b) = 1.07 (1.10 to 1.13), P < 0, 04). The relative risk of developing (RR) androgen deficiency in men with a smoking experience of more than 7 years was 3.76 and was statistically significant (95% CI = 1.07 ÷ 13.25). With an increase in the level of glycated hemoglobin, the risk of developing androgen deficiency also increased significantly (b = 0.08; Exp (b) = 1.01 (1.00 ÷ 1.02), P < 0.04). The exceeding of the glycated hemoglobin level above 7.5% demonstrated a statistically significant RR = 6.71 (95% CI = 1.19 ÷ 37.86). The reduction of LDL decreased the risk of developing androgen deficiency in the men surveyed at the level of a stable trend (b = –0.45; Exp (b) = 0.64 (0.35 ÷ 1.18), P < 0.10). At an LDL level of less than 3.50 mmol/l, the RR of androgen deficiency was 0.29 and was statistically significant (95% CI = 0.09 to 0.97). The rise in VLDL significantly increased the risk of androgen deficiency (b = 0.71; Exp (b) = 2.04 (1.11 ÷ 3.76), P < 0.02). At a VLDL level of 0.42 mmol/l, the RR was 2.58 (95% CI=1.38 to 3.29). As can be seen from the data provided, unsatisfactory compensation of type 2 diabetes mellitus increases the risk of developing androgen deficiency in men.

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AEP355

Mucormycosis of the ENT sphere in diabetic subjects: About 4 observations

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Introduction
Mucormycosis is a rare and often fatal fungal infection which is caused by a group of molds called mucormycetes.It usually occurs in immunocompromised subjects and especially diabetics. The aim of our work is to specify the epidemiological, clinical and therapeutic characteristics of ENT mucormycosis in diabetic subjects.
Material and methods
A retrospective study included 4 diabetic patients with ENT mucormycosis diagnosed over 18-year period, from January 2000 to December 2017.
Results
The study involved two men and two women, aged between 40 and 77. All patients were diabetic. There were 2 cases of sinonasal mucormycosis, 1 case of rhinocerebral mucormycosis and 1 case of otologic involvement with cerebral extension. The diagnosis was based on anatomopathologic and mycologic examination. Culture isolated Rhizopus oryzae in 4 cases. The four patients were put on Amphotericin B associated with surgical curettage. One patient presented with an allergy to Amphotricin B, hence the use of its liposomal form. The evolution was good in 2 patients, one of whom retained a sequellar facial paralysis. A fatal issue occurred in 2 cases with otocerebral and rhinocerebral involvement.
Conclusion
Otorhinolaryngologic mucormycosis is a rare fungal infection. Rhinocerebral involvement is the most common clinical form and otological involvement is exceptional. The prognosis remains severe, depending mainly on the early diagnosis and treatment.

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AEP356

Obesity before and during pregnancy-a powerful risk factor for hyperglycemia in pregnant Bulgarian women

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The epidemic of obesity, as well as the reduced physical activity are a complex of reasons for the increase in the frequency of Glucose tolerance disorders. The aim was to analyze the frequency and role of Obesity/ Overweight for the development of Hyperglycemia in the Bulgarian population of pregnant women.
Material
We screened 547 pregnant women, mean age 30.49 ± 5.12 years, divided into two groups: with Hyperglycemia (n-79) and with Normoglycemia (n-468).
Methods
Body mass index (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.
Results
Obesity was found for the whole group before pregnancy in 10.2% (56/547) resp. overweight in 20.1% (110/547). With regard to BMI before pregnancy, this relationship proved to be significant when comparing the mean ranks for Hyperglycemia (Mean Rank 260.42 vs 354.44, P < 0.001), when compared with Normoglycemia in the respective group. We obtained the same significant results in the analysis of the impact of obesity during pregnancy. The mean ranks for Hyperglycemia (Mean Rank 257.24 vs 373.28, P < 0.0001), when compared with the respective group with Normoglycemia. Therefore, women with a higher BMI before and during pregnancy are significantly at risk of developing glucose intolerance during pregnancy.
Conclusion
Obesity affects a large number of young people, but this factor is subject to modification. Young women who are obese/overweight should be consulted prenatally, and if they become pregnant, they should be tested for glucose tolerance disorders as early as possible.

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AEP357

Isolation of nerve growth factor in blood specimens from patients with type 1 diabetes mellitus

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Physiological role of nerve growth factor (NGF) was characterized for the sensory and vegetative nervous systems, as well as for the central, endocrine and immune systems. The growth simulator and a cytokine, NGF is known to be involved in the metabolism of various pathological conditions. Recent clinical and academic studies among patients with diabetes mellitus, insulin resistance and Alzheimer's disease have brought to light previously unreported cell and pathological conditions. Relevant epidemiological data can serve as the evidence for close association between cognitive deterioration and diabetes mellitus due to the defective glucose uptake in the neurons for energy generation. Insulin is known to control the synaptic plasticity due to internalization of neuroreceptors. Accordingly, it is of significant interest to find out if there is any association of diabetes mellitus, the body's failure to produce enough insulin, with the compromised function of neurotrophins. The work was initiated to isolate NGF in blood specimens from patients with type 1 diabetes mellitus.
Materials and methods
Successively, adsorption chromatography on silica glass, gel filtration by means of Toyopearl HW55 resin (Tosoh Bioscience GmbH, Germany), carboxymethylcellulose chromatography and preparative PAGE were used to isolate the NGF fraction from blood serum of diabetics (n = 7) and non-diabetics (n = 7).
Results and discussion
By means of a method for generation of fractions, we compared blood sera from diabetic and non-diabetic donors for neurogrowth activity. The product we isolated is a high molecular weight complex of NGF and protein carrier

of globulin nature with disulfide bond and neurite-stimulating activity of 2×10^2 BU/mg of protein, molecular mass of 160 kDa and pI 9.1–9.7. After treatment with dithiothreitol, we got a protein with molecular mass of 15–30 kDa and activity of 6×10^2 BU/mg of protein. All the properties indicated pertinence of the protein to NGF. Major complications, to name the dysfunction and degeneration of various peripheral neurons among them are typical of diabetes mellitus. Sensory impairments prevail; degeneration of small diameter sensory fibers results in major symptoms. Our findings demonstrated that blood serum NGF concentrations in the diabetics were 2.5 times lower than those in the non-diabetics. In diabetes mellitus, key components of the NGF signal pathway are found deregulated, the same goes to production of the NGF-controlled neuromodulators. Insulin therapy facilitated elevation of the regulator's concentrations, but they did not reach the standard one. This seems to confirm the hypothesis that in diabetes both neuronal and peripheral insulin sensitivity is impaired.

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AEP358

Impact of diabetes on liver fibrosis in chronic hepatitis C

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Introduction
Chronic hepatitis C (CHC) is associated with an increased incidence of insulin resistance and diabetes mellitus. Obesity and insulin resistance are associated with faster progression of fibrosis in these patients. The aim of our study was to assess the impact of diabetes on the severity of hepatic fibrosis in patients followed for CHC.
Methods
This is a retrospective study conducted between January 2017 and December 2020 including all patients followed for CHC. The evaluation of hepatic fibrosis was performed by measuring hepatic elasticity by the Fibroscan. Significant fibrosis was defined by a fibrosis score ≥ F2. Advanced fibrosis was defined by a score F3-F4.
Results
44 patients were included; 28 women (63.6%) and 16 men (36.4%) with an average age of 49 years (16–81 years). Diabetes was present in 13 patients (29.5%). Metabolic syndrome was associated to diabetes in all patients. Nine patients were treated by oral anti-diabetics. Others were treated by insulin injections. The level of glycated hemoglobin was < 7% in all patients. Significant fibrosis ≥ F2 was found in 7 patients (53.8%). Advanced fibrosis F3-F4 was observed in 3 patients (23.1%). And three patients had a score of fibrosis F0-F1. The analytical study did not show a significant difference in hepatic elasticity between diabetic patients (mean elasticity of 9.15 Kpa) and non-diabetic patients (mean elasticity of 8.18 Kpa); $P = 0.630$.
Conclusion
In our study, diabetes was found in a third of patients with chronic hepatitis C without an impact on the severity of the hepatic fibrosis.

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AEP359

Type 2 diabetes in young people About 30 cases preliminary results

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Introduction
Type 2 diabetes has long been considered a disease of overweight adults. However, its incidence is increasing rapidly in children and adolescents along with that of overweight and obesity. The aim of this study was to assess the prevalence and clinical profile of type 2 diabetes in young subjects.
Materials and methods
Descriptive prospective study from January 2019 to August 2020 including 30 diabetic patients aged 15 to less than 35 years hospitalized in our department and in whom the diagnosis of type 2 diabetes was evoked according to the criteria of the ADA 2020.
Results
The mean age of our patients was 24.02 ± 6.23 years, with a female predominance of 73.3%. Forty percent of our patients were already known to have diabetes with an average length of 1.67 years ± 2.70 and 60% had just been diagnosed. Type 2 diabetes was discovered after revealing ketosis in 14 patients, incidentally in 12 patients, after ketoacidosis in 2 patients, and after gestational diabetes in 2 patients. The cardiovascular risk factors found were obesity in 26.7% of cases and the syndrome metabolic in 20% of cases. The complications found were diabetic retinopathy in 13.3% of cases and diabetic neuropathy in 33.3% of cases. Acanthosis nigricans was present in 66.6% of our patients.
Conclusion
Type 2 diabetes is common in young people, hence the importance of its prevention in this category of the population which must be focused on lifestyle changes.

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AEP360

Dunnigan syndrome in Central South Africa: A case report

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Introduction
Familial partial lipodystrophy type 2 is caused by several pathogenic variants of lamin LMN gene. Males and females are equally affected by the autosomal recessive condition which manifests before age 2. They gradually loose fat in the upper and lower extremities as well as the gluteal area.
Case
We present a 31 year old female athlete who presented with oligomenorrhoea, diabetes mellitus, and severe fasting hypertriglyceridemia in 2007, followed by tuberous xanthoma fat deposition in 2009, hypertension and Asthma in 2019. Examination revealed a lean body habitus and evidence of severe insulin resistance (IR) i.e. hirsutism and diffuse acanthosis nigricans. The complications came early and were difficult to manage with tools available in our public setting. She used private health care until her return in 2019. She has two unaffected siblings. She received the following treatment: Pioglitazone 15 mg, Novomix 30: 54 u & 46 u, Metformin 1 g bd, Bezalip 400 mg/d + Atorvastatin 40 mg/d, Losartan 50 mg bd.
Investigations
Bloods: (2007) TC 27.5, TG 280, HbA1c 12.5%, AST 16, ALT 14, FPG 29 (2020) TC 4.3, TG 6.64, HbA1c 10.7%, HDL 0.76.
Molecular genetic analysis

Gene	Exon	cDNA	Amino acid	Classification	Zygosity
LMNA	8	C.1444 > T	p.Arg482Trp	Pathogenic	Heterozygous

Conclusion
Although this is a rare condition, early diagnosis and counselling is critical in order to minimize metabolic and systemic complications, including cardiovascular death by screening the family and treating everyone affected.

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AEP361

Syndromic mitochondrial diabetes: About three Tunisian families

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Introduction
Mitochondrial diabetes (DM) is characterized by a broad spectrum of phenotypic and genotypic involvement. Among 86 patients with DM, we chose to study the peculiarities of syndromic DM diagnosed in three families in order to be able to establish a correlation between this diversity of phenotypic expression and the biomolecular substratum of the mitochondrial genome.
Results
These are four patients (index case) belonging to 3 families with an average age of onset at 22 years (3–32), sex ratio 3 F/1H. Maternal transmission of diabetes in half of cases with a phenotype reminiscent of type 1 diabetes (MIDD1) in all patients. The sequencing of the mitochondrial genome

using the candidate gene and mitochondrial genome approach approach allowed us to highlight the mitochondrial biomolecular peculiarities within our population, in fact the two patients presenting a phenotype suggestive of Wolfram syndrome presenting a central diabetes insipidus. and bilateral optic atrophy had a mutation in the gene encoding ND1 (mitochondrial complex I enzyme). Concerning the patient presenting phenotypic traits suggestive of a MELAS syndrome associating pyramidal syndrome, epilepsy and lactic acidosis, an m.1640A > G mutation of the tRNA gene Val in the homoplasmic state was found underlining the genotypic heterogeneity of this syndrome. Finally, we report for the first time the coexistence of a primary amyloidosis and a MIDD1 by mutation m3243A > G (tRNA Leu) in the fourth patient who had presented extra pancreatic manifestations common to the type hypertrophic cardiomyopathy, glomerular nephropathy and neuropathy. peripheral.
Conclusion
Certainly, progress in molecular biology and a better understanding of the signaling lines of intracellular proteins will make it possible to clarify the etiopathogenic link and to establish a correlation between the clinical phenotype and the spectrum of mitochondrial genetic damage.

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AEP362

Clinical features of patients with diabetic ketoacidosis and acute pancreatitis

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Introduction
Acute pancreatitis (AP) is the most common affection of the pancreas, it often leads to glycemic disorders. On the other hand, diabetic ketoacidosis (DKA) is associated with nonspecific increase in serum amylase levels. The aim of this study was to evaluate the clinical characteristics of acute AP concomitant with DKA.
Methods
We conducted a retrospective and descriptive analysis of clinical records of patients diagnosed with DKA and AP, between 2000 and 2020 in endocrinology department. All patients fulfilled the current diagnostic criteria of both, DKA and AP. Clinical, biological and radiological data were collected.
Results
A total of 18 patients (7 males and 11 females) were enrolled in the study. The mean age was 40 years, ranging from 16 to 70 years. Of 18 patients, 11 had prior history of diabetes and five had hyperlipidemia. Two patients had a history of alcohol use. All the patients presented nausea and vomiting at time of admission. Abdominal pain was absent in five patients and four were comatose on admission. The mean BMI was 26.6 kg/m^2. Both serum amylase and lipase levels were elevated in all patients with a mean value of 324 (NR: 10–45 UI/l) and 272 UI/l (NR:10–60 UI/l) respectively. AP confirmed by an abdominal computed tomography (CT) scan finding was occurred in 16 patients. The etiology of acute pancreatitis was gallstone in five, hypertriglyceridemia in two, and idiopathic in eleven patients.
Conclusions
Although DKA can be associated with elevated amylase and lipase in 16–25% of cases, acute pancreatitis may co-exist with DKA in at least 10–15% of DKA patients [1]. The pathogenesis of AP in DKA varies, but at least in some transient and profound hyperlipidemia is an identifiable factor. AP is more likely in severe DKA with significant acidosis and hyperglycemia.
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AEP363

Solid pseudopapillarytumor of the pancreas: Report of a special case

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Introduction
Solid pseudopapillary tumors (SPT) of the pancreas area rare exocrine pancreatic tumor behaving in a low-grade fashion, with limited local invasion risk and a rare metastatic evolution. They mainly affect young women. Their etiopathogenesis remains uncertain. We report the case of a 15-year-old boy,having congenital anomalies, who presented a solid and pseudopapillarytumour of the pancreas.
Case report
A fifteen-year old boy with a familial history of diabetes, infertility andepilepsia was known to have a polymalformative syndrome made up of a single left kidney and bone malformations (dorsal scoliosis and a butterfly vertebral defect at the L4 lumbar spinal level). He was admitted in October 2019 on the general surgery department of the UHC Habib BourguibaSfax for acute abdominal pain and an epigastric mass. Biological assessment was correct, whereas MRI showed a 10 cm cystic tumor lesion of the pancreas with a thick wall significantly enhanced especially on late sequences without obvious invasion of neighboring structures suggesting SPT of the pancreas. A caudal spleno-pancreatectomy with a high segmental resection removing the tumor as a single piecewas then done. The anatomopathological examination confirmed the diagnosis of SPT without lymph node metastases or local invasion. A prediabetes was revealed after surgery with a fasting plasma glucose (FPG) level of 5.8 mmol/l and a glycated hemoglobin(A1C) level of 6.17%. One year later, the patient was admitted in the endocrinology department of the UHC HediChakerSfax for an inaugural ketosis-prone diabetes. He reported an important weight loss in the last two months and a flu a week before his admission. The rest of the somatic exam was normal as well as the biological assessment except an A1clevel at 16.9%.An abdominal CT scan revealed a remaining pancreas (cephalic) of homogeneous density and enhancement. The pancreatic and thyroid antibodies were negative.A detailed physical examination, ophthalmologic examination and cardiac ultrasound did not find other associated malformations. Although a diabetes secondary to pancreatectomy seemed the most probable, we completed with a DNA sample in search of monogenic diabetes.
Discussion-Conclusion
TPS is extremely rare in men. Also, the association of TPS with a single congenital kidney or bone malformations had not been reported in the literature to our knowledge.

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AEP364

Characteristics of the metabolic syndrome in the elderly with diabetes

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Introduction
The metabolic syndrome (MS) presents a major public health problem, especially in elderly diabetics. The objective of this study is to assess the frequency and characteristics of MS in elderly diabetics.
Patients and methods
Retrospective study of 94 diabetic subjects over the age of 65 years who were hospitalized in the endocrinology department of Mahdia or followed at the outpatient clinic between November and December 2020.
Results
The mean age was 71 ± 5 years with extremes of 65 and 90. The female predominance was remarkable. Almost all of our patients had type 2 diabetes. The mean duration of diabetes was 12 ± 8 years. MS was present in 74.6% of patients. In these patients, elements of MS other than diabetes were: hypertension in 24% of cases, hypoHDLemia in 18% of cases, hypertriglyceridemia in 42% of cases and android obesity in 54% of cases. One third of these patients presented with cardiovascular disease: myocardial infarction (18%), stroke (6%), arteritis of the lower limbs (10%) and significant carotid stenosis (1%).
Conclusion
Through our study, we found that MS is very common among elderly diabetics. Adequate management of these patients appears to be necessary in order to avoid cardiovascular morbidity and mortality.

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AEP365

Diabetic retinopathy: prevalence and risk factors in a type 2 diabetic population

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Introduction
One of the major complications of diabetes that can lead to blindness is diabetic retinopathy. The objective of our work is to determine the prevalence of this complication in a type 2 diabetic population as well as its various risk factors.
Methods:
This is a retrospective study including 100 type 2 diabetic patients followed up in the 'C' department of nutrition and diabetology at the National Institute of Nutrition in Tunis.
Results
The average age was 56.8 years old. A female predominance was noted in two-thirds of cases (66%). The mean duration of diabetes was 11.28 years. The mean HbA1c was 10.69 ± 2.51%. The average BMI was 29.8 ± 5.59 kg/m^2. Diabetic retinopathy was present in 46% of patients. The frequency of this complication was significantly correlated with the age (P = 0.022) and the duration of progression of diabetes (P = 0.005). Diabetic retinopathy was linked to higher HbA1c and BMI levels but this was not significant. It was more frequent in hypertensive patients (P = 0.07) who represented more than half of the population. The mean systolic blood pressure was higher in the presence of diabetic retinopathy but this was not significant. This complication was more frequently noted in dyslipidemia (N = 82) without this being significant. The triglyceride level was higher in patients with diabetic retinopathy (2.04 ± 1.11 g/l vs 1.78 ± 0.76 g/l). The latter also had a significantly higher LDL cholesterol level (P = 0.01). Active smoking was reported by 20% of the population with no statistical relation to the occurrence of retinopathy.
Conclusion
Diabetic retinopathy was a frequent complication in our population. As risk factors, we noted the age, duration of progression of diabetes, poor glycemic control, presence of overweight, hypertension and dyslipidemia. As one of the leading causes of blindness worldwide, screening for risk factors for diabetic retinopathy and their control is imperative.

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AEP366

Diabetes-related knowledge among type 2 diabetic patients in Sfax, south Tunisia

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Introduction
Type 2 diabetes mellitus is a major non communicable disease which needs continuous and improved interventions. Knowledge assessment studies are useful for providing baselines for healthcare policies and educational programs.
Aim of this study
To evaluate diabetes-related knowledge among type 2 diabetes patients.
Methods
A cross sectional study was conducted on adult patients with type 2 diabetes who had been diagnosed since at least 6 months and taking medical treatment. Data were collected from November 2019 to February 2020, through a designed questionnaire. We used SPSS version 20 for data analysis.
Results
In total, 233 type 2 diabetic patients were surveyed, including 142 (60.1%) females. The mean age was 58.8 (SD = 10.8). One hundred seventy-five (75.4%) of cases were living in urban area. Forty-seven patients (20.3%) were non-educated, and 118 patients (50.9%) had primary education level. One hundred fourteen participants had low socioeconomic status. Overall, 78.5% of patients had a family history of diabetes. The mean duration of diabetes was 11.8 (SD = 9.1) years. Of all respondents, 132 (56.9%) were on oral diabetic tablets only, and 33 (14.2%) were on insulin only. The mean BMI was 30.6 (SD = 6.6).The mean glycated haemoglobin was 8.78 (SD = 1.98). About 57% of patients had confirmed diabetes complications. Of all interviewed, 157 (67.4%) confirmed receiving diabetes information. Overall, 78.1% of patients knew that polyuria and polydipsia are frequent symptoms of hyperglycaemia. Forty patients (17.2%) were knowledgeable about causes of hypoglycaemia. Regarding, diabetes risk factor, 85% of patients were knowledgeable about the genetic factor, while 76.4% and 65.7% of patients were knowledgeable about obesity and sedentary lifestyle, respectively. About 85.4% of patients knew that poor control of diabetes could increase the risk of complications. Regarding the management of diabetes, 93.6% and 91.4% of patients knew the importance of individualized diet plan and regular physical activity, respectively.
Conclusion
This study showed that diabetic patients had limited level of diabetes-related knowledge, which could negatively affect their diabetes control and quality of life. Accordingly, there is an urgent need for improving educational program based on patients' needs and characteristics.

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AEP367

Quality improvement project on pilot joint diabetes-renal clinics in a district general hospital in United Kingdom

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Diabetes is the leading cause of end stage renal failure. So, identifying patients at risk and intensifying management of blood pressure, lipids and glycaemic control can reduce and delay progression to organ replacement therapy. The aim of our study was to determine whether our pilot 3 monthly joint diabetes-renal clinics set up in April 2018 was able to achieve targets outlined by national guidelines and whether patient satisfaction and improved outcomes could lead to further service expansion. We collected retrospective data using electronic records for all 48 patients attending the pilot joint diabetes-renal clinic over a 2-year period. Patient satisfaction was assessed through a self-reported questionnaire. 40 patients had type 2 and 8 patients had type 1 diabetes. The number of hospital visits had significantly decreased from a mean 4.5 to 1.25 visits per year; mean age 68.3 years; mean current eGFR was 27.4 ml/min/1.73 m^2 (median 26.5) from a mean baseline of 30.2 ml/min/1.73 m^2 (median 29). The rate of decline of eGFR was 0.11 ml/min/month during this period; mean current blood pressure 154/75 mmHg with 33.3% of patients meeting the target < 130/80 mmHg; current HbA1c 68 mmol/mol vs 77 mmol/mol at baseline; LDL cholesterol 2.03 mmol/l vs 2.7 mmol/l at baseline. 91.6% patients who had no identified contraindication were on lipid lowering drugs. 37.5% patients were not on ACE inhibitors, the top 3 reasons being troublesome hyperkalaemia, significant eGFR drop on initiation and allergic reactions. All 32 patients assessed through a self-reported questionnaire found having both specialties at the clinic appointment to be beneficial as they attended fewer hospital appointments, and they needed less duplication of blood tests as a result of the joint clinic. 21.8% and 18.7% patients felt that it would be beneficial for a diabetes specialist nurse and a dietician to be available at the appointment, respectively. All patients felt that there was clear communication about any changes made to their medication and treatment plan at the appointments. Our findings suggest that the rate of deterioration of renal function can be slowed by aggressive risk factor management. More importantly patient satisfaction considerably improved by attending the joint clinics and will also lead to savings in health care. This will lead to a business case to expand this service further and develop joint diabetes-cardio-renal service to improve the care of patients with complex long-term conditions.

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AEP368

Type 1 diabetes and Klinfelter syndrome: A case report

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Introduction
Klinfelter syndrome (SK) is the most common sex chromosome disorder. Affected males carry an additional × chromosome, which results in male hypogonadism, obesity and an insulin resistance field explaining the frequent association of KS and type 2 diabetes. However, cases of type 1 diabetes (T1D) in KS are rarely reported in the literature. We report a case.
Observation
This is a 31-year-old patient admitted with newly discovered diabetes associated with weight loss. The diagnosis of autoimmune T1D was made based on positive T1D antibodies and the patient was put on insulin. The examination objectified a skinny man with tall stature, small testes and gynecomastia. Hypogonadism was suspected due to the absence of secondary sexual characteristics with a Tanner at G1P2A1. Hormonal assays confirmed hypergonadotropic hypogonadism. SK was then evoked clinically and confirmed by a karyotype showing a chromosomal mosaic 47, XXY/46, XX.
Discussion and conclusion
The association of T1D and KS is still unclear, but studies suggest that patients with KS have a higher susceptibility to autoimmune diseases. This is because low levels of testosterone and high estrogen in KS may predispose hypogonadal males to develop defects in T cell activity that lead to autoimmune disorders, in particular destruction of Langerhans β cells.

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AEP369

Seasonal variation of diagnosis of Type 1 diabetes mellitus: A real phenomenon-Preliminary results

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Introduction
Diabetes is a growing health concern, considered as a worldwilde multifactorial public health challenge especially in developping countries. The concept of seasonality in T1DM diagnosis, has been suggested by different studies, implying the existence of several environmental factors as triggers and potentiators of β-cell destruction. The purpose of this study is to elucidate epidemiological profile and the seasonal variation of type 1 diabetes mellitus (T1DM) diagnosis in our center.
Patients and methods
This is a retrospective and prospective data analysis of 115 patients at T1DM onset, followed up in in the endocrinology department of Oujda's Mohammed VI university hospital. For all statistical tests, P value below 0.05 was pictured as statistically significant.
Results
A total of 115 patients admitted at the onset of T1DM were involved in the study. The overall mean age at diagnosis was 17.3 years ± 8.8. Diabetic ketoacidosis at initial presentation was diagnosed in 54% of patients including 75% cases with pulmonary infection. Classic b-cell autoimmune markers were surveyed ; and 64% were found positive for antiglutamic acid decarboxylase antibodies (GADA).The average of initial hemoglobin A1c value was 11.95 ± 2.15%, and the average serum 25OHD concentration was 14.64 ng/ml ± 6.38. More children were diagnosed with T1DM during the cold months as opposed to the warm months, with non significantly difference between boys and girls ($P = 0.54$). Patients were majoritary born during automne: 24.8% with and the correlation was statistically significant ($P < 0.05$). The number of patients diagnosed with type 1 diabetes was higher during the cooler months of the year compared to the warmer ones. The increase of Vitamin D deficiency during cold months was not statistically significant ($P = 0.17$)
Conclusion
The number of patients diagnosed with type 1 diabetes was higher during the cold months of the year compared to the warmer ones; just as the international reports; implying seasonal viral infections in the progression of the autoimmune process. The global pattern of seasonality of onset of T1DM, puts the local individual studies into a globalc ontext and provides a springboard for further research into aetiological aspects of childhood Type 1 diabetes.

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AEP370

The peculiarities of diabetes in the elderly

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Introduction
The number of elderly diabetics continues to increase and represent a large and great fraction of the elderly and diabetics. Thus the objective of our study is to show the particularities in this population.
Materials and Methods
This is a retrospective study included 107 type 2 diabetic patients aged 65 years and older hospitalized in an Endocrinology-Diabetology and Nutrition department of Mohamd VI university hospital center oujda, over a period of 6 years. The data collection and analysis performed by SPSS V21.
Results
The average age of our patients is 72.5 ± 14% years, with a sex ratio of 0.55. The average duration of evolution is 10 ± 14% years. The reason for hospitalization was dominated by diabetic imbalance in 60% followed by simple ketotic decompensation in 20% of cases. Hypertension and dyslipidemia were present in 67% and 21% of patients respectively. Overweight and obesity were the most frequent abnormalities on clinical examination: 28% and 15% respectively. Mean HbA1c at admission was 10.3 ± 2.3%. Dyslipidemia in 35% of cases. 64% had macroangiopathy: Ischemic heart disease (35%), ischemic STROKE (12.3%), arteriopathy (5%), stroke (13%), 46% had microangiopathy: nephropathy (31%), retinopathy (20%), neuropathy (10%). Therapeutically, the majority of our patients were put on insulin: 65%, Hb1aC in 3 months was on average 8.2 ± 2%.
Discussion-Conclusion
The prevalence of diabetes in the elderly is steadily increasing, and management must be tailored to each patient's individual profile, given the frequency of complications, co-morbidities, and high risk of hypoglycemia.
R Gómez-Huelgas, F Gómez Peralta, L Rodríguez Mañas, F Formiga, M Puig Domingo, J J Mediavilla Bravo, C Miranda, J Ena . Treatment of type 2 diabetes mellitus in elderly patients, Rev Esp Geriatr Gerontol: Mar-Apr 2018;53(2):89 99. doi: 10.1016/j.regg.2017.12.003. D. Graillot V. Quipourt, B. Bouillet, J.-M. Petit, P. Manckoundia, Type 2 diabetes in the elderly: what specificities?,. La Revue de Médecine Interne – Volume 33, Issue 10–2012 doi: 10.1016/j.revmed.2012.06.001
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AEP371

Epidemiological aspects and therapeutic conduct necrosant fungal ear infections: about 20 cases

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Aims
Necrotizing external otitis (NEO) is osteomyelitis of the base of the skull. Previously Pseudomonas Aeruginosa was incriminated in 90% of cases. However, fungal NEO have been emerging in recent years. It is a pathology that occurs primarily in immunocompromised terrain such as diabetic and may affect the patient's functional and vital prognosis.
Materials and methods
A retrospective study of 20 cases of fungal NEO conducted at Sousse ENT department over an 11-year period (2006–2016).
Results
The average age of the patients was 67 years (3 to 90 years). The sex ratio was 1.7. 80% of our patients were diabetic. The average time to diagnosis was of 27 days. The most common clinical signs were intense and sleepless otalgia resistant to medical treatment present in all our patients and otorrhea in 45% of cases. A peripheral facial palsy was present in 5 cases. An infectious biological check-up has been requested in all our patients and has objectified breeding of VS and CRP. A brain and temporal ct scan was performed in all of our patients and showed osteolysis signs in all our patients: endocrine extension was present in 15% of cases, mastoiditis in 25% of cases, extension to deep spaces in 5% of cases and to the parotid lodge in 5% of cases. All our patients have had bacteriological and mycological samplings at admission with initial probabilistic antibiotherapy anti pyocyanic, diabetes balance

and local care. Mycosic origin was confirmed in 19 cases following of mycological samples or histological examination. The sample was negative in one case. The germs found were Candida (47%), Aspergillus sp (47%), and rhizopusoryzae (6%). Pseudomonas aeruginosa was associated in one case. The lack of improvement under antibiotic treatment, the negativity of bacteriological samples as well as mycological results led us to implement an antifungal treatment. The evolution was favorable in 14 patients, 2 were referred for hyperbaric oxygen therapy, 2 were lost of sight and 2 were patients died during treatment.
Conclusion
Diagnosis of mycosic origin of fungal SDO difficult to isolate agent response. The negativity of bacteriological samples and the lack of response to treatment encourages us to take mycological samples. Despite the negativity of these, we are always able to prescribe antifungals as early as possible to preserve the functional and vital prognosis of patients with debilitated terrain.

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AEP372

Atypical presentation of Type 1 diabetes mellitus

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Introduction
Diabetic ketoacidosis (DKA) is associated with Type 1 diabetes mellitus (T1DM), whilst hyperglycemic hyperosmolar state (HHS) with Type 2 (T2DM). HHS has been well described as a presentation of T1DM in children, but not in adults. We present present a case of T1DM presenting in a young adult as HHS, with severe hyperglycemia but without acidosis.
Case report
A 21 year old male presented with a 4 5 day history of weakness, thirst, polydipsia and polyuria. He had vomited once. He was previously well but had received Growth Hormone for idiopathic short stature between the ages 15 18. He has a cousin with T1DM. On examination he was afebrile, pulse 62, BP 125/57, BMI 22. Blood glucose was 993 mg/dl, Na^+ 131 mM, K^+ 5.2 mM, creatinine 1.2 mg/dl, pH 7.353, bicarbonate 23.5 mM, serum osmolality 319 mOsm/kg. Anion gap not measured. Urine ketones 15. HbA1c 10.2%. In view of his age he was treated as for DKA with intravenous fluids and insulin. He displayed substantial insulin resistance and at discharge required a total of 82U daily, about 1.4 U/kg/day, . Subsequently his insulin requirement fell and was 24U daily two months after discharge. Serological studies showed positive anti-GAD and anti-islet cell antibodies at over 2000 [< 5] and over 900 [< 30] respectively. He is now well controlled on treatment with an insulin pump and continuous monitoring system, most recent HbA1c 6.6%. However, his younger sister age 9 has recently been diagnosed with celiac disease. Previous serological testing of our patient for celiac disease was negative but we are now repeating this as well as checking diabetes antibodies in the sister.
Discussion
This patient presented with a picture typical for HHS in T2DM, with severe hyperglycemia but without metabolic acidosis. Urine ketone testing showed minimal ketones, as a result of this case we have introduced blood ketone (betahydroxybutyrate) into the hospital. In spite of his normal weight he exhibited severe insulin resistance presumably as a result of glucotoxicity, but with sufficient residual insulin secretion to prevent ketoacidosis. Whether there is an association with his previous GH treatment is unclear. The recent diagnosis of celiac disease in his sister strengthens the implication of immunogenetic factors.

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AEP373

Diabetic ketoacidosis precipitated by COVID-19 in patient without respiratory symptoms: 2 case reports

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Introduction
Diabetes mellitus (DM) is one of the risk factors associated with severe illness in Coronavirus disease 2019 (COVID-19) leading to increased hospital admissions and mortality. COVID-19 can precipitate hyperglycemic emergencies like diabetic ketoacidosis (DKA) in patients with DM. We report 2 cases of diabetic ketoacidosis (DKA) secondary to COVID-19 with an atypical clinical picture mainly made up of neurological disorders without respiratory signs.
Observations
Case 1: A 67-year-old patient, Type 1 diabetic for 34 years, is admitted for DKA. The symptoms go back 10 days made of asthenia and disorders of consciousness without respiratory signs. On admission the patient was drowsy and afebrile. Hemoglobin A1c was 11%. There was lymphopenia, mild cytolysis, and increased c-reactive protein (CRP). The chest x-ray showed an interstitial syndrome with no obvious pulmonary opacity. The lumbar puncture was normal as well as the cerebral CT scan. In view of the absence of evident factor that precipitated DKA, we performed a SARS-CoV-2 RT-PCR test which had returned positive. The patient was transferred to the COVID unit. The course was marked by repetitive episodes of hypoglycemia with significant reduction in daily insulin doses. The patient improved with PCR negative after 12 days. Case 2: A 57-year-old patient, type 2 diabetic for 23 years on oral antidiabetics, is admitted for DKA. Symptoms can be traced back to a week marked by the onset of asthenia and vomiting without coughing or dyspnea. On admission the patient was subfebrile and drowsy. He even fell from his bed because of the neurological disorders. He had lymphopenia, mild hepatic cytolysis and a slight increase in CRP. On the chest x-ray there was an alveolar-interstitial syndrome. The respiratory condition worsened on the 3rd day of his hospitalization requiring the use of Oxygen therapy. SARS-CoV-2 RT-PCR test returned positive and the patient was transferred to the COVID unit with good evolution after 10 days.
Conclusion
These case reports highlight important issues in DM patients with DKA. First, we documented the variability of the clinical picture of COVID-19. We have recognized patients without respiratory symptoms, with severe metabolic complication. Second, SARS-CoV-2 must be considered as a cause of metabolic decompensation even in patients without respiratory symptoms. In this regard, adequate use of personal protective equipment should be considered in the attention of these patients until SARS-CoV-2 is ruled out.

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AEP374

Wolfram syndrome: A diagnostic challenge

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Introduction
Wolfram syndrome (also known as DIDMOAD syndrome) is a rare, genetic, endocrine disorder characterized by the early onset of diabetes mellitus and optic atrophy. It is frequently associated with diabetes insipidus, deafness and neurological signs.
Observation
A 26-year-old woman was burn out of a consanguineous marriage. Diabetes mellitus was revealed at the age of 6 by ketoacidosis, treated from the outset with insulin therapy. Antiglutamic acid decarboxylase and anti-islet cell antibodies were negative.Three years later, a decline in visual acuity was reported. On ophthalmology evaluation, bilateral optic atrophy associated with pigmentary damage to the peripheral retina were reported. At the age of 12, she presented two episods of generalized tonic clonic seizures (negative etiologic investigation) and was started on antiepileptics. At the age of 15, secondary enuresis was installed and a water deprivation test revealed diabetes insipidus which responds well to desmopressin. Wolfram's diagnosis was brought up. Through audiometry and imitanciometry, moderate hypoacusis was detected with bilateral neurosensory auditory loss. Renal ultrasonography revealed a struggling bladder and dilation of the urinary tract.
Discussion-conclusion
Wolfram syndrome is a rare diffuse neurodegenerative disease, predominantly in the central nervous system and the endocrine abnormalities, causing a complex and disabling syndromic. It constitutes a diagnostic challenge for the diabetologist since diabetes is confused at its onset with type 1 diabetes and is often its first manifestation

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AEP375

Iatrogenic hypercalcemia and depression. A case report

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Introduction
Calcium is an important metabolite. Abnormal blood calcium levels can affect brain function resulting in clinical signs. Iatrogenic hypercalcemia is a disorder rarely described in literature and there are few reported cases of association with neuropsychiatric manifestations. Psychiatric symptoms and abnormal physical symptoms are usually observed with a serum calcium level above 12 mg/dl. Our case report findings suggest the importance of control of serum calcium in patients treated with active vitamin D preparations or calcium supplements.
Case report
We present a clinical case of a 64 years old woman with no significant past medical, psychiatric or substance use history. She was presented at the emergency unit with mental confusion, disorientation, headaches, significant physical weakness, difficulty moving her body, loss of appetite, nausea and vomiting, abdominal pain and constipation. These signs had started last years but were worsened the last months. Medical history: She was diagnosed with primary hypoparathyroidism 40 years ago and was treated with calcium supplements and vitamin D analogs. Last 10 years, she did not have medical control but continued the same dose of drugs by herself. Laboratory tests: calcemia 12.4 mg/dl, PTH 0.6 (8 76 pg/ml) 25OH vitamin D 10.1 ng/ml (> 30). TSH 2.3 (0.4 4.2 mIU/ml). Blood tests, liver and kidney function resulted normal. Head-CT scan resulted normal. Firstly, she was treated with liquids i/v, diuretics and oxygen therapy with discontinuation of calcium supplements and vitamin D analogs. Then she was transferred to Endocrinology Department for further treatment. After no other medical cause was found, depression due to iatrogenic hypercalcemia was diagnosed. During her hospital stay she followed psychotherapy sessions with the psychologist, onwards the psychiatrist started the treatment with antidepressants. After calcium correction, her neurological and psychiatric manifestations were improved. She discharged the hospital in improved condition, under treatment with vitamin D analogs, calcium supplements, vitamin D3, and antidepressants. One and two weeks later she resulted with normal levels of calcium and improvement of physical and mental condition. She continues to be in a stable condition, followed by endocrinologist and psychiatrist.
Conclusion
All physicians must be aware about hypercalcemia and long-term consequences especially depression and mental health, to prevent the lack of diagnosis or misdiagnosis. It is very important periodic monitoring of calcium levels in patients under treatment with calcium supplements and vitamin D.

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AEP376

Pancreatic cancer masquerading as uncontrolled diabetes

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We describe the case of a 77 year old male admitted with acute confusion. He had a background of Type 2 Diabetes Mellitus, alcohol excess, hypertension, and was a heavy smoker. A venous blood gas showed a high anion gap metabolic acidosis (pH 7.327, a modestly elevated lactate at 1.3), a glucose level of > 27.8 mmol/l, with a capillary ketone level of 5.0 mmol/l. His calculated serum osmolality was 276 mmol/kg, although account was not taken of the possibility of concomitant alcohol intoxication which might have led to a higher calculated osmolality. Unfortunately, a measured serum osmolality was not included in the initial blood tests in the emergency department. He was approaching diabetic ketoacidosis, and was likely in a hyperosmolar hyperglycaemic state. A fixed rate insulin infusion was started. Biochemical parameters improved within hours of initiating Insulin, and were accompanied by improvement in symptoms. A urinary tract infection, manifested by urinary retention, was treated. Subsequent history taking revealed significant weight loss and epigastric discomfort in the context of a new Iron Deficiency Anemia. CT imaging revealed a 5.2 cm mass in the tail of the pancreas. CA 19–9 level was 5855 kU/l. His diabetes was reasonably controlled with an HbA1c of 57 mmol/mol one year before admission. Subsequent months saw an alarming rise in his HbA1c, reaching a level of 146 mmol/mol one month prior to admission. Non-compliance was suspected. In our patient the precipitant of HHS may have been a urinary tract infection. He had two well-established risk factors for pancreatic cancer, namely, smoking and Type 2 Diabetes. There are conflicting data regarding the significance of alcohol as a risk factor for pancreatic cancer. Two pooled analyses suggested that, if there is an effect of alcohol, it is small and limited to heavy drinkers. There are suggestions that Diabetes may be a consequence rather than a cause of pancreatic cancer. A recent onset of Diabetes may be an indicator of underlying pancreatic cancer or herald its onset. Here, rapidly worsening glycaemic control, culminating in HHS may have been a harbinger of the pancreatic cancer diagnosis. It is unfeasible to screen every older asymptomatic adult with new onset Diabetes or unexplained deterioration in glycaemic control with cross-sectional imaging. However, healthcare professionals must be alert to the possibility of an underlying pancreatic cancer given its poor prognosis at all stages, especially when there are risk factors and symptoms.

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AEP377

The estimation of comorbid endocrine and metabolic disorders based on CIRS score in emergency workers of the Chernobyl accident having cardiovascular diseases

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Objective was to analyze the place of endocrine and metabolic disorders among other comorbid diseases in the Chernobyl accident emergency workers (EW) who had cardiovascular diseases as main pathology.
Materials and methods
The health state was analyzed in 420 male EW, who worked at the Chernobyl NPP at 1986–1987 yrs, and 188 males not exposed to ionizing radiation (the control group, CG). Patients of both groups had a hospital treatment due to cardiovascular pathology during 2011–2019 yrs. For estimation of comorbid diseases the Cumulative Illness Rating Scale (CIRS) was used.
Results
The CIRS total score was significantly higher in EW comparing with CG (10.3 ± 2.9 vs 8.8 ± 3.0 units, $P = 0.000$). According to relative number of patient with revealed pathology of different CIRS categories, 'Endocrine/ metabolic and breast' ranks 5 following 'Heart' (1), 'Neurological' (2),'Vascular' (3) and 'Musculoskeletal and skin' (4) systems. The rest 7 categories (we did not analyze 'Psychiatric illness') had less patients with corresponding organ systems diseases. In 'Endocrine…' category mild problems (score 1) was revealed in 34.8% EW, moderate problems (score 2) in 15% and severe/extremely severe (score 3–4) in 6.2% EW. Regardless of score number EW did not differ from CG patients (29.8, 13.8 and 5.9% correspondingly). For comparison in CIRS category 'Heart' patients with score 1 was 43.6% EW vs 45.7% CG ($P > 0.05$), score 2–19.5% vs 22.3% ($P > 0.05$) and score 3–4 – 35.2% vs 26.6% ($P < 0.05$). By mean score calculated for every category 'Endocrine…' ranks 4 (0.8 ± 0.9 in both EW and CG, $P = 0.293$) following 'Vascular' (2.5 ± 0.8 in EW and 2.3 ± 1.0 in CG, $P = 0.06$), 'Heart' (1.9 ± 0.9 in EW and 1.7 ± 0.9 in CG, $P = 0.024$) and 'Neurological' (1.6 ± 0.8 in EW and 1.1 ± 1.0 in CG, $P = 0$). Amongst endocrine and metabolic disorders diabetes mellitus, thyroid gland goiters and obesity govern score presence but the score value was determined by diabetes mellitus severity course and body mass index. Thyroid gland goiters were frequent pathology as well but with mild course.
Conclusions
In patients with cardiovascular diseases as main pathology comorbid endocrine and metabolic disorders met sufficiently frequently in EW and non-irradiated patients and had high score value skipping ahead only cardiovascular, neurological and musculoskeletal diseases.
Keywords: emergency workers of the Chernobyl, cardiovascular disease, comorbidity, Cumulative Illness Rating Scale, endocrine and metabolic disorders.

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AEP378

Prescription of Statins in the elderly with diabetes

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Introduction
The prevalence of cardiovascular disease in the elderly is very important. The prevention of cardiovascular risk is essential in order to avoid the morbidity and mortality associated with these diseases. The objective of this study was therefore to assess the frequency of prescription of statins in elderly with diabetes and to analyze the benefit risk ratio of this prescription.
Patients and methods
Retrospective study which involved 94 diabetic subjects aged over 65 years who were hospitalized in the endocrinology department of Mahdia or followed at the outpatient clinic between the month of November and the month of December 2020.
Results
The mean age was 71 ± 5 years with extremes of 65 and 90. All of our patients had type 2 diabetes. The mean duration of diabetes was 12 years ± 8. A quarter of the patients had chronic renal failure (24.46%). Hypothyroidism was found in 14.9% of our patients. The subjects who required treatment with statins according to the recommendations represented 57% of patients, of whom 92.6% were treated. Of these patients, 26.7% achieved the therapeutic goal of LDL-cholesterol according to the level of cardiovascular risk. Patients over 80 years of age accounted for 7.4% of all elderly subjects. None of these patients was prescribed with statins. For patients treated with statins, no adverse effects have been reported despite advanced age and associated comorbidities. No cardiovascular events were noted after the prescription of statins in this cohort. A statin withdrawal was observed in two patients with no obvious medical cause. It would be related to non-adherence to therapy in these patients.
Conclusion
Through this study, we observed good tolerance after taking a statin in diabetic patients despite advanced age with an obvious benefit given the absence of cardiovascular events and the absence of side effects.

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Endocrine-Related Cancer

AEP379

Ectopic cushing's syndrome due to an acinic type parotid carcinoma

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Introduction
Ectopic Cushing's syndrome(ECS) is responsible for 15–20% of all cases of ACTH dependent Cushing's syndrome. We present here a very rare case of ECS due to an acinic parotid carcinoma (ACC).
Presentation
A 44 year old woman with a medical history of metastatic ACC parotid carcinoma and type 1 diabetes mellitus (T1DM), referred to our department, due to cushingoid features, progressive fatigue, inability to walk and severe hypokalcemia (serum potassium (P) 2.4 mEq /l) refractory to replacement. The last four months she gained weight, had difficulties to control her diabetes, inability to climb stairs and became hypertensive. Physical examination revealed a cushingoid appearance, with centripetal obesity, moon face, enlarged supraclavular fat pads, proximal muscle weakness, mild pigmentention and thinning of the skin and pheripheral oedema. Her blood tests revealed hypercortisolemia with loss of diurnal rhythm [cortisol 8pm 64 μg/dl, (< 18 μg/dl), salivary cortisol 8pm 23.2 μg/dl (< 0.783, μg/dl), 24 h UFC 3468 μg (< 120 μg/dl)], high ACTH levels [ACTH 439 pg/ml, (< 60 pg/ml)] and hypokaliemic metabolic alcalosis.(*P* 2.4 mEq/l, ABG's: *ph* = 7.47, PCO_2 = 31 mm/Hg, PO_2 = 105 mm/Hg, HCO_3 = 22.6 mmol/l). Recent imaging revealed extended metastatic disease, with no pathology of pituitary or adrenal glands. The diagnosis of ECS was made and due to the severity of her clinical picture and her rapid deterioration, no further confirmatory test were done and the patient started on fluconazole 400 mg iv/d, metyrapone 3 gr/d, spironolactone 100 mg/d and potassium replacement. Due to the extensive metastatic disease, resection of the tumor was not possible. Eight days later the patient had a remarkable clinical improvement and laboratory findings showed serum and salivary cortisol within the normal range. Five months after the diagnosis of ECS, her hypercortisolemia remained controlled but the patient had bone marrow infiltration and passed away.
Conclusions
Acinic cell parotid carcinoma, an aggressive tumor, is a very rare cause of ECS, with only six more cases to be reported so far. All patients presented with severe weakness and hypokaliemia. Due to the scarcity and the aggressiveness of these tumors, earlier diagnosis and treatment can be still a changeling issue but may affect the outcome.

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AEP380

Multiple metastases of parathyroid carcinoma and papillary thyroid carcinoma in a female patient treated with long-term hemodialysis

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The combination of thyroid and parathyroid carcinoma (PC) are extremely rare. We present a case with metastases of both tumors to the lymph nodes of the neck in a woman who received renal replacement therapy with long-term hemodialysis.
Case report
In 1984, when she was 24 years old, the patient began working at a nuclear power plant as a chemical water treatment operator. The total length of service was 25 years. In 2009 (at the age of 49) the patient presented decreased renal filtration (creatinine 110 μmol/l, GFR 51 ml/min/1.73 m^2) as well as increased PTH (2500 pg/ml (15–65)) and total calcium (3.36 mmol/l (2.15–2.55)). In 2010, the left lower parathyroid gland (PG) was removed, and the left thyroid lobe resected. A histological examination revealed PC (ñT2Nx). Immunohistochemical (IHC) examination revealed the PTH staining, the tumor cell nuclei was immunopositive for parafibromin; the Ki-67 proliferation index was 5%. Over the next 3 years, the PC was in remission. The hemodialysis therapy was started. After 12 months PC progression was diagnosed and a final thyroidectomy was performed along with total parathyroidectomy and central lymph node dissection using intraoperative navigation methods (single-channel gamma detection probe, Gamma Probe 2, and fluorescence angiography with indocyanine green (ICG). During the surgery, the lesion in the thyroid bed on the left showing significant uptake of the isotope (^{99m}Tc-MIBI) and ICG was exposed. Microscopic examination showed a focus of PC in the fatty tissue, and two lymph nodes with subtotal metastases of papillary thyroid cancer (follicular variant). The morphological features of the PC are similar to the histological picture of the PC removed in 2010. IHC examination of the PC revealed diffuse expression of PTH and parafibromin. The Ki-67 proliferation index was 7%. This treatment led to achievement of laboratory targets: PTH 160 pg/ml, albumin-corrected calcium 2.53 mmol/l, Ca^{++} 1.23 mmol/l. Ultrasound, CT with contrast, SPECT/CT, needle washing liquid PTH (more than 5000 pg/ml) demonstrated an ongoing relapse of the disease with multiple metastases of PC to the neck lymph nodes. However, the dimensions of the lesions are not 'target' ones and, in view of the absence of uncontrolled hypercalcemia, follow-up was continued.
Conclusion
We believe it is important to publish different variants of PC and its combinations with other conditions in order to summarize available data and subsequently create clear recommendations for the prediction, treatment and monitoring in this complex group of patients.

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AEP381

Case report: Secondary adrenal insufficiency and primary hypothyroidism following Nivolumab therapy in a patient with metastatic melanoma

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Introduction
In recent years, we have observed significant progress in cancer treatment associated with the development of immunotherapy. Nivolumab, an anti-PD-1 antibody, blocks the interaction between PD-1 and its ligands and inhibits the signaling pathway by preventing the tumor-derived PD-L1 from blocking T lymphocytes. In patients with metastatic melanoma, it is used either in monotherapy or in combination with other drugs. Immunotherapy is associated with the possibility of immune-related adverse effects (irAE) including endocrinopathies (3–23%). Thyroid disorders are the most common. Hypophysitis, adrenal insufficiency and diabetes are possible complications which require immediate treatment. We report the case of

a patient with metastatic melanoma following Nivolumab therapy who developed adrenal insufficiency and primary hypothyroidism.
Case report
63-year-old male with personal history of melanoma metastatic to lymph nodes, liver and spleen has received treatment with nivolumab every 15 days for 5 months. He was referred to our department for fatigue, appetite loss and weight loss of 10 kg in the last 2 months and relative hypotension. Laboratory data revealed elevated thyroid-stimulating hormone and low free thyroxine and positive TPO antibodies; low morning cortisol without correspondence increase of ACTH. Other pituitary hormones were normal. No enlargement of the pituitary gland was apparent by magnetic resonance imaging. The patient was diagnosed with nivolumab induced secondary adrenal insufficiency and primary hypothyroidism. Hormone replacement with levothyroxine (100 mg/day) and oral hydrocortisone (20 mg/day) was started. Nivolumab was discontinued, resulting in amelioration of his symptoms and hydrocortisone was successfully tapered. Nowadays, the patient is on treatment with levothyroxine replacement and has restarted nivolumab every 15 days, metastatic lesions gradually have decreased in size without any additional treatment. During follow-up, the patient presented normal cortisol response to the Short Synacthen Test.
Conclusions
In the management of patients receiving immunotherapy, awareness of the possibility of irAE is crucial. Many of the irAE are linked to the endocrine system. Before anti-PD-1 treatment introduction, an evaluation of the patient for autoimmune diseases should be performed. Thyroid antibodies and type 1 diabetes-related antibodies are considered risk factors and therefore—when detected—organ-specific immune complications should be expected. We suggest routine monitoring of fasting blood-glucose, blood pressure and serum sodium and thyroid function during nivolumab and other cancer immunotherapies. When unexpected fatigue, hypoglycemia, hypotension or hyponatremia appeared, adrenal deficiency should be taken into consideration.

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AEP382

Nutritional assessment and Ghrelin system as predictors of clinical evolution in gastro-enteropancreatic neuroendocrine neoplasms

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Background
Patients with neuroendocrine neoplasms (NENs) might present with malnutrition due to the tumor itself and/or its treatment. Poor nutritional status and weight loss can lead to poor outcomes, including decreased quality of life, increased complication rates and mortality. Ghrelin is an orexigenic hormone, which is implicated in appetite regulation, body weight, inflammation and immune cell activation. Its gastric secretion mainly depends on the nutritional status of the body, consequently, it may affect the clinical evolution and prognosis of these patients.
Objective
To evaluate nutritional parameters of patients with gastroenteropancreatic (GEP)-NENs and to explore the influence of the mRNA expression of some ghrelin system components in the nutritional status of GEP-NENs patients and their clinical outcomes.
Methods
Clinical data of 104 patients was collected. The mRNA expression of some ghrelin system components was determined using qPCR in 64 tumor samples. Statistical analysis was performed with SSPS v.24.
Results
In our cohort, decreased BMI was associated with relapsed disease and decreased albumin with increased mortality($P < 0.05$). Patients who currently remain disease-free had increased BMI at diagnosis compared with patients with active disease ($P < 0.05$); the survival rate in our cohort was 95 months. The presence of metastasis at diagnosis tended to related with BMI and serum LDL levels. Almost one third of patients (27.8%) presented altered nutritional parameters at diagnosis. Patients with gastric NENs tended to present with lower levels of serum ferritin, lymphocites and total cholesterol compared with other locations. The molecular tumor expression of ghrelin tended to correlate with some nutritional parameters including weight at diagnosis, serum ferritin, total cholesterol and LDL levels.
Conclusions
BMI, serum nutritional parameters and the molecular expression of some ghrelin system components might be related with the clinical evolution of GEP-NENs patients. Routine nutritional evaluation and early nutrition intervention should be implemented to improve the outcome in these patients. Further studies are still required.

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AEP383

Paraganglioma of the basis cranii due to somatic mutations ind SDHB and PTEN genes

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Head and neck paragangliomas (HNPGLs) are a type of neuroendocrine tumour. They arise from the sympathetic ganglia and can be either sporadic or due to hereditary syndromes (up to 40%). Most HNPGLs do not produce significant amounts of catecholamines[1]. Often, HNPGLs are detected in late stages due to compression or infiltration of cranial structures[1]. We report a case of a paraganglioma of the basis cranii due to somatic variants of SDHB (succinate dehydrogenase gene B) and PTEN (phosphatase and tensin homolog) with both an unusually serious presentation and a surprisingly good outcome. A 39-year-old Caucasian woman with no prior medical history was found unconscious and emaciated in her home. In the intensive care unit (ICU) the patient was treated for multi-organ failure with multiple complications and difficulties in stabilizing her blood pressure with values up to 246/146. She spent a total of 72 days in the ICU and on the 31st day clinical assessment revealed foramen jugulare syndrome and paralysis of the right n. facialis. A CT cerebrum, MRI, PET-CT, MIBG-scintigraphy and a Ga-Dotatoc PET confirmed a right-sided tumour of the basis cranii of 6.5 × 4.5 cm. A urine test showed high amounts of norepinephrine (35.1–45.4 nmol/l, ref < 1.09 nmol/l) and a tumour biopsy confirmed the diagnosis of a paraganglioma. Phenoxybenzamine and Labetalol was used to stabilize blood pressure. She underwent two tumour embolization treatments before total tumour resection on day 243. Plasma norepinephrine normalised after surgery (0.77 nmol/l, ref: < 1.09 nmol/l) as did her blood pressure (approx. 130/80). The damage to the cranial nerves was permanent. The patient has made a remarkable recovery and will need rehabilitation to improve her physical performance. Next generation sequencing (NGS) of tumour tissue revealed somatic mutations of SDHB (c.565T > G, p.C189G) and PTEN (c.834C > G, p.F278L). The NGS genome panel showed no germline variants and whole genome sequencing was negative. An SNP-array of tumour DNA showed loss of heterozygosity of p.1 (including SDHB) and p.11. It is very rare that a patient with a somatic variant in the SDHB gene does not hold a germline variant. SDHB variants are often associated with malignancy and future follow-up with scans and clinical assessments will show whether this is a case of a benign or malignant paraganglioma.
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AEP384

Oncogenic role of splicing factor SRSF2/SC35 in pancreatic and prostate adenocarcinomas

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Introduction
Alternative splicing allows the generation of multiple RNA isoforms from a single pre-RNA molecule, and thereby contributes to a multitude of physiological processes, but can also be involved in many diseases, including cancer. Indeed, disruption of alternative splicing has been linked to key cancer features, such as tumor growth, metastasis and hormone responsiveness and is increasingly regarded as a novel and transversal cancer hallmark. The dysregulation of the splicing machinery could constitute the underlying cause in many of these alterations and, consequently, is an attractive target of study. In this context, it has been previously described that a member of SR splicing factor family, SRSF2, play a relevant role of as an oncodriver in various cancers like hepatocellular carcinoma and myelodysplastic syndromes.
Objective
We aimed to investigate the presence, relevance and potential role as diagnostic/prognostic biomarker and therapeutic target of SRSF2/SC35 in two tumoral pathologies strongly influenced by the patient endocrine-metabolic status: 1) prostate cancer (PCa), the most diagnosed tumors among men worldwide; and 2) pancreatic ductal adenocarcinoma (PDAC), one of the most lethal cancers.
Methods
The expression of SRSF2 was measured in tumor vs. non-tumor adjacent tissue in a set of 79 PDAC and 45 PCa human samples. The results were validated using publicly available external cohorts. The role of this splicing factor was assessed *in vitro* by analyzing a set of functional parameters in response to siRNA-induced SRSF2-silencing in various PDAC and PCa cell lines.
Results
Our data revealed that SRSF2 was overexpressed in both tumors and its expression was associated to poor prognosis and relevant malignancy features, including tumor stage, presence of lymph node invasion and/or metastasis, which was confirmed using independent cohorts of patients. SRSF2-silencing significantly reduced cell migration, proliferation, invasion, and colony formation in PDAC and PCa cell lines in comparison with control cells through the alteration of key oncogenic signaling-pathways and the modulation of the expression of relevant genes.
Conclusions
These results suggest a role of the splicing factor SRSF2 in both pancreatic and prostate adenocarcinoma oncogenesis and aggressiveness, thus paving the way to explore its possible value as a biomarker and therapeutic target in both types of cancers.
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AEP385

Ectopic ACTH secretion from a metastatic gastric carcinoma with neuroendocrine component

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Background
Ectopic ACTH secretion accounts for 9–18% of ACTH dependent Cushing's' syndrome. The most common causes are intrathoracic neuroendocrine tumours. Gastric tumours as a cause of ectopic ACTH secretion are remarkably rare.
Case report
A seventy-five-year-old gentleman complained of a four month's history of epigastric discomfort, anorexia, and weight loss. He was a known diabetic and hypertensive. A computed tomography (CT) scan showed diffuse enhancement and thickening of the pylorus up to the pyloric antrum for a length of eight centimetres with large hepatic and coeliac lymph node metastases. An oesopho-gastro-duodenoscopy showed an ulcerating mitotic lesion on posterior antral wall, extending from the antrum through the pylorus and into the first part of the duodenum. Within two weeks he developed recurrent vomiting, new onset lower limb oedema and orthopnoea. His diabetes and hypertension had suddenly become difficult to control. Blood results showed severe new onset hypokalaemia of 1.75 mmol/l with metabolic alkalosis. ECG showed global T wave inversions and U waves. The combination of hypokalemia, metabolic alkalosis and a stomach lesion triggered a series of investigations to assess if severe hypercortisolaemia could be the underlying diagnosis. A 9am cortisol level was 3325 (145–619 nmol/l), overnight dexamethasone suppression test 2602 (< 50 nmol/l), 24 hr urinary cortisol 4316 (57.7–806 nmol/24 hrs) and ACTH levels 358 (10 48 pg/ml). Gastric biopsies showed a moderately to poorly differentiated intestinal-type adenocarcinoma with neuroendocrine differentiation. The poorly differentiated component expressed neuroendocrine markers CD56, synaptophysin and chromogranin, the latter being weakly expressed. Ki 67 index was 70%. It was concluded that the patient had a non-neuroendocrine neoplasm with a focal neuroendocrine component secreting ACTH. The hypokalaemia was managed with aggressive central and peripheral potassium replacement and spironolactone. Metyrapone was started to block adrenal cortisol synthesis with doses being cautiously titrated according to his 24 hour urinary cortisol results. These decreased to 1254 and 1822 nmol/24hrs. Insulin was started. He was unfit for surgery and was planned for six cycles of a combination of Carboplatin/Etoposide chemotherapy once every 3 weeks. He received three cycles of Carboplatin but his health deteriorated. Repeat CT scan showed an increase in liver metastases and adrenal hypertrophy. He was given adequate pain relief, fluids and he died a few days later.
Conclusion
This case highlights the accelerated presentation, rapid malignant progression and poor prognosis of hypercortisolism due to ectopic ACTH secretion.

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AEP386

Testosterone replacement therapy(TRT) and prostate cancer

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Title – Testosterone replacement Therapy (TRT) and prostate cancer
Hypogonadism is a condition with low serum testosterone level, which can manifest as depression, lack of libido, decreased bone mineral density and muscle weakness In patients with hypogonadism returning serum testosterone to normal levels results in improvement in cognition, mood, sexual function, physical performance, normalises bone density and erythropoiesis.
Case
We describe the case of 64-year-old man who was diagnosed with primary testosterone deficiency in the year 2008. His past medical history also includes essential hypertension, asthma, obesity and fatty liver. He does not have a family history of malignancy. He started on Testosterone replacement Therapy (TRT) in the form of Testogel and it was titrated to achieve and maintain optimum testosterone level. In October 2019, we noticed PSA (Prostate specific Antigen) raise to 5.2 mg/l and patient was referred to urology team. At that time, he did not have lower urinary tract symptoms; he had good erectile function on testosterone supplement, in urology he had a MRI of prostate and Trans perineal biopsy which came back as prostate adenocarcinoma which was of intermediate risk. Testosterone replacement was stopped; Following a Multidisciplinary team meeting Oncologists managed him for his Prostate cancer. He received Brachytherapy and Radiotherapy with good response. Oncologists suggested to us that testosterone replacement therapy can be restarted not earlier than 18 months and only if PSA level will remain within the normal range.
Key learning
There is no proven correlation between normal or high serum testosterone levels and prostate cancer. However, regular checking of PSA level helps to diagnose prostate cancer early. In this case, the patient was referred to urology department immediately after the abnormal test result and had a good outcome Some studies showed that ~ 15% of hypogonadial men with PSA lower than 4.0 mg/l will have prostate biopsy showing cancer. Men with low testosterone levels have also shown to have worse prognoses in prostate cancer with higher grade, more aggressive cancer while men with normal or higher testosterone level would more likely to have less advanced forms of cancer. The possible explanation is that lower levels of testosterone would not activate the androgen response elements in the PSA promoter, so these patients will be diagnosed much later. PSA can raise shortly after initiation of TRT but overall there is no proven increased risk of developing prostate cancer while on TRT.

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AEP387

MiR-146b, -21, -221, -222, -181b expression is related to clinicopathologic features of PTC

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Introduction
Inadequately managed papillary thyroid carcinoma (PTC) patients result in potentially higher fatal outcomes due to a lack of sufficient prognostic data/markers, inadequate periodic individualized follow-up risk assessments and/or insufficient initial treatment. MiR-146b, -21, -221, -222, -181b are potential biomarkers for risk stratification of PTC.
Aim
The aim of our study was to analyze expression of five miRNA molecules (miR-21; miR-221; miR-222; miR-146b; miR-181b) in PTC formaline fixed paraffin embedded (FFPE) tissue samples and evaluate the relation to clinicopathological parameters.
Methods
We analyzed expression of miR-221, miR-222, miR-146b, miR-21, miR-181b in the 312 patients FFPE PTC tissue samples and evaluated their expression relationship with clinicopathological parameters.
Results
MiR-221, miR-222 expression was higher in the PTC tissue samples with extrathyroidal extension (P = 0.049, 0.003, respectively). Higher expression of miR-21 was related to unifocal lesions (P < 0.011), and concomitant autoimmune thyroiditis (0.007). In a group of PTC patients with T1a and T1b sized tumors, the expression of miR-146b, miR-21, miR-221, miR-222 in PTC tissue samples was lower than in patients with T2, T3, T4(P = 0.032; 0.0044; 0.003; 0.001, respectively). Patients with lymph node metastases had higher expression of miR-21, -221, -222 and -181b (P < 0.05). High expression of miR-146b, miR-221, miR-21 panel is associated with decreased overall survival (Log rank P = 0.19).
Conclusion
5 analyzed miRNA's expression have significant relations to clinicopathologic parameters so further investigations of these molecules are necessary while searching for prognostic PTC biomarkers.

Table 1. Clinicopathological features of PTC and miRNAs (-146b, -221, -21, -222, -181b) expression in PTC tissue samples

Relative expression 2^-ΔCt: MEAN ± SD					
PTC clinicopathological feature	miRNA-146b	miRNA-21	miRNA-221	miRNA-222	miRNA-181b
Multifocality					
Single (*n* = 244; 79.20%)	3.673 ± 0.211	1.658 ± 0.096	0.843 ± 0.595	2.548 ± 0.130	0.0006 ± 0.00003
Multiple (≥ 2) (*n* = 68; 21.80%)	3.123 ± 0.343	1.177 ± 0109	0.605 ± 0.0629	2.196 ± 0.188	0.0006 ± 0.00004
P	0.327	0.011	0.054	0.416	0.850
Extrathyroidal extension					
Yes (*n* = 131; 41.99%)	3.289 ± 0.280	1.644 ± 0.113	0.905 ± 0.087	2.606 ± 0.156	0.0005 ± 0.00004
No (*n* = 181; 58.01%)	3.383 ± 0.237	1.487 ± 0.109	0.709 ± 0.055	2.374 ± 0.152	0.0006 ± 0.00004
P	0.086	0.082	0.049	0.030	0.108
T (TNM)					
T1a, T1b (*n* = 160; 51.28%)	3.220 ± 0.241	1.386 ± 0.933	0.642 ± 0.477	2.158 ± 0.136	0.0007 ± 0.00004
T2, T3 (*n* = 152; 48.72%)	3.880 ± 0.269	1.721 ± 0.128	0.943 ± 0.842	2.786 ± 0.171	0.0006 ± 0.00004
P	0.032	0.044	0.003	0.001	0.317
Lymph node metastases					
Yes (*n* = 48;15.38%)	4.488 ± 0.539	2.054 ± 0.0288	1.108 ± 0.188	3.496 ± 0.355	0.0008 ± 0.00009
No (*n* = 264; 84.62%)	3.370 ± 1.889	1.458 ± 0.077	0.731 ± 0.046	2.276 ± 0.109	0.0006 ± 0.00003
P	0.057	0.014	0.037	< 0.0001	0.01
Autoimmune thyroiditis					
Yes (*n* = 78; 25%)	4.155 ± 0.416	1.889 ± 0.198	0.794 ± 0.091	2.720 ± 0.266	0.0006 ± 0.00006
No (*n* = 234; 75%)	3.350 ± 0.197	1.440 ± 0.082	0.790 ± 0.676	2.388 ± 0.116	0.0006 ± 0.00003
P	0.102	0.007	0.675	0.546	0.818

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AEP388

Clinical, genetic & imaging characteristics of mediastinal paraganglioma – a case series

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Introduction
Paragangliomas (PGLs) are neuroendocrine tumours that arise from neural crest-derived chromaffin cells. They can develop anywhere these cells exist from the base of the skull to the pelvis. All PGLs have neuro-secretory potential and can produce symptoms due to catecholamine excess. While the majority are benign they do have malignant potential. Mediastinal PGLs are rare and often have a strong genetic predisposition. A higher proportion of these tumours can be secretory when comparted to head and neck PGLs. Novel functional imaging modalities have increased tumour detection rates. Surgical resection is often challenging due to their proximity to vital structures. Here we present our experience of 8 patients with mediastinal PGLs with a median of 5.5 years follow up (range 2–16 years).
Case descriptions
We report 8 cases (3 female, 5 male) of mediastinal PGLs in patients aged 19–81 years (median age 58). 5 presented with a solitary mediastinal PGL, 2 with multiple lesions and 1 with metastatic spread. 4/8 were diagnosed as a result of cascade screening. These all had a heterozygous pathogenic SDHB variant and were asymptomatic. Genetic analysis of the remaining 4 patients revealed no genetic abnormality in 3/8 and an SDHA variant of uncertain significance in 1/8. 3/8 were diagnosed incidentally and the remaining 1 patient was diagnosed due to symptomatic catecholamine excess. Serum or urinary samples demonstrated catecholamine excess in 37.5% of cases. The functional imaging modalities utilised included FDG PET (2/8), DOTATATE PET (3/8) and MIBG scintigraphy (7/8). Gallium DOTATE and FDG PET CT demonstrated 100% sensitivity in identifying these tumours. MIBG scanning demonstrated 57% sensitivity. 6/8 underwent surgery. 2 patients were diagnosed with ischaemic heart disease pre-operatively and underwent a simultaneous coronary artery bypass graft. Post-operative follow up ranges from 1 to 16 years. No recurrent or metastatic disease has been identified in these 6 cases. 1/8 was managed conservatively. Peptide receptor radionuclide therapy was used to treat 1 patient with metastatic disease. Latest imaging demonstrates stable disease in these 2 cases
Conclusion
Mediastinal PGLs are rare but carry a strong genetic predisposition. More are being identified due to improved functional imaging techniques. Interpretation of these imaging modalities requires careful consideration. A high proportion of mediastinal PGLs can be secretory. Surgical intervention should be performed in a specialist cardiothoracic centre and a multidisciplinary approach is needed for risk stratification, pre- and post-operative management. With this approach excellent outcomes can be achieved.

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AEP389

Levels of Pro-inflammatory biomarkers in Papillary thyroid cancer

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Introduction
Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy. Apart from genetics, autoimmunity has been implicated in its pathogenesis. But, reports have been conflicting ranging from causative, protective and

neutral role of immunomodulation. In this context, we set out study the role of Pro- inflammatory cytokines in PTC in South Indian population.
Material and methods
This pilot prospective case-control study was conducted on surgically managed PTC patients. Institutional ethical committee approval was obtained. Diagnosis of PTC was based on imaging, fine needle aspiration cytology and later confirmed by histopathology. Exclusion criteria were subjects with any systemic or chronic inflammatory disease or any medication which interferes with the normal function of the hypothalamic-pituitary-gonadal axis. Serum samples were collected from 45 PTC subjects and 43 age matched healthy controls. Interleukin-6 (IL-6), Tumour necrosis factor-alpha (TNF-α) and high sensitive C reactive protein (hsCRP), leptin levels were measured in all serum samples. Statistical analysis was performed by one way ANOVA with Dunnet's test and Pearson correlation tests.
Results
The mean hSCRP level in PTC and controls were 18.4 ± 3.1 mg/ml and 5.3 ± 1.2 mg/ml respectively. The mean TNF-α level, IL-6 level and Leptin levels were 294 ± 31 pg/ml, 13.5 ± 4.5 pg/ml and 1.96 ± 0.7 ng/ml respectively. Serum leptin level in controls was 3.6 ± 1.7 ng/ml. There was statistically significant difference of all the pro-inflammatory cytokines compared to controls (P value < 0.05) with negative correlation for leptin levels.
Conclusions
Our study shows raised titers of pro-inflammatory markers – IL-6, TNF-ń and hsCRP, while reduced leptin levels correlated with PTC suggesting a contributory role. But, the exact immuno-modulatory role of these markers in thyroid cancer needs more research.
Keywords: Papillary thyroid cancer; Tumour necrosis factor; Interleukin-6; Goiter; Auto-immunity; Leptin.
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AEP390

Assessment of different markers of ovarian reserve in women with differentiated thyroid cancer treated with radioactive iodine

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Objective
It has been shown that treatment with radioactive iodine (RAI) of women with differentiated thyroid cancer (DTC) is connected with decreased serum concentration of anti-Müllerian hormone (AMH). To date, others markers connected with ovarian reserve have not been investigated yet. Therefore, the aim of the present study was to evaluate the effect of RAI on serum concentration of inhibin B, follicle stimulating hormone (FSH), AMH and antral follicle count (AFC) in women with DTC treated with RAI.
Materials and methods
We examined 25 women at the median age of 33, who were treated with single dose of RAI. Serum concentrations of inhibin B, FSH, AMH and AFC were assed at baseline and one year after RAI treatment.
Results
We found decreased serum levels of AMH (P = 0.02), inhibin B (P = 0.03) and AFC (P = 0.03) but not FSH (P = 0.23) one year after RAI treatment in comparison to the baseline.
Conclusions
We concluded that RAI treatment have signifficant impact on serum concentrations of AMH, inhibin B and AFC in premenopausal women with DCT, therefore this markers are usefull for assesment of ovarian reserve. Additionally, an assesment of ovarian reserve markers and the protection of oocytes, prior to treatment with RAI, should be considered in premenopausal women.
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AEP391

A rare cause of postmenopausal hirsutism – granulosa cell tumor of the ovary

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Androgen excess in post-menopausal women usually results from ovarian or adrenal pathology. Identifying pathology is significant as many ovarian tumors can be malignant in nature. We report a case of granulosa cell tumor which presented with virilizing signs. A 66-year-old postmenopausal lady presented with temporal hair loss and weight gain. She had to drop out of her church choir as she had a change in her voice. She was concerned about her facial hair growth which was significantly affecting her social life. She had no known comorbidities and her past medical and family histories were noncontributory. She was on over the counter herb-based nutritional supplements. On examination, she appeared muscular, had temporal recession of hair, had a deep low-pitched voice. Modified Ferriman – Gallwey score was 3/36; involved mainly face. Biochemical evaluation revealed FSH – 44 mIU/ml, LH- 14.71 mIU/ml, Total testosterone – 530.3 ng/dl, Free testosterone – 14.43 ng/dl, bioavailable testosterone – 368 ng/dl, SHBG – 17 nmol/l, DHEA-S – 329.03 ng/ml, androstenedione – 1.72 ng/ml, TSH – 3.06 mIU/l. Renal and liver functions were normal. Ovaries and adrenals were normal on abdominal MRI; there were multiple uterine fibroids. A re-evaluation after a month of discontinuing the nutritional supplements revealed persistently high testosterone of 517 ng/dl, free testosterone – 10.9 ng/dl, bioavailable testosterone – 279 ng/dl, and a free androgen index of 59.2%. 8 am cortisol was 6 mg/dl. GnRH suppression with GnRH analogue was conducted. A reduced level of testosterone (150 ng/dl) post GnRH suppression suggested an ovarian source of testosterone. She was suggested to undergo bilateral salpingo-oophorectomy along with hysterectomy. Pathologists were requested for careful inspection of ovaries. Histopathology revealed granulosa cell tumor of the ovary measuring 1.2 cm × 1 cm with no significant nuclear atypia along with uterine leiomyoma and adenomyosis. The tumor was limited to one ovary. On follow-up, after a month, her voice improved and there was a decrease in hair-fall and change in body habitus. Androgen secreting tumors form about 1% of all ovarian tumors. Granulosa cell tumors belong to sex cord-stromal tumors. Generally, they secrete estrogen but rarely may secrete androgens. Due to the malignant behavior of the tumors, early diagnosis plays an important role.
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AEP392

Malignant pheochromocytomas and paragangliomas: clinical and pathological characteristics of a tertiary hospital' cohort

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Introduction
Pheochromocytomas (PHEO) and paragangliomas (PGL) are neuroendocrine tumors arising from the chromaffin cells of the adrenal medulla and extra-adrenal autonomic paraganglia, respectively. They are rare and generally benign neuroendocrine tumors. However, malignancy (defined as the evidence of metastases in nonchromaffin sites distant from the primary tumor) occurs in 2 to 26%. Malignant PHEO and PGL are very challenging malignancies associated with poor prognosis.
Objective
Descriptive analysis of the clinical and pathological characteristics of patients with malignant PHEO and PGL followed since 1987 at the Endocrinology Department of a tertiary hospital.
Material and methods
Retrospective cohort study based on the clinical files with clinical, biochemical, imaging, histologic examination, genetic and overall survival characterization.
Results
13 patients, mean age at diagnosis 40.77 ± 16.80 years, 53.8% female. At diagnosis: 10 (76.9%) patients with PHEO(2 of them with bone metastasis), 2 (15.4%) with PGL and 1 (7.7%) patient with PHEO and PGL. Diagnosis made by: hypertension difficult to control in 7 (58.3%) patients, symptoms related to the mass in 3 (25%) and incidentaloma in 2 (16.6%). 5 (50%) patients presented elevated urinary and plasma metanephrines, 3 (30%) elevated plasma metanephrines (with normal urinary metanephrines) and 2 (20%) increased urinary metanephrines (without plasma metanephrines results). On CT only one patient had tumor size < 4 cm, 4 (50%) had heterogeneous enhancement and 2 (25%) had necrosis suggestive areas. All patients underwent surgical treatment. In histologic examination, the mean PASS score was 6.50 ± 2.77 and only 1 (12.5%) patient had a PASS score < 4. Metastasis occurred 8.00 ± 6.15 years after diagnosis: bone (n = 3), pulmonary (n = 2), peritoneal (n = 2), kidney (n = 1), pancreas (n = 1), liver (n = 1) and contralateral adrenal

gland (n = 1). A genetic study was carried out in 9 patients (MAX, RET, SDHAF2-B-C-D, TMEM127, VHL, NF1) and only 1 was positive for NF1. 2 (15.4%) patients died from complications of the disease, 1 (7.7%) died from pneumonia and 10 (76.9%) are being followed, only one of them without active disease. Mean survival was 13.46 ± 11.98 years.
Conclusion
PHEO/PGL are neuroendocrine tumors with aggressive potential that is very difficult to predict. In this cohort, regarding malignant PHEO/PGL, 83% had symptoms, 88.9% tumors > 4 cm and 87.5% PASS score ≥ 4, characteristics that seem to be more frequently associated with malignancy. Long-term follow-up is essential, as metastases can occur several years after diagnosis. In our data, metastases occurred up to 18 years after diagnosis.

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AEP393

Severe hypoglycemia: First manifestation of an advanced hepatocellular carcinoma

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Background
Hypoglycemia is a well-established as a serious paraneoplastic complication of hepatocellular carcinoma (HCC). However, hypoglycemia presenting the first presentation of HCC is not frequent. In this regard, we present the case of a patient who had hypoglycemia as first manifestation of HCC.
Observation
A 55yearold man presented to the Emergency Department with loss of consciousness preceded by dizziness, weakness and blurred vision due to severe hypoglycemia (20 mg/dl), from which he recovered after treatment with intravenous glucose. Then, he was admitted to our department. This symptomatology occurred for one month twice a week. He denied any recent alcohol consumption or the use of other drugs. Past medical history included only schizophrenia treated with Haloperidol and Trihexyphenidyl since 25 years. The patient was lethargic and his BMI was 18 kg/m^2. Clinical examination noted a hard and irregular hepatomegaly with collateral venous circulation. No splenomegaly was found. His cardiovascular and respiratory system findings were within normal limits. Laboratory testing revealed hypoglycemia as documented by a very low serum glucose 1.04 mmol/l, serum creatinine 52 µmol/l, serum glutamic oxaloacetic transaminase level of 243 IU/l and serum glutamic pyruvic transaminase level of 71 IU/l. The patient's insulin level was < 0.1 IU/ml and the blood cortisol level was elevated, thus excluding respectively the diagnosis of insulinoma and adrenal *insufficiency*. The hepatitis B surface antigen level and the test for the hepatitis C virus antibody were negative. Abdominal ultrasound revealed enlarged dysmorphic liver, seat of multiple nodules saving no segment. Computed tomography revealed multiple hepatic lesions consistent with multifocal multicentric HCC and multiple pulmonary metastases. Subsequent investigations showed serum α-fetoprotein more than 4000 UI/ml (normal range < 4 UI/ml), IGF1 = 0.001 ng/ml, and IGF2 = 561 ng/ml. Therefore, the diagnosis of HCC and non-islet cell tumor hypoglycemia (NICTH) was considered. Initially, the patient was treated with continuous 10% dextrose infusion and due to the advanced disease stage, he was not a candidate for surgical or palliative cytoreductive therapies. He received only palliative treatment, including oral prednisolone 30 mg once daily in addition to frequent high complex carbohydrate meals with some improvement in the severity of hypoglycemia.
Conclusion
Hypoglycemia due to NICTH is an established paraneoplastic complication of HCC. The prognosis for metastatic or unresectable HCC is poor. The use of frequent, high complex carbohydrate meals and oral steroids are options for management of this condition.

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AEP394

Untreated phaeochromocytoma and co-existing severe pulmonary hypertension: Friend or foe?

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Phaeochromocytomas are neuroendocrine neoplasms originating from chromaffin cells of the adrenal medulla, causing 0.1–0.2% cases of hypertension. Although rare, phaeochromocytoma is potentially life-threatening, leading to hypertensive crises if unrecognised or mismanaged. Chronic thromboembolic pulmonary hypertension (CTEPH) is a potential complication of thromboembolic disease, usually resulting from ongoing vascular obstruction following pulmonary emboli. We report a complex case of a patient with phaeochromocytoma and CTEPH and discuss unique management challenges. A 56-year-old lady was referred to Endocrinology in July 2017 following an incidental finding of a 2.9 cm right adrenal nodule on CT pulmonary angiogram. She was diagnosed with a pulmonary embolism in 2016, and also had a diagnosis of dilated cardiomyopathy, attributed to excess alcohol intake. She had no symptoms suggestive of catecholamine excess (palpitations, chest pain, episodic pallor), and was taking Ramipril, Bisoprolol, Ivabradine and Rivaroxaban. Examination revealed multiple cutaneous neurofibromas, blood pressure was 115/70 mmHg. Biochemical investigations showed elevated plasma metadrenalines (1431 pmol/l, range 80–510 pmol/l), normetadrenalines (3452 pmol/l, range 120–1180 pmol/l) and 3-methoxytyramine (205 pmol/l, range 0–180 pmol/l), consistent with a diagnosis of phaeochromocytoma. Testosterone, dehydroepiandrosterone sulphate and androstenedione levels were within normal range. A MIBG scan showed solitary uptake in the region of the right adrenal gland, with no extra-adrenal lesions. Bisoprolol was stopped, and phenoxybenzamine was up-titrated to 20 mg twice daily. She was referred for adrenalectomy but declined surgery despite extensive counselling about the risks of untreated phaeochromocytoma. In May 2020, she was referred to the regional pulmonary hypertension service due to deteriorating respiratory status and syncope with hypotension. Escalation of therapy with systemic vasodilators was pursued, and potential lung transplantation was discussed. She remained significantly hypotensive despite stopping all anti-hypertensives and having ongoing catecholamine excess from untreated phaeochromocytoma. Following multidisciplinary discussions between endocrinologists, respiratory physicians, endocrine surgeons and anaesthetists, the difficult decision was reached that due to poor physiological reserve, simultaneous lung transplantation and adrenalectomy would carry significant mortality risk and was therefore not performed. This is a fascinating case of unique dual pathology and underlying physiological paradox. Treatment of CTEPH creates vasodilatation and anti-sympathetic effects, thereby ameliorating symptoms of increased right ventricular pressure. In this patient, the presence of catecholamine excess leading to alpha-adrenergic overstimulation and subsequent vasoconstriction was probably a life-sustaining mechanism, allowing maintenance of some cardiac output following intensification of pharmacological treatments for CTEPH. This case also adds to growing evidence justifying biochemical screening for phaeochromocytoma in asymptomatic patients with neurofibromatosis, despite it not being recommended in existing guidelines.

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AEP395

131I-MIBG treatment in malignant pheochromocytoma: A case report

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Introduction
A pheochromocytoma is a tumor arising from adrenomedullary chromaffin cells that commonly produces one or more catecholamines. About 80 to 85% of chromaffin-cell tumors are pheochromocytomas. It is recommended that initial biochemical testing should include measurements of plasma free metanephrines or urinary fractionated metanephrines. ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy is a functional imaging modality, in patients with increased risk of metastatic disease.[1] Radiolabelled MIBG treatment is indicated in tumours showing adequate uptake and retention of the radionuclide and these include pheochromocytomas, paragangliomas and medullary thyroid cancer.[2]
Clinical case
In 2015, a 50 year-old woman, with hypertension was sent to Endocrinology practice in the setting of palpitations, headache, flushing

and uncontrolled blood pressure values for 3 months, over an incidental discover (from an abdominal computed tomography – TC) of an adrenal nodule (33 × 36 × 40 mm) with extensive central necrosis suggestive of pheochromocytoma. Laboratory workup revealed normal plasma fractionated metanephrines and 24-hour urine fractionated metanephrines and catecholamines . ^{123}I-MIBG scintigraphy showed high uptake in the right adrenal gland, confirming pheochromocytoma diagnosis. The patient started α-blockade with phenoxybenzamine 10 mg bid and was submitted to right adrenalectomy. Histology was compatible with pheochromocytoma (Pass score: 3). In 2019, routine surveillance laboratory workup showed increased urinary metanephrine and normetanephrine levels: 545 mg/24H (< 320) and 408 mg/24H (< 390), respectively. Scintigraphy revealed new foci of ^{123}I-MIBG uptake on the sternum body and on the diaphysis of the left femur, highly suggestive of metastatic disease. ^{68}Ga-DOTANOC-PET/CT showed metastatic lesions with high expression of somatostatin receptors in the axial skeleton: L4 and 9th left rib, along with the lesions found with ^{131}I-MIBG scan. The patient was proposed to ^{131}I I-MIBG treatment (6400 MBq). Post-treatment ^{131}I-MIBG scintigraphy still reveals uptake on the 9th left rib and left femur diaphysis but the other lesions showed no uptake. The patient is now asymptomatic and under tight clinical and imagiological surveillance.

Conclusion

This case reveals the importance close, active surveillance of these patients. 131I-MIBG can be very effective as a treatment of malignant pheochromocytoma, with great safety profile and no significant side effects.

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AEP396

Parathyroid carcinoma: A case report

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Introduction

Parathyroid carcinoma is a rare endocrine carcinoma, which represents less than 1% of all cases of primary hyperparathyroidism. It usually affects people between 44–55 years old without differences between sexes. Sometimes it is related to HRPT2 gene mutations and it has a variable prognosis.

Presentation of case

A 56-year-old man was referred to our centre to complete an hypercalcemia study. He had an unremarkable past medical history and he did not take any regular medications. He presented a few months history of asthenia and weight loss. Serum investigations: Calcium 12.8 mg/dl (Albumin corrected), P: 2.14 mg/dl, PTH 578 pg/ml, 25-OH vitamin D: 33 nmol/l, Glomerular filtration rate: 53.45 ml/min. On examination he had a firm, well defined right thyroid nodule. Neck ultrasound revealed a 46.2 mm (TI-RADS 5) nodule in right thyroid lobe and a 18.6 mm (TI-RADS 4) nodule on left thyroid lobe. On the first nodule the fine needle aspiration citology (FNAC) showed a probably parathyroid carcinoma meanwhile on the second nodule FNAC showed an atypia of undetermined significance (Bethesda III). 99 mTc thyroid scintigraphy demonstrated an hypermetabolic mass on right lower parathyroid gland. CT scan showed an heterogeneous hypodense mass with lobulated margins, and inner calcifications, which displaced the trachea and contacted the lower pole of the right thyroid lobe and esophagus. Until surgery treatment with cinacalcet at progressive doses was started achieving lower calcium values (10.9 mg/dl). Intraoperatory biopsy informed about nodule with marked nuclear atypia cell proliferation and solid growth pattern; undergoing total thyroidectomy and lower right radical parathyroidectomy. Pathologist confirmed parathyroid carcinoma with marked nuclear atypia, inflammatory component and signs of focal vascular invasion. The other nodule was described as hyperplasic. After surgery PTH was 49.5 pg/ml and calcium levels were 9.4 mg/dl 24 hours later. In the follow up the patient presented hypocalcemia and needed high calcium doses and vitamin D supplies. This prolonged requirement despite of calcium supplies in addition to a bone densitometry which informed of osteoporosis leaded us to a postsurgical hungry bone syndrome. At present the patient keeps stable and pending of genetic study result.

Conclusion

– Parathyroid carcinoma should be considerated in the differential diagnosis of hypercalcemia. – An early diagnosis and surgical resection is essential to reduce morbidity and mortality. – Genetic study can help to detect this pathology in relatives.

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AEP397

Anticancer activity of hydroxytyrosol and five semisynthetic lipophilic derivatives in prostate cancer cells

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Prostate cancer (PCa) is the second most diagnosed cancer type and the sixth cause of cancer death among men worldwide. Due to the usual slow course of the progression of this disease, there is a growing interest in finding chemopreventive therapeutics with a low risk of side effects. In line with this, recent studies have shown that hydroxytyrosol (HT), one of the main extra virgin olive oil phenolic compounds, exerts a protective role against different cancer types. Moreover, semisynthetic derivatives of HT could improve its bioavailability and pharmacological activities. Thus, in this study we aimed to compare the *in vitro* anticancer effects of HT and five semisynthetic derivatives, including alkyl ethers, esters, and nitro-derivatives against different PCa cell lines. Antiproliferative effects of HT and two lipophilic derivatives [hydroxytyrosyl acetate (HT-Ac) and ethyl hydroxytyrosyl ether (HT-Et)] were significantly higher in cancerous PC-3 and 22Rv1 cells than in non-malignant RWPE-1 cells, whereas the nitro-derivatives were more cytotoxic in RWPE-1. In addition, HT, HT-Ac and HT-Et significantly reduced migration capacity in RWPE-1 and PC-3 as well as prostatosphere size and colony formation in 22Rv1 cells. Nevertheless, HT-Ac and HT-Et, but not HT, were able to decrease phospho-AKT/AKT levels and colony and prostatosphere formation in PC-3. In sum, our results together with previous studies showing the antioxidant capacity of HT and its lipophilic derivatives suggest that they could be considered as potential therapeutic tools in PCa.

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AEP398

Clinical presentation, phenotype, and germline variants of pheochromocytoma and paraganglioma: A three-decade clinical experience

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Introduction

Pheochromocytomas are rare catecholamine-producing neuroendocrine tumours arising from chromaffin cells of the adrenal medulla or extra-adrenal sympathetic paraganglia(paragangliomas).

Aim

To characterise demographic, clinical, and biochemical/genetic features of a cohort of patients with pheochromocytoma and paraganglioma (PPGL), assessing for differences between two-time periods over a three-decade span.

Methods

A retrospective, cross-sectional study was performed on patients with histologically proven PPGL diagnosed between 1988 and 2020 at our center. Demographic,clinical, biochemical and imagiological data at presentation, genetic testing and clinical outcomes at the last follow-up were retrieved. To investigate potential differences over the past 30 years, we divided the cohort into two groups based on the year of diagnosis and a previous published

analysis. Group 1 was comprised of patients diagnosed between 1988–2010 (n = 25) and group 2 between 20102020 (n = 24).
Results
Forty-nine patients(53.1% male) were included; mean age at diagnosis was 46.0 ± 17.0 years with a median follow-up time of 5.6 (2.3–9.6) years. Pheochromocytoma was diagnosed in 85.7% (n = 42);bilateral in 3 patients; the remainder were paragangliomas. One individual presented a simultaneous bilateral pheochromocytoma and abdominal paraganglioma. Most patients presented with de novo or refractory hypertension(53.1%),typical spells(34.7%) or an incidentally found lesion on imaging(30.6%).Urinary fractionated metanephrines were measured in all patients,89.8%(n = 44) had evidence of increased catecholamine secretion(3 were paragangliomas). Noradrenergic phenotype was found on 27.3% with adrenergic co-secretion on the remainder. Conventional and functional imaging(mostly MIBG scan) was performed in most. At diagnosis, median PPGL dimension was 40 (29–64) mm and 10.2% were metastatic. Genetic testing was performed in 36.7%(n = 18) with a germline variant on a PPGL susceptibility gene found in half of them(MAX, VHL and SDHB).On group comparison, there is a trend for lower age at diagnosis with a statistically significant increased($P < 0.05$) antihypertensive treatment use with lower systolic blood pressure at diagnosis. We also found an increased use of genetic testing and lower use of MIBG as functional imaging modality in more recent years, reaching statistical significance.
Conclusion
We detail the presentation and work-up of a cohort of PPGL; over a 30-year period the proportion of patients submitted to genetic testing increased significantly(from 21% to 54%).Our work identifies currently followed patients to be referred for genetic testing.

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AEP399

Heterogeneity of the clinical presentation of the MEN1 LRG_509t1 c.781C > T (p.Leu261Phe) variant within a three-generation family

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Background
Multiple neuroendocrine neoplasia type 1 is a rare, heterogeneous genetic disorder with an autosomal dominant inheritance, predisposing to benign and malignant tumors. The phenotype of MEN1 syndrome varies between patients in terms of tumor localisation, age of onset and clinical aggressiveness, even between affected members of the same family. We report a heterogenic phenotype of the MEN1 variant c.[781C > T] (LRG_509t1) previously reported only once in a family with isolated hyperparathyroidism.
Methods
A large Polish kindred with suspicion of MEN1 syndrome underwent clinical evaluation and genetic testing.
Results
A heterozygous missense variant in exon 4 of the gene was identified in the sequence of the MEN1 gene (LRG_509t1), i.e. c.781C > T, leading at protein level to the amino acid change p.Leu261Phe in three-generation family. In the screened family, 5/6 affected members already developed hyperparathyroidism. In the index patient and two other family members, aggressive course of the disease, with dissemination of pancreatic-neuroendocrine tumor (insulinoma and non-functioning neuroendocrine tumors) was observed. In the index patient, late diagnosis and slow progression of the dissemination process was observed during 24 years of follow-up.
Conclusion
The very rare variant of MEN1, LRG_509t1 c.781C > T /p.Leu261Phe (LRG_509t1) diagnosed within a three -generation family has heterogenic clinical presentation. Further follow-up of the family members should be performed to confirm the spectrum and exact time of clinical presentation of this alteration.

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AEP400

CGMS-monitored preoperative diazoxide therapy of a pancreatic insulinoma: A case report

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Insulinomas are predominantly benign pancreatic neuroendocrine tumors presenting with hyperinsulinemic hypoglycemia. Surgical resection is currently the standard treatment for pancreatic insulinoma, but other treatment options, such as oral medication with diazoxide may be necessary for symptomatic patients who are not candidates for surgical resolution or for those who need bridging therapy till the surgical intervention. We present the case of a 54-year-old man who was admitted to our Endocrinology Department with a 2-year history of epileptic seizures of unknown origin. The seizures occurred, when he was on a weight loss diet. Neurological workup (including a negative MRI of the head and EEG) could not define the etiology of the seizures. Laboratory studies showed hypoglycemia with hyperinsulinemia almost every 3 hours. An endosonographic investigation was planned to identify the suspected insulinoma, but this got delayed because the patient was diagnosed with SARS-CoV-2 infection. He became subfebrile, developed lethargy and cough, but did not require oxygen supplementation. Chest CT showed pneumonia and abdominal CT revealed a 17 × 17 mm lesion in the pancreatic tail, which was believed to be consistent with the radiological manifestation of an insulinoma. Surgical removal of the tumor was planned following recovery from COVID-19. In the meantime, for symptomatic treatment he was started on diazoxide therapy. To reveal asymptomatic hypoglycemia and to take advantage of the hypoglycemia alert function of the device, the tissue glucose level of the patient was real-time monitored with continuous glucose monitoring system (CGMS). CGMS was started 1.5 days before the introduction of diazoxide therapy and was continued for a total of 6 days. The patient was discharged with diazoxide to be used during recovery from COVID-19. After his recovery the surgical resection was successfully performed. The patient was discharged without diazoxide therapy and did not show hypoglycemic tendency. Hypoglycemia increases cardiovascular mortality, therefore avoidance or prompt treatment of hypoglycemic episodes is imperative in patients with insulinomas, until definitive surgical intervention can be performed. Our case highlights that CGMS can be successfully used to detect asymptomatic hypoglycemia in patients with insulinoma, and can also confirm the response to medical therapy.

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AEP401

Association of gastric GIST and Cushing syndrome

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Gastrointestinal stromal tumors (GIST) are in high risk of developing additional malignancies, hereditary and also nonhereditary kind. Genetic changes are involved in the formation of GIST, about 80% are associated with KIT gene mutation and 10% of cases are associated with PDGFRA gene. These two mutations are found in both familial and sporadic GIST. We report a 65 years old female patient with a history of surgery for gastric GIST (T2N0). During the follow-up, after 4 years, she was diagnosed with left adrenal incidentaloma (35 mm). The endocrine exam revealed multiple thyroid nodules with large calcifications on ultrasound. Calcitonin was slightly increased with possible interference from proton pump inhibitors medication that she was using at the time. Vitamin D was low 15 ng/ml (N > 30 ng/ml) with a slightly increased PTH and normal serum calcium. Adrenal hormonal tests concluded: 8 a.m Cortisol: 25 μg/dl (N.V. 4.5–23 μg/dl), ACTH: 7 pg/ml (N.V. 7–63 pg/ml), CLU: 400 μg/24 h (N.V. 36–137 μg/24 h). The negative dexamethasone test (1 mg overnight, 2 mg for two days and 8 mg at midnight) along with the presence of adrenal tumor were suggestive for ACTH independent Cushing syndrome. The patient was referred to surgical department for curative treatment of the adrenal tumor. GIST and other endocrine neoplasias may occur in Carney triad and Neurofibromatosis type

1. This case is in accordance with other patients reported in the literature with same cancer association: GIST and Cushing syndrome, our goal being to determine sporadic occurrence or genetic affiliation between these two.

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AEP402

Gonadal dysfunction in male patients with neuroendocrine tumors

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Introduction
Hypogonadism is a potential manifestation of many chronic diseases including cancer, presumably related to their severity. Since novel anti-cancer treatments have significantly increased survival rates of affected patients, issue of hypogonadism becomes more significant, given the importance of issues like quality of life and potential for reproduction. The aim of our study was to analyze gonadal axis function in male patients with neuroendocrine tumors.
Subjects and methods
We retrospectively analyzed 43 male patients aged 57.7 ± 13.5 years (15–76) with diagnosed neuroendocrine tumor and available hormonal data, prior to initiation of specific anti-cancer treatment. None of the patients had concomitant pituitary adenoma. All patients underwent standard oncological evaluation, with tumor staging and grading. Blood samples were taken for determination of testosterone, FSH (follicule-stimulating hormone) and LH (luteinizing hormone), as well as routine biochemical analyses. Basic antropometric parameters were measured. Statistical analysis was performed by SPSS software.
Results
Minority of patients in our group were younger than 50 years of age (8, 18.6%). All, but 2 had metastatic disease, with unknown primary in 39.5% (17), pancreatic in 30.2% (13), lung in 20.9% (9), small intestinal in 7.0% (3), and pharyngeal tumor in 2.3% (1) of cases. Three patients had grade 1 tumor (7.0%), 14 grade 2 (32.6%), and 26 grade 3 (60.5%). Low testosterone level was diagnosed in 4 patients (9.3%). After exclusion of one patient with ectopic Cushing's syndrome, malignant disease could be atributed as a cause in remaining cases (6.97%), hypogonadotropic in 2 cases, and hypergonadotropic in 1. Overall 6 patients had elevated LH levels (5.9 ± 3.4, 1–15), suggesting a certain degree of subclinical primary hypogonadism in 14.0% of our patients. There was no correlation between testosterone levels and any of biochemical and antropometric parameters ($P > 0.05$). There was no significant difference in testosterone levels between patients with different tumor grades ($P = 0.579$). Elevated FSH level was observed in 32.6% (14) patients, suggesting spermatogenesis failure. Only one patient younger than 50 had elevated FSH (15.9 ± 19.5, 0.5–102.0), and none had elevated LH, while there was no significant difference in tumor grades between two age groups ($P = 0.711$). Afore mentioned differences in FSH, LH and testosterone did not affect survival in our group of patients ($P > 0.05$ for all).
Conclusion
Based on preliminary data, presence of neuroendocrine tumor doesn't seem to have a significant impact on gonadal function, at least in younger patients. Risk for spermatogenesis failure should be explored further).

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AEP403

Neuroendocrine neoplasms of the larynx: About 4 cases

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Objectives
studying the clinical and evolutionary characteristics of neuroendocrine laryngeal tumors and their management modalities.
Materials and methods
A retrospective study with 4 cases of neuroendocrine tumors (NET) of the larynx ENT service of the Farhat Hached hospital of Sousse.
Results
Our series consisted of 3 men and a woman. The average age was 49 years [35–63 years]. Alcohol and tobacco poisoning was reported in 3 cases. The two main signs were chronic dysphonia associated with dyspnea. The average time of evolution was 8 months. The cervical examination had objectified metastatic lymphadenopathy in 1 patient. The indirect laryngoscopy objectified a tumor lesion of the epiglottic left fold in one case, a tumor lesion taking the 3 stages of the larynx with a fixed hemilarynx in 3 cases. There was no distant metastasis in all cases. Anatomopathological study of biopsies with immunohistochemical analysis supported a well-differentiated carcinoid tumor in 1 case, small cell NET in 2 cases, and low-differentiated high-grade NET in 1 case. Therapeutic management consisted of radiation chemotherapy in 2 cases, in total laryngectomy with curage functional lymph node in 2 cases. The evolution was marked by tumor recurrence in one case indicating surgery correction. Cerebral and spinal metastases were observed during follow-up in 2 patients.
Conclusion
Neuroendocrine tumors are exceptional tumors of the larynx. The diagnosis is on anatomopathological and immunohistochemical examination. Management treatment depends on the histological subtype. Surgery is the treatment of choice for typical carcinoid tumors, atypical carcinoid tumors and paragangliomas. The treatment of small cell NET is based on radiation chemotherapy.

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Environmental Endocrinology

AEP404

Cadmium levels in human breast tissue and estradiol serum levels: Dose-response data analyses

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Cadmium (Cd) is a ubiquitously present toxic metal with an established ability to induce endocrine disruption, in literature often referred to as metalloestrogen. Some of the major uncertainties connected with endocrine disrupting chemicals (EDCs) in general, are low-dose exposure and the presence of nonmonotonic dose-response curves. This study aims to elucidate the presence of a dose-response relationship between the measured Cd levels in the tissue (internal dose) and estrogen levels in serum (hormonal response). The study was conducted at the Clinic for Oncology of the Clinical Hospital Center 'Bežanijska kosa', Belgrade, Serbia in the period between January and September 2019 and included 55 patients diagnosed with breast cancer and 41 women with benign breast changes. All participants were further classified based on their menopausal status. Prior to surgery, venous blood samples were obtained from the anterior cubital vein after a 12 h fasting period and estradiol levels were determined in serum. After surgical tissue removal, Cd levels were determined in the tumor and the surrounding healthy breast tissue. Tissue samples were mineralized using wet digestion and Cd levels were determined using atomic absorption spectrometry. Dose-response modeling was performed using PROAST software version 67.0 (the Dutch National Institute for Public Health and the Environment, RIVM). Data on estradiol and Cd levels were analyzed as continuous individual data using menopausal status the presence of malignant/benign change as variable factors. Benchmark response was set to 10% and the averaging method was used to calculate the Benchmark dose (BMD) interval. Akaike information criterion was used to evaluate the model. The mathematical relationships between the concentration of Cd in the surrounding healthy/tumor tissue and the levels of estradiol in the serum of the subjects has been shown and BMD values were calculated. Rather low calculated BMD values indicate that even levels lower than 1 ng Cd/g breast tissue can lead to a 10% change in measured estrogen serum levels. These results implicate the presence of the dose-response behavior of EDCs and propose this method for investigating the possible presence of nonmonotonic dose-response curves, as well. Moreover, the obtained results testify that the BMD concept can be used as an approach to analyze human data. Further research on this topic is necessary so that the extrapolation of data from animals to humans can be, at least partly, replaced by the process applied in this study, thus facilitating risk assessment, especially for EDCs.

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AEP405

Development of *in vitro* rat, dog and human deiodinase inhibition assays with LC-MS/MS analysis for the identification of endocrine disruptors

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Thyroid hormones are important regulators of metabolism and development. Iodothyronine selenodeiodinases can both activate and inactivate thyroid hormones (Bianco *et al*. 2002) thus *in vitro* assays to quantify deiodinase inhibition are considered to be a valuable tool for studying effects on thyroid hormone metabolism by potential endocrine disruptors. The prohormone thyroxine (T4) is converted to 3,5,3'-triiodothyronine (T3) by outer-ring deiodination, or to 3,3',5'-triiodothyronine (reverse T3/rT3) by inner ring deiodination. These compounds can then be further de-iodinated to diiodothyronine (T2). This work describes the development of screening *in vitro* methodology for the analysis of thyroid hormone metabolism by LC-MS/MS. Recombinant deiodinase enzymes D1, D2 and D3 for rat, dog and human were ectopically expressed in HEK293 cells and used to set up species-specific and isoform -specific incubation conditions to determine optimal protein and incubation kinetics for each enzyme. The conversion of T4 or rT3 by each respective recombinant deiodinase was assessed, and reactions were monitored by LC-MS/MS assay for formation of T2 or T3 for D1, T3 for D2 and rT3 for D3. Using known inhibitors of deiodinases, 6-propyl-2-thiouracil (PTU) for D1 and aurothioglucose (ATG) for D2 and D3, we demonstrate that the rat, dog and human deiodinase assays generate robust and reproducible data. These deiodinase assays are now routinely performed to assess the potential endocrine disrupting properties of small molecules.

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General Endocrinology

AEP406

Thoracic trauma associated gynecomastia

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Introduction
Gynecomastia is characterized by the abnormal enlargement of one or both male breasts due to proliferation of the glandular tissue, with many possible underlying causes. A documented rare cause of gynecomastia is chest trauma.
Case report
We present a case of a 53-year-old male patient, with a personal history of arterial hypertension and depressive disorder, medicated with fluoxetine, perindopril, amlodipine and indapamide. The patient had a documented history of a three-story fall six months before, with associated chest trauma and rib fracture, which required admission in an intensive care unit. The patient was referred to an endocrinology consult following a slightly painful, progressive increase in volume of the right breast, with no associated nodules or masses, which started after the fall. The blood analysis were in the normal range, including alpha-fetoprotein < 1.3 ng/ml, FSH 7.1 mUI/l (RV 1.4–18.1), LH 6.3 mUI/l (RV 1.5–9.3), prolactin 7.7 ng/ml (RV 2.1–17.7), beta-HCG < 0.1UI/l, total testosterone 270 ng/dl (RV 193–740). The patient underwent a breast ultrasound scan that confirmed bilateral, asymmetrical gynecomastia, with a right breast gland of 22 mm and left gland with 12 mm. Due to the presence of a hypoechogenic retroareolar area on the right gland the patient underwent an ultrasound-guided micro biopsy. The histological result was benign. After one year of follow-up the patient still presents with gynecomastia, although in slight regression.
Discussion
We report a case of gynecomastia where the only identified trigger was the acute chest trauma. The underlying pathophysiological mechanisms remain unclear, but some authors propose that the local release of growth factors plays a role, leading to the differentiation and proliferation of precursor cells, resulting in mature glandular enlargement.

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AEP407

Arrhythmias and cardiac conduction disorders in patients with acromegaly

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Cardiovascular complications including arrhythmias and cardiac conduction disorders (ACCDs) are leading risk factors for high mortality rate in acromegaly. ACCDs are the main cause of sudden cardiac death in patients with acromegaly. These disorders are detected in up to 40% of patients. Different pathogenetic mechanisms contribute to the development of concentric biventricular myocardium hypertrophy which leads to electrophysiological myocardium feature changes. The goal of the study is to evaluate the prevalence of heart complications in patients with acromegaly.
Materials and methods
A single-center cross-sectional study, which included 461 patients (151 men and 310 women) with acromegaly, was conducted. All patients underwent a standard medical examination including hormonal blood tests, electrocardiogram, echocardiography and electrocardiogram daily monitoring. Eighteen patients with arrhythmias (11 men and 7 women) had cardiac magnetic resonance imaging (MRI) with gadolinium-based contrast.
Results
The prevalence of ACCDs in patients with acromegaly was 42%. The most common types of ACCDs were sinus bradycardia – 19.1% of cases and conduction disorders of bundle branch blocks – 14.5%. Men were more likely to suffer from arrhythmias and cardiac conduction disorders than women (54.2% and 37.4%, respectively, $P = 0.0005$). Patients with ACCDs had a longer medical history of acromegaly (average duration 10 vs 7 years, respectively, $P = 0.04$). Cardiac conduction disorders were commonly observed in patients who were treated with somatostatin analogs comparing to patients who didn't undergo this therapy (50% and 38.6% respectively, $P = 0.004$). Pacemakers were implanted in 3 patients, and an implantable cardioverter defibrillator was used in one patient due to susteined ventricular tachycardia. Sixty one percent of patients with acromegaly and ACCDs who underwent MRI had signs of myocardial fibrosis.
Conclusion
ACCDs are common in patients with acromegaly, predominantly males, increasing in prevalence with a longer history of the disease or somatostatin analog therapy. Myocardial fibrosis is supposed as one of the most likely cause of ACCDs in patients with acromegaly.

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AEP408

A new cause of endogenous hyperinsulinism?

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We present the case of a patient who started having repeated episodes of symptomatic hypoglycemia at the age of 50.
Medical history
Father had type 2 diabetes. Former smoker, moderate alcohol consumption. Chronic otitis media with cholesteatoma, surgically removed. Congenital cataract operated at the age of 3.
Clinical course
At around the age of 50, the patient started having sporadic episodes of sympathoadrenal and neuroglycopenic symptoms, with plasma glucose levels of 60 mg/dl, that ceased after the intake of sugars. The episodes occurred more frequently in the early morning fasting state, but also before meals during daytime. His general practitioner detected a fasting glucose level of 42 mg/dl and HbA1c of 3.3%, refering the patient to Endocrinology. During the following years, a fasting evaluation evidenced hypoglycemia with inappropriately elevated levels of insulin and C-peptide (insuline/glucose ratio 0.61). A CT and an abdominal arteriography didn't show pancreatic lesions. The patient was diagnosed with endogenous hyperinsulinism without detection of insulinoma. At age 56, the episodes of hypoglycemia became more frequent and treatment with diazoxide was initiated, with dose titration up to 250 mg/day and partial response with a decrease in the number of episodes. Further testing was performed: glicazide was detected in HPLC of a sample obtained during hypoglycemia, but this could not be confirmed in three subsequent analyses;

proinsulin levels were elevated; no insulin antibodies were present. Localizing studies were repeated: CT, echo-endoscopy and abdominal arteriography were carried out without findings; and MRI revealed slight contrast enhancement in the head of the pancreas. That same year, another MRI did not confirm such abnormality. During the follow-up, the dose of diazoxide was progressively reduced to 100 mg/day, and remained well-tolerated. Between the ages of 63 and 68, there was a gradual increase in the frequency of episodes of hypoglycemia and a decrease in the associated symptoms. At age 68, the case was reevaluated with a new sulfonylureas analysis that was performed during hospitalization with a negative result, a new localizing study (CT, MRI and echo-endoscopy) without findings and a MODY panel genetic test, which revealed a mutation in GLIS3 gene. This gene can function both as an activator and a repressor of transcription in pancreatic beta cells, which could explain the endogenous hyperinsulinism in our patient.

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AEP409

Characterization of neuroinflammatory makers and related-genetic variants in athletes from a long duration ultramarathon mountain cycling race and endurance exercises

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Introduction
Exercise induces changes in the inflammatory profile that can comprehend changes during and immediately after exercise with long-term effects. This inflammatory profile could impact the cognitive function and so, the performance.
Objectives
Compare the inflammatory status from long duration and endurance exercises and correlate it with an immune and neuroendocrine genetic profile.
Material and methods
Fifty-five non-professional athletes (mean age 44.8 ± 7.1 years) participating in a 9-day mountain cycling ultramarathon (TransPortugal) and 27 endurance athletes participating in 1-year of competition: 17 amateurs (mean age 43 ± 7.0 years) and 10 Professional (mean age 20 ± 1.6 years) were evaluated. Before and after race/season, were determined metabolic parameters by standard methods; IL6, TNF-alpha, BDNF and cortisol determined by ELISAs. Functional genetic polymorphisms IL-6 (rs 10 08 795), IL-1ß (rs 16 944), TNF-alpha (rs 18 00 629), IDO1 (rs 96 57 182) and 5HTTVNTR (VNTR-17bp) were determined by endpoint-analysis and PCR/RFLP.
Results and conclusions
Before the competitions, TransPortugal athletes had lower levels of inflammation (PCR and TNFα) than endurance athletes. TransPortugal athletes presented higher levels of insulin ($P < 0.001$) and HOMA-IR ($P < 0.001$), contrarily to endurance athletes that presented higher levels of glucose ($P < 0.0001$) and HOMA-ß ($P = 0.006$). The impact of a 9-days long duration exercise were reflected on inflammatory profile with an extensive increase of IL-6 and PCR ($P < 0.0001$) and uric acid ($P = 0.027$). The TNF-α levels continued to be higher in endurance athletes in relation to TransPortugal athletes ($P < 0.0001$). The IDO1-TT ($P = 0.002$), 5HTTVNTR-12/12 and IL-1ß-GG ($P = 0.038$) genotypes were more associated to TransPortugal athletes in relation to endurance athletes. This profile could contribute to a better performance. TransPortugal athletes with IDO1-TT genotype presented higher levels of TNF-alpha post-race ($P = 0.046$) and haptoglobin pre-race ($P = 0.029$); IL-1ß-GG genotype higher levels of IL-6 post-race ($P = 0.048$); and the 5HTTVNTR-12/12 genotype higher levels of haptoglobin post-race ($P = 0.039$) and lower levels of glucose ($P = 0.055$) and PCR post-race ($P = 0.059$). For endurance athletes, we only found merely modulation of IDO1 and IL-1ß associated to glucose and HOMA-ß pre-race ($P < 0.05$) and 5HTTVNTR-12/12 genotype presented higher levels of TNF-alpha pre-race ($P = 0.033$). In conclusion, accordingly to the inflammatory status, seems that TransPortugal athletes are more prepared for competition that endurance athletes and with a genetic profile that could explain some interindividual variations leading to modulation of inflammatory process and neuromodulation.

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AEP410

Successful treatment of nesidioblastosis during the time of pandemic: A case report

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Introduction
In the background of persistent hyperinsulinemic hypoglycemia the insulinomas of the pancreatic beta cells may be present, but in some rare cases we fail to identify a well-defined lesion and the insulin hypersecretion is caused by nesidioblastosis, a diffuse proliferation of the pancreatic islet cells. However, the localization of the lesion is necessary for proper treatment, in certain cases finding the insulinoma is difficult and can only be helped by special examination techniques, like selective intraarterial calcium stimulation.
Case report
We report the case of a 36-year-old man who has acoustic neurinoma in his previous history. His present symptoms started one and a half year ago. In the background of collapses, dizziness, agitation, somnolence, hypoglycemia was found caused by hyperinsulinemia. The Whipple triad during the fasting test confirmed the diagnosis of the hormone producing lesion. The careful non-invasive examinations (abdominal ultrasound, CT and MRI) could not identify the insulinoma. In November 2020 he was admitted to our hospital with severe symptoms of hypoglycemia. Despite the iv. glucose substitution, calcium antagonist and octreotide therapy the hypoglycemia persisted, so calcium stimulation was performed, which showed significant elevation of C-peptide and insulin levels of the middle third of the pancreas, but also an elevation could be found in the tail region. Partial pancreatectomy was scheduled, which needed to be postponed because the patient acquired SARS-Covid 19 infection. Later the partial pancreatectomy was performed, and the histology showed nesidioblastosis. The patient was released from the hospital on calcium-antagonist and diazoxide therapy with good clinical response.
Conclusion
The differential diagnosis of insulinoma and diffuse nesidioblastosis from the clinical and biochemical perspective is challenging when no imaging technique could localize the lesion, but in the perioperative diagnosis the highly sensitive and specific selective intraarterial calcium stimulation can be helpful. The final diagnosis is based on histopathological findings, which determines the further therapeutic steps. In our case, despite the delays and inconveniences caused by the SARS-Covid 19 pandemic, we could achieve a good clinical response with partial pancreatectomy and chemical suppression.

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AEP411

Post-menopausal virilizing tumor of the ovary

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Introduction
Leydig cell tumors are rare entities, representing less 0.1% of all ovarian tumors. Generally these tumors are benign and unilateral. Most originate from the hilus cells and, less frequently, from the ovarian cortical stroma. Leydig cell tumors are functioning tumors, frequently associated with virilization symptoms in post-menopausal women.
Case report
We report the case of a 77 year-old female patient, caucasian, with personal history of autoimmune hepatitis, type 2 diabetes, dyslipidemia and Hashimoto thyroiditis. The patient had a history of 4 pregnancies,

with no complications, and menopause at 42 years old with no hormone replacement therapy. The patient presented with a 4 years history of virilization symptoms, namely hirsutism (Ferriman Gallwey Score 11). The blood analysis showed a total testosterone 290 ng/dl (RV < 41), free testosterone 5.60 ng/ml (RV 0.10–4.70), delta-4 androstenedione 2.9 ng/ml (RV 0.4–3.7), 17-hydroxyprogesterone 1.80 ng/ml, dehydroepiandrosterone sulfate 72 mg/dl (VR 26–460). A transvaginal ultrasound was ordered, which showed enlarged ovaries when adjusted to age, but with normal echostructure and no other findings. A pelvic magnetic resonance imaging exam was performed, revealing only a 16 mm uterine nodule, in favor of a submucous leiomyoma. After excluding adrenal causes of virilization, it was decided to underwent laparoscopic bilateral oophorectomy and hysterectomy. The histopathology revealed a 8 mm ovary tumor, with foci of luteinized cells, and reinke crystals, positive for inhibin and calretinin and negative for estrogen and progesterone receptors, findings that supported the diagnosis of nonhilar Leydig cell tumor. Following the surgery, the testosterone and free testosterone levels returned to normal. It is important to point out that a patient's sister presented with the same symptoms and blood analysis findings around the same age as our patient, but she refused further medical investigation.

Discussion

Accurate diagnosis of virilizing tumors of the ovary is often challenging, due to the fact these tumors might be too small to be detected in imaging exams. In this case, after excluding adrenal production of androgens, the main diagnostic hypothesis was a virilizing tumor of the ovary. For this reason the favored approach was surgery. The histopathological result confirmed the hypothesis and the patient symptoms and abnormal laboratory findings resolved. Since the patient's sister had the same symptoms in the same age group, we suspect the existence of a possible familial genetic syndrome. However no genetic investigation was completed for cost-effectiveness reasons.

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AEP412

Psychological Impact of COVID-19 national lockdown meAsures on tRansgenDer people in Italy: The PICARD study

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During 2020 spring, national lockdown was adopted in Italy to prevent COVID-19 pandemic spread. Restrictive measures, including lockdowns, were associated with impaired psychological outcome, mainly increased perceived stress and anxiety, in general population. As transgender people (T*) are associated with higher prevalence of perceived stress, anxiety, and depression, higher psychological vulnerability during lockdowns cannot be excluded. The aim of the PICARD study was the evaluation of psychological impairment in T* during the COVID-19-related Italian national lockdown, as compared with healthy subjects. The study enrolled 112 T* (41 T* women, 71 T* men; age: 18–55 yrs) and 224 age- and gender-matched cisgender controls. General Anxiety Disorder-7 (GAD7), Perceived Stress Scale (PSS), and Patient Health Questionnaire 9 (PHQ9) questionnaires (higher scores indicated higher psychological impairment) were telematically and anonymously administered to study participants during the last three weeks of national lockdown to screen their general anxiety, perceived stress, and depression status levels. Demographic, social, and clinical information were also collected. Compared with cisgender controls, T* experienced significantly higher scores in GAD7, PSS, and PHQ9 questionnaires ($P < 0.001$). In particular, T* men experienced significantly higher scores in all questionnaires ($P < 0.001$), whereas no significant differences were observed between T* and cisgender women. In the T* population, higher GAD7, PSS, and PHQ9 scores were contemporary observed in T* < 25 vs > 35 yrs ($P < 0.001$), T* without name change vs ongoing ($P < 0.01$), T* with no gender-affirming surgeries versus reconstructive surgeries ($P < 0.02$), and T* suffering from lockdown-related domestic violence vs who did not ($P < 0.04$). Higher GAD7 and PSS scores were contemporary observed in unemployed vs employed T*($P \leq 0.05$), whereas higher PSS and PHQ9 scores were contemporary observed in T* living with their parents vs alone ($P < 0.02$) and with partner ($P < 0.03$). Isolated higher PSS scores were observed in T* not performing vs performing hormonal treatments ($P < 0.001$). In conclusion, compared with cisgender controls, T* suffered increased psychological morbidity, namely general anxiety, stress perception, and depressive status, during Italian national lockdown. In particular, younger T*, unemployed T*, T* still living with their parents, and T* in the earliest stage of their transitional process (i.e. without birth name change, hormonal treatments, or gender-affirming surgeries) were more psychologically vulnerable. Therefore, empowerment of psychological counseling for T* during COVID-19 pandemic should be considered by health care services.

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AEP413

Evaluation of serum levels of chemerin and resistin in patients with rheumatoid arthritis. Two adipokines at the crossroad between rheumatology and endocrinology

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Introduction

Adipose tissue is already considered as a metabolic active endocrine organ secreting numerous substances called adipokines. A growing body of evidence links two of these adipokines- chemerin and resistin, to the pathogenesis of rheumatoid arthritis (RA) based on their effect on vascular function and creating an environment of low grade inflammation. Nevertheless, the exact mechanism of how these molecules act on the target cells of joint elements are not fully understood.

Objective

The aim of this pilot study is to examine the association of the serum concentrations of chemerin and resistin with clinical markers of inflammation and disease activity in patients with rheumatoid arthritis. The aim of this pilot study is to examine the possible interaction between serum concentrations of the two secreted adipokines- chemerin and resistin and some well known markers of inflammation and disease activity in patients with rheumatoid arthritis.

Methods

Serum was collected from 20 patients (17 women, 3 men) and another 31 cases with no joint diseases were included as controls (21 women, 10 men). The levels of chemerin and resistin were measured by enzyme-linked immunosorbent assay (ELISA). Antropometric parameters were evaluated with standart procedures in a fasting status (0800 h) in the entire cohort. Rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum level of uric acid (UA) were evaluated in the subgroup of 20 patients. Disease activity score was determined using the Disease Activity Score-28 for Rheumatoid Arthritis with ESR (DAS28-ESR).

Result

The serum concentration of resistin was significantly higher in RA patients (13.28 ± 6.18 ng/ml) than in the healthy controls (7.04 ± 2.09 ng/ml, $P < 0.001$). In contrast, there was no significant difference in chemerin levels between the patient and the control groups [247.0 (226.5–314.6) ng/ml vs. 228.8 (203.1–276.0) ng/ml, $P > 0.05$, respectively]. However, the serum chemerin concentration correlated positively with ESR ($r = 0.649$, $P = 0.002$), CRP ($r = 0.546$, $P = 0.013$), RF ($r = 0.465$, $P = 0.039$), and DAS28-ESR ($r = 0.807$, $P < 0.001$). In comparison, the serum level of resistin correlated positively only with CRP ($r = 0.537$, p 0.015), and DAS28-ESR index ($r = 0.470$, $P = 0.037$).

Conclusion

Taken together, these findings suggest that both chemerin and resistin might contribute to the inflammatory changes associated with RA, performing

pro-inflammatory activity. The two adipokines might also serve as novel biomarkers for reflecting disease activity.

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AEP414

Menopausal hormone therapy and women's health: an umbrella review of systematic reviews and meta-analyses of randomized controlled trials and observational epidemiological studies

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Importance
There remains uncertainty about the impact of menopausal hormone therapy (MHT) on women's health. A systematic, comprehensive assessment of the effects on multiple outcomes is lacking.
Objective
To comprehensively summarize evidence on the benefits and harms of MHT across diverse health outcomes in women.
Data sources
MEDLINE, EMBASE and 10 other databases from inception to November 26, 2017, updated December 17, 2020.
Study selection
Systematic reviews or meta-analyses of randomized controlled trials (RCTs) and observational studies investigating effects of MHT, including estrogen-alone therapy (ET) and estrogen plus progestin therapy (EPT), on any health outcome or indicator in perimenopausal or postmenopausal women in all countries and settings.
Data extraction and synthesis
Two investigators independently extracted data and assessed study quality. Random-effects robust variance estimation was used to combine effect estimates.
Main outcomes and measures
All health outcomes included in previous systematic reviews, including menopausal symptoms, surrogate endpoints, biomarkers, various morbidity outcomes, and mortality.
Results
Sixty systematic reviews were included, involving 102 meta-analyses of RCTs and 38 of observational studies, with 121 unique outcomes. The overall quality of included systematic reviews was moderate to poor. In meta-analyses of RCTs, MHT was beneficial for vasomotor symptoms (risk ratio [RR] 0.29, 95% confidence interval [CI] 0.17–0.50) and vaginal atrophy (intravaginal ET: RR 0.31, 95% CI 0.12–0.81), as well as sexual function, all fracture, vertebral and non-vertebral fracture, diabetes mellitus, cardiovascular mortality (ET) and colorectal cancer (EPT), but harmful for stroke (RR 1.17, 95% CI 1.05–1.29) and venous thromboembolism (RR 1.60, 95% CI 0.99–2.58), as well as cardiovascular disease, cerebrovascular disease, non-fatal stroke, deep vein thrombosis, gallbladder disease, and lung cancer mortality (EPT). In meta-analyses of observational studies, MHT was associated with decreased risks of cataract, glioma, and esophageal, gastric and colorectal cancer, but increased risks of pulmonary embolism, cholelithiasis, asthma, meningioma, and thyroid and ovarian cancer. ET and EPT had opposite effects for breast and endometrial cancer, endometrial hyperplasia and Alzheimer's disease. Importantly, current evidence supporting the beneficial effects on coronary heart disease and all-cause mortality in young women (known as 'timing hypothesis') is only tentative.
Conclusions and relevance
MHT has a complex balance of benefits and harms on multiple health outcomes. Some effects differ qualitatively between ET and EPT. Clinicians should evaluate the credibility of the methods of systematic reviews prior to considering applying their results in clinical practice. A re-examination of current practice guidelines may be needed.

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AEP415

Cushing's syndrome: Do Cushing's patients have similar diagnostic and treatment journeys and outcomes to mine?

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Background
Having experienced Cushing's syndrome and disease, this author is now a Doctor of Philosophy student studying these medical conditions with the main aim of finding out if others diagnosed with these illnesses have experienced similar diagnostic and treatment journeys with similar outcomes.
Method
An online 2020 survey was conducted on 86 Cushing's members of the Pituitary Foundation, (Females = 71, Males = 15). The questionnaire contained 40 questions and the results analysed and reported quantitively and qualitatively.
Main Results:
The mean age of the females was 44, the males 39, (Ages 19–70 years). The mean length of time for a diagnosis of CS was 4.9 years, and for CD, 3.2 years. The male results were 2.5 years and 1.3 years respectively. The mean number of physicians consulted prior to diagnosis was 3. All members had blood tests prior to their diagnosis (Mean = 4). A range of diagnostic medical imaging examinations/procedures were named by 81% of the members. A collective total of 170 diagnostic imaging examinations/procedures were conducted prior to diagnosis. 49% had pituitary surgery, 55% had adrenal surgery and 36% of the members had been advised that they would always require to take steroid medicines. 22% had radiotherapy and 5% had chemotherapy. 81% found that their Cushing's illness had impacted on their work status, social life, personal and family relationships. 45% of the members found their endocrine team did not involve their family, while 52% found the team to be very supportive. 44% of the members were given advice to join a support group. 90% of them agreed that there is insufficient public awareness, 44% also agreed that there was a lack of knowledge/awareness by health professionals and suggested a range of educational training methods and promotional material. The QoL was measured using a Likert 5-point scale. The results showed slightly higher QoL scores at the time of completing the questionnaire than prior to diagnosis and during treatment. On examining the differences between the responses to these questions, no significant difference was found, (P =.406), I e there was no evidence of an improvement in their health status.
Conclusion
The many factors which combine to reduce QoL in those who are diagnosed with Cushing's illnesses were identified. Despite medical interventions the comorbidities, both physical and psychological create long-term detrimental effects, and in many cases cannot be reversed. The management of this disease can be improved by raising awareness in health professionals.

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AEP416

A single-center observational study of patients with ectopic ACTH syndrome

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Background
Ectopic ACTH syndrome (EAS) is a rare cause of endogenous hypercortisolism.
Objective
To analyze clinical, biochemical features and treatment outcomes of patients with EAS.
Materials and methods
Retrospective, observational study on 129 patients (79 women, 50 men) with EAS diagnosed between 1990 and 2020. Plasma levels of ACTH (reference range: morning 7.2–63.3 pg/ml), late-night serum cortisol (64–327 nmol/l), late-night salivary cortisol (LNSC) (0.5–9.6 nmol/l) were measured by ECLIA Cobas 601; 24-h urinary free cortisol (24 hUFC) (100–379 nmol/l) – on Vitros ECi. Various imaging studies were performed in all patients to find the source of ACTH.
Results
The median age at diagnosis was 40 years [28;54]. 80 patients (62%) had bronchopulmonary neuroendocrine tumor (NET), 7 – thymic carcinoid, 7 – pancreatic NET, 5 – pheochromocytoma, 1– cecum NET, 1– appendix carcinoid tumor, 1 – medullary thyroid cancer and 27 (21%) patients had an occult source of ACTH. Mean time to diagnosis for patients with EAS was 32.5 months, 11 patients (8.5%) had cyclic course of the disease. Median basal plasma ACTH level at the time of the diagnosis was 141.1 pg/ml [101.9;202], median 24 hUFC was 2821.0 nmol/l [1691;6534.6], median late-night serum cortisol at 23:00 h and LNSC were 1228 nmol/l [959.1;1431.3] and 71.8 nmol/l [40.5;121], respectively. The most common complications in the active stage of the disease were type 2 diabetes mellitus (55%), cardiovascular disease (55%), arterial hypertension (84.5%), osteoporosis with low-energy fractures (60.5%). The median follow-up period of the patients was 27 months [10.5;61.0] with a maximum follow-up of 372 months. Currently, primary tumor was removed in 82 (63.6%) patients. Regional and distant metastases were revealed in 22 patients (17%). At the time of the last observation 58 patients (45%) were exhibited a full recovery, 12 (9%) – had relapse of the disease and received treatment with octreotide (20–50 mg/4 weeks) or ketoconazole (400 mg/day) to control severe hypercortisolism and 26 patients (20%) died from multiple organ failure ($n = 21$), pulmonary embolism ($n = 4$) or COVID-19 ($n = 1$). Bilateral adrenalectomy was performed in 23 patients (18%), in 16 of them there was an occult source of ACTH-producing tumor and in 7 patients – in order to control hypercortisolism at incurable stage of the disease.
Conclusion
In our study EAS was most commonly associated with intrathoracic tumors such as bronchopulmonary and thymic carcinoid. Surgical treatment of patients with the established source of the disease leads to remission of hypercortisolism in most cases.

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AEP417

Design of an online platform to support young diabetics transitioning to adult care: an experiment at the endocrinology service of casablanca university hospital

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Introduction
The quality of the transition process from pediatric care to adult care represents an important factor in ensuring uninterrupted follow-up of care for T1D adolescents. By avoiding the risks of poor adaptation, better organization of care would facilitate this transfer. New technologies, notably websites and mobile applications, have been adopted throughout the world to support young patients transitioning to adult care, and their families.
Goal
Our work revolves around the design and development of an online platform, enriched with informative content that is geared toward preparing young diabetics for the transition from pediatrics to the service of Endocrinology and Diabetology for adults at the Casablanca University Hospital.
Methodology
A questionnaire was developed to investigate the needs of young diabetics during transition and to identify their preferred online communication channels. A requirements specification document has been drafted to identify the objectives of the site. The web agency developed the website on the Wordpress platform using PHP as a programming language; a simplified administration interface has been implemented to facilitate the modification of the content by the service's team.
Results
50 T1D patients aged 15 to 18 responded to the questionnaires. The data collected was used to create a website that met their needs, including the accessibility of information about their illness via easily digestible content. Information about the Endocrinology service has been added to familiarize young patients with their next service.
Conclusion
Transition interventions based on technology as a modern means of communication are increasingly used to further involve young people in their health care. Hence www.jisr.info is a website that provides young T1D patients with the right tools to improve their experience during transition to adult care.

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AEP418

Designing a chatbot for young diabetics: Unprecedented experiment at the endocrinology service of the casablanca university hospital

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Introduction
Technological progress, the quest for optimization and the evolution of artificial intelligence have given birth to Chatbots. Also called a conversational agent, a chatbot is an artificial intelligence capable of conducting interactive human conversations. The main advantages of Chatbots are their availability 24/7, their accessibility (a Chatbot can take the form of a contact on Facebook Messenger), and the ease of access to information thanks to the common language imitating human conversation. Our goal was to design a technological tool that involves adolescents in the management of their diabetes via a robotic personal assistant.
Methodology
In order to define the functionalities of the chatbot and to collect the needs of T1D patients in terms of support and continuous learning, a questionnaire was designed. We used Flow XO, a visual chatbot editor that can be deployed on a wide range of websites, applications and social networks. A button to subscribe to our chatbot via Facebook messenger has been added to our service's website www.jisr.info.
Results
50 young type 1 diabetic patients aged 15 to 18 responded to the questionnaires. The data collected was used to develop the functionalities of the Chatbot. By clicking on the 'Subscribe to our Chatbot' link, our Chatbot, Karim, is added as a 'Friend' on Facebook. Karim supports DT1s in interpreting their blood sugar levels, can tell them what to do in the event of hypoglycemia or diabetic ketosis, and can also set reminders and give quick access to relevant information such as emergency numbers.
Conclusion
This Chatbot is an innovative means of health intervention allowing young T1D patients to get more involved in the management of their disease. This is a pilot version which will be enriched with new functionalities over time.

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AEP419

Treatment approach of insulinoma

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Introduction
Insulinoma is the most frequent pancreatic endocrine tumor and is confirmed in case of a hyperinsulinic hypoglycemia with elevated C-peptide and absence of sulfonylureas. Tomodensitometry, MRI, endoscopic ultrasound

are the imaging means used to assess localization before surgery as it is not always determined by one mean only, and in a few cases, all means may not determine localization.
Methods
This is a descriptive, retrospective study including 10 patients with confirmed insulinoma. We collected imaging results, medical treatment, surgical management and histologic finding.
Results
For the 8 patients receiving surgery, 2 didn't have a precise localization for the tumor. Intra-operative palpation found a lesion in 3 cases, and intra-operative ultrasonography was done in 7 cases and found a lesion in 6 cases (one of them was the patient with no confirmed pre-operative localization). All 5 cases of confirmed tumor in the head of the pancreas were precisely diagnosed pre-operatively, 4 had an enucleation and one had a cephalic duodenal pancreatectomy (CDP). After enucleation, histologic examination confirmed 3 were well differenciated insulinomas and one had an islet cells hyperplasia (ICH), with a persistant hypoglycemia. The patient treated with CDP had a well differenciated tumor. The 2 cases with a suspected lesion in the tail of the pancreas and the patient with no confirmed localization had a caudal pancreatectomy (CP) with ICH in histologic finding. Medical treatment was used either for preoperative management, for post-operative control of persistant hypoglycemia or in case where surgery couldn't be done. One patient had an inoperable malignant insulinoma, and was put on diazoxide and octreotide with a good tolerance and no hypoglycemia. One patient refused the surgery, and was put under corticosteroids with lessening of hypoglycemia. The patient with no confirmed localization had diazoxide and corticosteroids for preoperative and post-operative control with persistence of hypoglycemia. In the case of persistant hypoglycemia after enucleation, lanreotide, corticosteroids and CP were used with a good control of hypoglycemia.
Conclusion
In our serie, preoperative and intra-operative investigations were able to determine the precise localization in 7 out of 8 cases, allowing a guided surgery with a preferred enucleation if it was in the head and CP if it was in the tail. Localized tumors were definitively treated in all cases, and persistence of hypoglycemia occurred only if ICH was confirmed, a strict follow-up must then be done.

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AEP420

Clinical characteristics of organic hypoglycemia

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Introduction
Spontaneous hypoglycemia in non-diabetic adults represent a challenge in confirming the organic cause, requiring in that case specific medication or surgery, in a setting of a possible life-threatening disease.
Methods
We conducted a retrospective study of patients admitted in our department for spontaneous hypoglycemia. Functional and factitious etiology were excluded. Clinical and biologic features were collected and were compared for 2 groups: the patients with confirmed adrenal insufficiency (group 1) and the patients with endogenous hyperinsulinism (group 2).
Results
Fourteen patients were included with confirmed organic hypoglycemia, 4 patients in the group 1 and 10 patients in the group 2. Mean delay between beginning of the symptoms and the day the patient consulted was 7.27 months in the first group and 8 months in the second group. Fasting was impossible in all the cases it was documented. There were 4 women in the group 1 vs 7 women and 3 men in the group 2. The first group had a lower mean age (37 ± 13 years vs 41 ± 15 years), lower body mass index (normal in all patients in group 1, superior to 25 kg/m^2 in 4 cases over 10 in the second group). Three patients in the first group described a loss of weight, and one with no change, while 6 patients in the second group described a gain of weight and 4 with no change. The group 1 had more neurogenic symptoms than neuroglycopenic ones, while in group 2, all patients had neuroglycopenic symptoms. Group 1 had 3 cases of fasting hypoglycemia and 1 case of late postprandial hypoglycemia, while group 2 had 6 cases of fasting hypoglycemia, 1 case of hypoglycemia after physical activity and 3 cases with no precise moment. Mean glycemia was lower in the second group comparing to the first group (0.27 ± 0.08 g/l vs 0.39 ± 0.13 g/l, P = 0.07).
Conclusion
Our study found differences in gender ratio, age, body mass index, signs and symptoms between the two groups, with lower mean glycemia in the endogenous hyperinsulinism group. A larger study must be conducted to find higher significant results for these clinal parameters.

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AEP421

Epidemiological aspects of adrenal insufficiency detected by the Synachten test and insulin hypoglycemia during withdrawal from prolonged corticosteroid therapy

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Introduction
Adrenal insufficiency is the most common complication after long-term corticosteroid therapy, to affirm or exclude the diagnosis of adrenal insufficiency several authors suggest basal cortisol testing as first-line, however, others prefer stimulating tests (insulin hypoglycemia (IGH) or synacthen testing). The aim of our work is to Analyze the frequency and determinant of the biological adrenal insufficiency detected by stimulating tests.
Material and methods
This is a retrospective study concerning 27 patients, who have taken long-term corticosteroid therapy at doses higher than 7.5 mg/day stopped and hydrocortisone relayed at variable doses, 49 tests were performed. over a 6-year time period.
Results
The mean age was 41.4 ± 14.6 years, mean duration of corticosteroid therapy was 27.7 ± 45 months, the cortisol limit for exploration by a dynamic test was reached after an average of 15 months in 45% of cases. 63% of patients did not respond to the test, with a mean cortisol level of 13.7 ng/l, and 37% responded to the stimulation test, with a mean cortisol level of 20.1 ng/l. Half of these responder patients were tested by Synacthen 250 mg immediate and half with IGH.
Discussion-conclusion
Follow-up of patients after prolonged corticosteroid therapy allows to predicts the ideal time to perform corticotropic axis stimulation tests and then to stop or maintain hydrocortisone substitution, it also prevents acute adrenal insufficiency.

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AEP422

The effect of COVİD-19 process on patients with endocrinological disease in a pandemic hospital: What Happened to the others?

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Objective
To evaluate the effects of the pandemic process on those with an endocrinological disease that will require close follow-up from the last visit before the pandemic.
Design
This was a retrospective study.
Methods
Patients of 3903 with thyroid, calcium-bone metabolism, adrenal gland, pituitary diseases, and neuroendocrine tumor (NET) were retrospectively scanned. The remaining 855 (656F/199M) patients with active disease or

still needed the multidisciplinary approaches were included in the study. How many patients who continued the disease-related medical procedures could complete these procedures on time in the pandemic period were determined, and the medical deprivation rate (MDR) was calculated.
Results
The pre-pandemic period of our patients with thyroid disease (n = 594), calcium-bone metabolism disorder (n = 130), adrenal disease (n = 85), pituitary disease and NET (n = 46), had MDR 85%, 56%, 81% and 89%, respectively. For each subgroup of the patients; the lowest MDR (67%) was in medullary thyroid carcinoma, the highest MDR (89%) was in differentiated thyroid carcinoma; the lowest MDR (6%) was in osteoporosis, the highest MDR (100%) was in the active Paget's disease; the lowest MDR (0%) was in primary adrenocortical insufficiency, the highest MDR (100%) was in hyperfunction adrenal adenomas; the lowest MDR (81%) was in the pituitary incidentaloma or non-functional adenomas, and the highest MDR (100%) was in Cushing's disease, active prolactinoma, TSHoma, and NET, respectively.
Conclusion
This study analyzed the medical deprivations experienced by patients with endocrinological diseases during the pandemic period and showed that these patients' follow-up and treatment should not be underestimated during the pandemic period.
Discussion
With the decrease in the number of COVID-19 cases in countries affected by the pandemic, the impact of patients with other diseases who experienced medical deprivation became more prominent.

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AEP423

COVID-19: Is there an urgent need to further assess how Cushing syndrome patients have reacted to this pandemic and what mechanisms are in place to support them?

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Background
Similar to other patients with life-threatening medical conditions, the fear of contracting COVID-19 for Cushing Syndrome (CS) patients is a natural reaction which has created a number of urgent questions, requiring answers. These questions include: how my body will react to the virus; will my current comorbidities increase; what will happen if I don't have my regular clinic appointments, surgery and chemotherapy treatments? What do I do if I am hospitalised and will my endocrinologist contact me to advise?
Methods
A Quality of Life (QoL) CS 2020 survey on 86 members of a support group during the onset of the pandemic accidently revealed in one of the QoL open questions, the thoughts and fears of contracting the virus. A thematic analysis was conducted on the 29 members who expressed their fears, to ascertain patterns of importance and interpret any challenges/issues which might be affecting their QoL and thus reduce their QoL scores.
Results
The analysis revealed that all 29 were fearful of contracting COVID-19 and recorded a lower QoL score than those of the other participants, (P <.001). The main reasons given were: that they may not be able to tolerate additional medications; 3 of them had been diagnosed with Addison's disease, 8 with pulmonary, cardiovascular and inflammatory conditions and 6 with diabetes. All 29 had cancelled outpatient appointments including 1 who was awaiting chemotherapy and 16 their radiology appointments. 9 were awaiting surgery which had been postponed. 11 were disappointed that their endocrinologist had not contacted them but were glad that they belonged to a support group. 26 were already experiencing depressive illnesses as a consequence of their CS, reported that lockdown measures had made them feel isolated, depressed and in 1 case suicidal.
Conclusion
Endocrine advice and support is even more crucial during a pandemic. The fears engendered cause further challenges for these patients and undoubtedly a reduction in their QoL. This survey had identified the breakdown of social life and personal relationships due to their illness and this had led to loneliness and depression. COVID-19 is suggested in this survey, to exacerbate these, with serious long-term consequences. If support and advice are not in place, then morbidity and mortality rates may increase exponentially. It is imperative that these patients must be able to continue their diagnostic and treatment journeys in order to save their lives and further save cost for healthcare services and improve long-term patient outcomes.

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AEP424

The association of Vitamin D deficiency with COVID-19 severity and mortality

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Background and objective
There are few studies showing the association between vitamin D deficiency and COVID-19 severity and mortality. This study designed to investigate the relationship between vitamin D deficiency and the severity and mortality of COVID-19.
Methods
The present cross-sectional study was conducted on 48 COVID-19 patients with positive PCR test results. Patients were divided into three groups according to their serum 25-OH vitamin D3 levels: group 1 < 20 ng/ml, group 2. 20–50 ng/ml, and group 3, ≥ 50 ng/ml. The relationship of the levels of vitamin D3, as well as the history of diabetes, hypertension, Ischemic Heart Disease (IHD), Glomerular Filtration Rate(GFR) ≤ 60 ml/min, LDH ≥ 500 U/l, and Lymphocyte count ≤ 1500 with the severity of the disease and its mortality were investigated.
Results
A significant relationship was observed between vitamin D ≤ 20 ng/ml and the severity of the disease (P < 0.001) and mortality (P = 0.001, adjusted OR = 2.4) in COVID-19 patients. It was also shown that GFR ≤ 60 ml/min (P = 0.02, adjusted OR = 3.6), IHD (P = 0.04, adjusted OR = 2.8), LDH ≥ 500 U/l (P = 0.027, adjusted OR = 1.8) and lymphocyte count ≤ 1500 (P = 0.002, adjusted OR = 2.2) significantly affected the mortality.
Conclusion
The present study showed a significant relationship between vitamin D deficiency and the severity of the disease and mortality in COVID-19 patients. These results suggest the need for appropriate health policies during the COVID-19 pandemic.

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AEP425

Serum 25(OH)D level in patients with COVID-19

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Recently, vitamin D deficiency has been considered as a risk factor for the morbidity and the severity of acute respiratory infections. The aim of this study was to evaluate the interlinks between serum 25(OH)D level and severity of new coronavirus infection (COVID-19) in hospitalized patients.
Methods
We included 131 patients aged 21 to 93 y.o. (mean age 51.7 ± 13.8 years), 76 (57.1%) men, hospitalized following COVID-19 infection. We assessed serum 25(OH)D level for all of them using Abbott Architect i2000 with immunochemiluminescent assay.
Results
Twenty-five (19.1%) patients (15 males) had severe disease, and 108 subjects (80.9%) (61 males) had a moderate one. Fatal outcome was registered in 18 (13.7%) patients and 15 (83.3%) of them had severe course of disease. Half of the severely ill patients were obese. Also, obesity was seen in 64.0% of deceased patients, and was significantly more often than in the discharged ones – 21.3% (P < 0.001). Diabetes mellitus and cardiovascular diseases occurred with the same frequency, regardless of the disease severity. Serum 25(OH)D level ranged from 3.0 to 97.0 ng/ml (13.5 [9.6;23.3] ng/ml). Vitamin D deficiency was diagnosed in 90 (68.7%) patients including 37 with severe deficiency (25(OH)D level < 10 ng/ml). It was found that in patients with severe course, serum 25(OH)D level was significantly lower (9.7 [6.0;14.9] ng/ml) and vitamin D deficiency was more common than in patients with moderate course of the disease (14.6 [10.6;24.4] ng/ml,

P = 0.003). The same pattern was revealed in patients with fatal outcome, where 25(OH)D level was 9.6 [6.0;11.5] ng/ml, compared to levels seen in discharged patients (14.8 [10.1;24.3] ng/ml) (P = 0.001). We found that severe vitamin D deficiency was associated with increased risk of COVID-19 severity (OR = 3.79 [95% CI:1.53–9.39]; P = 0.005) and fatal outcome (OR = 4.07 [95% CI: 1.46–11.35], v0.009). The threshold for 25(OH)D level that was associated with an increased risk of severe course in this population was 11.7 ng/ml (AUCarea = 0.693; sensitivity 71.3% and specificity 68.0%, P = 0.003). Approximately the same 25(OH)D level was associated with an increased risk of mortality – 10.9 ng/ml (AUC_{area} = 0.746; sensitivity 73.9% and specificity 72.2%, P = 0.001).
Conclusions
COVID-19 patients have Vitamin D deficiency in most cases and severe vitamin D deficiency has been found to be associated with an increased risk of severity and fatal outcome of new coronavirus infection.

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AEP426

Telehealth experience of endocrinology research centre

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Introduction
Telemedicine is a useful tool for improving the availability of medical care, especially in the era of COVID-19. It is required to study the needs of the Russian population for telemedicine services for each specific disease.
Methods
In Russian Federation telemedicine consultations (TMC) have been legally allowed since 2018. According to the law, if the patient has not previously attended a face-to-face consultation, the doctor has no right to make a diagnose and prescribe treatment. Remote consultations after a face-to-face visits have no restrictions. All TMC were conducted by physicians of Endocrinology Research Centre in Moscow with medical information system with the identification of the patient's and the doctor's personalities. All data is shown as median [Q1;Q3], unless otherwise indicated.
Results
The number of TMC increased from 104 in 2019 to 1548 in 2020. A sharp increase in patients' requests results from COVID-19 pandemic. Adults received 1200 TMC (M:F = 167:1033, i.e. 13.9% and 86.1%, respectively). 460 were conducted with videoconferencing (38.3%). With the exclusion of repeated TMC, 973 individual adult patients applied for TMC in 2020 (M: F = 143: 830, i.e. 14.7% and 85.3%, respectively). The median age of adult patients was 38.0 years [31.0; 53.0], among women – 37.5 years [30.0; 52.0], among men – 42.5 years [34.3; 54.0]. 348 consultations were provided to children (M: F = 130: 218, i.e. 37% and 63%, respectively). 106 were conducted with videoconferencing (30.4%). With the exclusion of repeated TMC, TMC was provided to 272 children (M:W = 102:170, i.e. 37.5% and 62.5%, respectively). The median age of children was 10.0 years [6.0;14.0], among girls – 11.0 years [6.3;14.0], among boys – 10.0 years [4.0;13.0]. All 1548 TMńwere performed for 201 diseases (indicated by the ICD-10 code). 38 conditions accounted for 65% of all consultations. Among adults, 880 unique cases were identified (1 patient with one certain disease). The most frequent cases were E05.0 (8.8%), E21.0 (4.6%), E66.0 (4.4%), E04.2 (4.3%) and E06.3 (4.2%). Among children, 267 unique cases were identified, the most frequent were E25.0 (12%), E34.3 (7.5%), E66.0 and E10.8 (6% each), E23.0 (5.2%).
Conclusion
The demand for TMC in 2020 increased dramatically. In Endocrinology Centre the demand for TMC didn't correlate with the prevalence of certain diseases. It is necessary to develop telehealth technologies for other conditions and conduct further research to determine the feasibility of including TMC in the national guidelines.

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AEP427

A case of severe erosive rheumatoid arthritis developed in an elderly male patient after bilateral adrenalectomy performed for ectopic Cushing's syndrome

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Introduction
Some, cases of autoimmune diseases were previously reported after surgical remission of CD. In most cases, autoimmune diseases have generally been reported in younger females. However, some cases of Hashimoto's thyroiditis, multiple sclerosis, vitiligo, and sarcoidosis in male patients, after the restoration of hypercortisolemia have been reported as well. Nevertheless, an immediate occurrence of severe erosive rheumatoid arthritis (RA) in an elderly male patient after bilateral adrenalectomy while taking glucocorticoid replacement therapy has not been reported so far.
Case
A 67-year-old male patient admitted to our outpatient clinic with classical signs and symptoms of CS. CS was diagnosed by a failure of suppression of cortisol on low and high dose dexamethasone suppression tests, high urinary free cortisol, and high plasma ACTH levels. A pituitary adenoma could not be found on magnetic resonance imaging, therefore, an IPSS (inferior petrosal sinus sampling) was performed and the result was compatible with an ectopic CS. However, an ectopic tumor could not be found on the neck, chest, and abdominal CT scans, as well as on 68Ga- DOTATATE PET-CT. Bilateral adrenalectomy was performed and treatment with hydrocortisone and fludrocortisone was started. Six months later, the patient was admitted with bilateral small joint arthritis of the hands and morning stiffness. The serum Anti – CCP (Cyclic Citrullinated Peptide, erythrocyte sedimentation rate, and C-reactive protein were 6.2 U/ml (< 5 U/ml), 38 mm/h (< 20 mm/h), and 26 mg/l (< 5 mg), respectively. A hand x-ray showed bilateral space narrowing of the proximal interphalangeal joints with marginal erosions of the proximal interphalangeal joints, soft tissue swelling with periarticular osteopenia, and ulnar deviation of the 2. phalanxes. The patient was diagnosed with erosive RA and treatment with methotrexate was started.
Discussion
The occurrence of autoimmune diseases after remission of CS has been reported in some cases. The restoration of the physiological production of cortisol may cause an immune reaction, leading to the onset of autoimmune disease. RA is an autoimmune disease that is generally seen in females between 40–50 years of age. Our case is the first to report an elderly male patient with erosive RA after bilateral adrenalectomy who was taking physiological doses of hydrocortisone. Therefore, all patients with CS, including elderly male patients, should be closely observed for the occurrence of autoimmune disease after successful restoration of hypercortisolemia.

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AEP428

Sonoelastographic characteristics of parathyroid tumors

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In 2016–2020, 181 patients (mean age – 54.8; range 31–77 years) with tumors of parathyroid glands (PG) were operated. All patients had hyperparathyroidism. The diagnosis was confirmed by high levels of ionized calcium and parathyroid hormone (PTH) in the blood. Ultrasound was performed in all patients before surgery. The evaluation of ultrasound images of PG tumors was carried out according to the following parameters: echogenicity, echostructure, shape, clarity and evenness of contours, the presence of calcinates, features of vascularization. The PG sizes and localization were recorded.
Results
It was possible to accurately determine the localization of tumors in 92.4% of cases. In 14 cases, ultrasound was ineffective: in 5 cases, the PG tumor was mistakenly interpreted as a thyroid node, in 3 cases it was located behind the trachea, in 2 cases – in the mediastinum, in 4 cases-the PG tumor was not visualized. Most tumors were located in the projection of the right lobe of the thyroid – at 55.2% and 44.8% – on the left. In the projection of the lower poles of the thyroid was up 29.6% of the tumors, on the rear surface of the middle segments doll TG – 19.7%, and for the upper poles of the thyroid of 2.8%. When measuring the volume, most tumors were up to 1 cm^3 – 50.7%, from 1 cm^3 to 10 cm 3–40.9% of all adenomas, from 10 cm^3 and – 8.4%. The tumors had an oval or irregular shape on 87.3%. The majority of PG tumors (92.3%) had clear contours. Smooth contours had 61.5% of tumors, uneven contours – 38.5%. Tumors of PG were identified by ultrasound as hypoechoic focus (85.5%), as isoechoic (8%) and anechoic (2.8%) formations. PG tumors had a heterogeneous structure in 58.5%, homogeneous-41.5%. In 63.4%, PG tumors were hypervascular, while in 32.4%, the incoming vessel was clearly visualized, forming a 'vascular arc'. In 36.6%, the blood flow was hypovascular. The liquid component in PG tumors was rarely observed – in 12.7% of cases, and calcification elements were detected only in 4.2%.

Conclusion
The most likely ultrasound signs of PG tumors are: a single hypoechoic formation, with clear uneven contours, an irregular, elongated shape, located outside the thyroid gland, along its posterior surface, more often in the projection of its lower poles. An important criterion characteristic of a PG tumor is the hypervascular type of blood flow and the presence of an incoming feeding vessel.

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AEP429

Case report: The spectrum of autoimmune thyroid disease in association with chromosome 18p deletion syndrome

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Introduction
Chromosome 18p deletion syndrome is a rare chromosomal abnormality caused by the complete or partial delation of the short arm of chromosome 18, represented by facial dysmorphic features, hypodontia, microcephaly, short webbed neck, intellectual disability, reproductive system dysplasia, rarely with autoimmune disorders and IgA, IgG or IgM deficiency. A small subset of patients, approximately 9–10% have cardiac/brain disorders. Circa 150 cases were reported in literature, since it was first described by de Grouchy et al in 1963. Incidence is estimated to be roughly 1:50.000 live births.
Case report
We report the case of a 7 years and 2 months old girl with facial dysmorphism, who was referred to us after being reported symptoms of hyperthyroidism such as palpitations, dysphagia and episodes of diaphoresis. She was the first child born to a non-consanguinous young couple, with a normal gestational period. The parents denied any significant pathological history. She was born full term by caesarean section, Apgar score 8 and birth weight of 3.1 kg. Her height was 47 cm. Karyotyping revealed a deletion of the short arm of chromosome 18 (Cz18p11), causing defective neuropsychomotor development. Our physical examination revealed short statured 95 cm [–3.29 standard deviation score (SDS)], weight 13.5 kg (44% percentile), microcephaly, short neck, hypertelorism and epicanthal folds, enlargement of the thyroid gland. Her vital signs were: heart rate 145 beats/min, blood pressure 100/60 mmHg. Pubertal development B2P1A1. Ecocardiography revealed perimembranous ventricular septal defect and aneurysm of the membranous intraventricular septum. Transthoracic ultrasound showed ventriculomegaly. Thyroid ultrasonography revealed thyroid enlargement, heterogenous with slightly increased vascularity. Blood tests results showed hyposideremia and low ferritin levels. Gonadal hormones levels showed prepubertal status. PTH, ACTH, basal cortisol levels were normal. Initial thyroid function test showed TSH: 0.03 IU/ml, free T4 (fT4): 22.04 pg/ml (8.9–17.2), anti-TPO: 707 IU/ml(n < 35) and TRAb 36.96 IU/m(< 1.75) confirming the clinical diagnosis of Graves's disease. We started treatment with 10 mg/per day Thiamazol reaching euthyroidism. Five months later thyroid test were TSH 69 IU/ml, free T4 (fT4): 2.35 pg/ml (8.9–17.2), anti-TPO: 695 IU/ml(n < 35). Based on such findings we started Levothyroxine with titration of the dose until hormonal levels were normal.
Conclusion
We report a rare case of Graves's disease as a initial manifestation of thyroid autoimmune disease in association with 18p deletion syndrome. It is worth mentioning that autoimmune disorders are especially linked with the deletion of the long arm chromosome 18 leading us to the particularity of this case.

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AEP430

Sulfamethoxazole/Trimethoprim associated hypoglycaemia in a patient with renal transplantation history

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Background
Although rare, hypoglycaemia in patients without history of diabetes should be recognized and studied, in order to reduce associated morbidity. Cotrimoxazole (TMP/SMX) is commonly used in clinical practice and hypoglycaemia is a rare side effect associated with its use. Literature advocates that this effect is due to the fact that SMX has the same sulphanilamide structural group of sulfonylurea, mimicking the hypoglycaemic effect by stimulating pancreatic insulin secretion.
Clinical case
A 62-year-old black woman, admitted in infectious diseases ward, with a diagnosis of cerebral toxoplasmosis. Previous history of bilateral nephrectomy and kidney transplantation 8 years ago, under treatment with tacrolimus 4 mg id and prednisolone 5 mg id, with 25.4 ml/min/1.73 m^2 eGFR. She started pyrimethamine 75 mg od and sulfadiazine 1500 mg 4 times a day, which were discontinued due to vomiting at day 21. A switch to TMP/SMX (1920 mg 3/day) was performed, with good tolerance. On 6th day after starting this drug, the patient showed generalized tonic-clonic seizure and a blood glucose level of 21 mg/dl. Evaluation by endocrinology was requested for severe hypoglycaemia in a patient without diabetes. A 10% glucose infusion was initiated, but the patient maintained hypoglycaemia (capillary blood glucose ~ 30–41 mg/dl), requiring administration of an intravenous bolus of hypertonic glucose solution and also glucagon. The hypothesis of acute adrenal insufficiency and pituitary apoplexy were excluded. Retrospectively, an episode of hypoglycaemia was detected in routine analytical study, on the 3rd day after the beginning of TMP/SMX. Insulin and C-peptide levels were measured, with values of 99 uUI/ml (< 30) and 20 ng/ml (1–7.6), respectively, which were compatible with endogenous hyperinsulinism. TMP/SMX was suspended by the suspicion of iatrogenic hypoglycaemia. Glucose infusion was maintained for 2 days, without any further hypoglycaemic episodes. Ten days after the suspension of TMP/SMX, insulin (8.5 uUI/ml) and C-peptide (5.8 ng/ml) levels were back to normal.
Conclusion
High levels of C-peptide during the episode of hypoglycaemia confirm endogenous insulin secretion. TMP/SMX associated hypoglycaemia can occur in the presence of risk factors, such as high dosage and compromised renal function. Renal dysfunction can lead to decreased drug clearance, leading to gradual accumulation and manifestation of symptoms after a few days. After suspension, difficulty in reversing the hypoglycaemia was not only due to the half-life extension but also because of dose-dependent side effect.

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AEP431

A giant GIST of the greater omentum in a female transsexual patient, hopefully not a side effect of hormonal therapy

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Introduction
Many transsexual patients are concerned about the risk of cancer associated with hormonal gender-affirming therapy. However, the general risk seems to be very low. We hereby report the case of a strikingly large gastrointestinal stromal tumor (GIST) in a male-to-female transsexual patient, after 25 years of hormonal therapy.
Methods
Review of the patient's clinical records and the relevant literature.
Background
GISTs are mesenchymal tumors arising from the smooth muscle pacemaker interstitial cell of Cajal. Most are gastric, but GISTs occurring elsewhere in the gastrointestinal tract have a higher malignant potential. About 85% derive for mutations in the KIT gene (encoding a receptor tyrosine kinase protein). They may present as intramural smooth muscle cell tumors, similar to uterine leiomyomas. However, these last tumors express estrogen and progesterone receptors and are hormone-dependent. On the other hand,

GISTs have nor been shown to express these receptors and are generally not considered as hormone-dependent. The mainstay of GIST therapy is surgery, but tirosin-kinase inhibitors such as imatinib are useful as adjuvants.
Case report
A 46 year-old female transsexual patient had been on estrogen plus antiandrogen since she was 20 years old; currently on 4.59 mg of estradiol (transdermal aerosol) and 75 mg of cyproterone acetate (oral) daily, maintaining suppressed LH and FSH, and testosterone and estradiol within the normal fertile female range. She had undergone bilateral augmentation mammoplasty but not genital reassignment surgery. Last year, she presented a large indolent abdominal mass, and the FDG PET-CT scan showed a giant GIST (size 196 mm transverse × 92 mm posteroanterior × 124 mm craniocaudal), centered in the greater omentum but contacting non-invasively also the stomach, the left liver lobe, the pancreas and the transverse colon. The affinity for FDG was low (SUVmax 3.04), similar to that of the hepatic parenchyma, suggesting a low grade of malignancy. There were no pathological FDG deposits outside the tumoral mass, with no suspicious adenopathies and no signs of liver, lung, adrenal or bone metastases. The patient underwent surgery and is currently being treated with imatinib. The tumor tested negative for estrogen and progesterone receptors, and following the patient's wishes the hormonal therapy has not been withdrawn.
Conclusion
A GIST has never to our knowledge been reported in a transsexual patient. Although the unusual size of our patient's tumor might raise concerns about the possible implication of the hormone therapy, there is no clear rationale for them.

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AEP432

Endocrine function in centenarians

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Introduction
Centenarians are subjects living 100 years or older. They represent a model of successful aging. In 2020, the number of centenarians in the world was approximately 573.000. Multiple endocrine changes occur with normal aging. Most centenarians have managed to avoid, postpone, or overcome the important age-related and life-threatening diseases. The purpose of this review is to present the endocrine function in centenarians with special emphasis on two relevant endocrine glands in this population, the thyroid and the adipose tissue.
Methods
A systematic search of literature was conducted using the search terms centenarians, endocrine function, thyroid, thyroid hormones, thyroid-stimulating hormone (TSH), adipose tissue, and adipokines.
Results
According to most studies, free triiodothyronine (T3) levels decrease while reverse T3 and TSH levels increase with aging. There is also an increase in the levels of most adipokines produced by the adipose tissue (e.g., leptin, resistin, interleukin 6, tumor necrosis factor alpha, and adiponectin). Thyroid hormones play an important role in aging and lifespan. Lower thyroid hormone levels and higher TSH levels have been reported to be associated with increased longevity. Centenarians have higher TSH levels compared to controls, partly due to a genetic background. The elevated levels of pro-inflammatory adipokines (e.g., interleukin 6 and tumor necrosis factor alpha) can negatively impact aging and lifespan by promoting chronic diseases (e.g., obesity, type 2 diabetes, and ischemic heart disease). In contrast, elevated levels of adiponectin (anti-inflammatory adipokine) can be beneficial for lifespan. High adiponectin levels may represent a compensatory response to limit oxidative stress and inflammation. Adiponectin levels are elevated in centenarians and may explain the favorable metabolic phenotype of these individuals.
Conclusion
Hormones influence the aging process and longevity. Centenarians have higher TSH and adiponectin levels compared to controls. High TSH is likely related to a favorable outcome in centenarians regardless of its underlying mechanism. High adiponectin may contribute to extended longevity of centenarians.

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AEP433

Potential endocrine markers of severity and outcomes in critical patients with COVID-19

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Background
The current COVID-19 pandemic is the worst from world infection outbreaks have occurred frequently in the last two decades, and it has led to significant mortality. Although the respiratory system is the most prominent target of SARS-CoV-2, extrapulmonary involvement are important contributors of its morbidity and mortality. A number of symptoms occur in these patients due to the involvement of various endocrine glands. The nervous, endocrine, and immune systems contribute to the response and dynamic adaption to various stresses. Activation of the hypothalamic-pituitary-adrenal axis has been demonstrated in various active critical illnesses. Looking for potential endocrine markers appears to be useful for obtaining information of severity and outcomes in critical patients with COVID-19.
Materials and methods
Prospective descriptive study of critical patients with COVID-19 admitted to the ICU of the hospital from October, 2020, to January, 2021, including hormonal markers and mortality.
Results
In this study, a total 82 of critical patients with COVID-19 in the ICU were enrolled. Dehydroepiandrosterone Sulfate (DHEA-S), total testosterone, SHBG levels were measured in serum of patients. The mean age was 60.4 (standard deviation (SD) 8.7) years, the number of men was 63.4% percent. Regarding outcomes, 46.3% patients with COVID-19 died in the ICU. Mortality consists 38.4% vs 60% in men and women respectively. There are no significant differences in DHEA-S and SHBG levels in died and recovered women with COVID-19. As to men with COVID-19 there are no significant differencse in SHBG levels (21.29 (SD 12.59) nmol/l vs 34.45 (SD 24.53 nmol/l) and in DHEA-S levels (59.06 (SD 37.32) mkg/dl vs 62.03 (SD 33.34) mkg/dl) in died and recovered patients respectively. The mean levels of total testosterone were 2.41(SD 1.83) nmol/l in died patients vs 9.87(SD 6.88) nmol/l in recovered ones ($P < 0.001$).
Conclusion
We expect that the total testosterone may be a useful endocrine marker for poor prognostic outcomes for men with COVID-19 because of its strong association with risk of death.

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AEP434

Drinking only when thirsty or when eating solids can normalize serum sodium levels in most patients with SIADH and a high fluid intake, regardless of Urine Osmolarity

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Introduction
Institutional campaigns, and some health care professionals, encourage the elderly to drink large quantities of fluids, regardless of their level of thirst. Furthermore, SIADH-inducing medications can often cause dryness of mouth. Thus, patients when diagnosed with SIADH can have a high fluid intake (FI), drinking in the absence of thirst. However, fluid restriction, considered the first step in therapy of mild/moderate SIADH hyponatremia, has a poor evidence base, shows an irregular response, can interfere with the intake of protein in solid foods, and should not be used in intense heat. We studied the response of SIADH patients with a history of drinking large volumes of fluids without thirst (HHFI) to simple 'hygienic' fluid intake (HFI) measures.
Methods
Retrospective study of 34 patients diagnosed with SIADH and HHFI in a monographic hyponatremia outpatient clinic of a University hospital in Madrid, Spain. HFI: patients were instructed to drink only when thirsty, unless eating solids, and rinse without swallowing when dryness of the mouth and not thirst was present. Those attaining eunatremia were classified by Urine Osmolality (UOsm). Patients with Primary Polydipsia

(UOsm ≤ 100 mOSm/kg) were excluded. Serum Sodium (SNa) in mmol/l. UOsm in mOsm/kg. Eunatremia was defined as a SNa 135–145. SPSS 25.
Results
Mean age 72 (SD: 15) years, 20/34 (58.2%) women. Nadir SNa: 123 (SD: 6.7). The initial daily fluid Intake ranged from 2.5–10 l, median: 3.2 l [IQR 2.99–4.00]. Mean SNa at the start of HFI: 130 (SD: 5). Following HFI, 26/34 (76.5%) attained eunatremia: mean SNa 138.7 (SD: 3) $P < 0.01$. When classified by UOsm at diagnosis, eunatremia was achevied by 8/10 (80%) with UOsm 101–200; by 5/9 (56%) with UOsm 201–280; by 8/10 (80%) with UOsm 281–600, and 3/5 (60%) with UOsm > 600. When a UOsm cut-off point of 280 was used, 14/19 (73.6%) with UOsm 101–280 reached eunatremia, and 11/15 (73.3%) with UOsm > 280. In no patient was nutritional status worsened. 8/10 non-responders were treated with tolvaptan, achieving eunatremia. 2/10 non-responders were lost to follow-up.
Conclusions
Some SIADH patients at diagnosis have a history of drinking large volumes of liquids in the absence of thirst. Instruction directed towards limiting fluid intake to drinking when thirsty and at meals, as well as distinguishing between thirst and dryness of mouth, can permit attainment of eunatremia in a majority of these subjects, regardless of UOsm at diagnosis.

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AEP435

Congenital adrenal hyperplasia due to 3 beta hydroxysteroid dehydrogenase deficiency About two cases

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Introduction
3ßeta Hydroxysteroid Dehydrogenase (3ß HSD) deficiency is a very rare autosomal recessive disorder affecting the synthetic pathways of all active steroids in the adrenals and gonads.
Observation
The 4-year-old child M.A and his 8-year-old sister M.M, from a consanguineous marriage, with a family history of sexual ambiguity. The clinical examination found a sexual ambiguity in the boy: – micro penis; scrotal hypospadias with a single orifice; – scrotum bifid normally wrinkled and pigmented; – absence of palpable gonads in the bursae Concept of salt loss syndrome at the age of 1 month associated with hypomasculinization of the external genitalia. Hormonal exploration: high ACTH levels, low cortisol and testosterone, high SDHEA.

	Before treatment	After treatment
ACTH (pg/ml)	27 165	215
Cortisol 8 h nmol/l	158	3.12
17OHP (ng/ml)	22.8	0.65
SDHEA (ug/dl)	78.20	4.89
Testo (nmol/l)	7.83	0.06

Genitography
Mullerian residue of 18 mm ending in the bulbar urethra.
Barr test
Barr corpuscles: 0%; test in favor of a genetically male sex. Karyotype: 46XY. – Patient put on 10 mg of hydrocortisone and 9 alpha fludrocortisone. – He is referred for childhood surgery for the treatment of hypospadias. For sister Manel: a salt loss syndrome which appeared at birth without sexual ambiguity, treated with hydrocortisone and at 5 years old, onset of precocious pseudo puberty with acceleration of bone age, pubertal stage S2P2, Genitography: female urethra, karyotype: 46 XX. High ACTH (1122 pg/ml), low cortisol (4.64 nmol/l), 17OHP (0.33 ng/ml), SDHEA (8.21 mg/dl); testo (0.26 nmol/l). Put on hydrocortisone 20 mg/day and 9 alpha fludrocortisone.
Discussion
(3ß HSD) deficiency is a very rare form of congenital adrenal hyperplasia encompassing the forms with loss of salt and without loss of salt with a broad clinical spectrum including glucocorticoid deficiency and under-virilization in men manifested by micropenis and severe perineo-scrotal hypospadias. The prevalence is unknown due to the great rarity of the disease. Boys have different levels of under-virilization at birth. In both sexes, the salt loss forms lead to symptoms of dehydration and hypotension in the first weeks of life which can be fatal.The disease is caused by mutations in the HSD3B2 gene located on chromosome1p13.1.
Conclusion
The deficit of 3B HSD has benefited from advances in biochemistry and molecular biology which have opened up new perspectives in the field of pathophysiology, genetic determinism, diagnosis and antenatal treatment.

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AEP436

Analysis of glycemic variability in patients with diabetes mellitus type 2

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Objective
To identify risk factors affecting the severity of glycemic variability indicators in patients with diabetes mellitus type 2.
Materials and methods
The study included 92 patients with diabetes mellitus type 2 and an average age of 62.25 ± 9.52 years. A biochemical blood test was performed on an automated Cobas 6000 system. To assess the glycemic variability, the standard deviation (SD, mmol/l), the coefficient of variation (CV,%) and the mean amplitude of glycemic excursion (MAGE, mmol/l) were determined. Statistical processing of the data array was performed using the statistical program MedCalc v.11.6.0.0. (MedCalc Software Inc.). The level $P < 0.05$ is considered as a criterion for the statistical confidence of the results.
Results
According to the results of logistic regression, BMI has a greater effect on CV (RR = 0.83; 95% CI 0.75–0.32 $P = 0.002$), SD (RR = 0.90; 95% CI 0.83–0.97, $P = 0.009$), MAGE (RR = 0.89; 95% CI 0.81–0.97, $P = 0.014$) than the experience of type 2 diabetes mellitus on CV (RR = 1.10; 95% CI 0, 99–1.21 $P = 0.053$), SD (RR = 1.09; 95% CI 0.99–1.19, $P = 0.05$), MAGE (RR = 1.06; 95% CI 0, 97–1.16, $P = 0.136$) and the level of TG on CV (RR = 0.53; 95% CI 0.27–1.05 $P = 0.070$), SD (RR = 0.80; 95% CI 0, 57–1.10, $P = 0.176$), MAGE (RR = 0.83; 95% CI 0.57–1.20, $P = 0.335$). A decrease in BMI increases the degree of manifestation of GV indicators by an average of 1.1 times. The threshold value of BMI was 28.6 kg/m^2 for CV AUC = 0.77 (sensitivity 64.0% [95% CI 42.5; 82.0], specificity 88.0% [95% CI 77.8; 94.7], $P = 0.002$), for SD AUC = 0.69 (sensitivity 41.67% [95% CI 27.6; 56.8], specificity 90.9% [95% CI 78.3; 97.5], $P = 0.0003$), for MAGE AUC = 0.68 (sensitivity 46.8% [95% CI 29.1; 65.3], specificity 86.4% [95% CI 75, 0; 94.0], $P = 0.0021$).
Conclusions
A risk factor that increases glycemic variability is a BMI less than 28.6 kg/m^2. A decrease in BMI increases the degree of manifestation of GV indicators by an average of 1.1 times.

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AEP437

Insulinoma during pregnancy: A case report

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Introduction
Insulinoma is a rare neuroendocrine tumor with an incidence of 1 to 4 per million person-years. It is the most frequent endocrine tumor of the pancreas and is revealed by a spontaneous hypoglycemia in the absence of insulin or any antidiabetic medication.Only few cases of confirmed insulinoma with pregnancy have been described in the literature. We describe a case of insulinoma discovered early in pregnancy.
Case report
A 24-year-old woman was admitted in our department at 12 weeks of gestation for morning asthenia and loss of conscience, with glycemia inferior to 0.5 g/l. Endogenous hyperinsulinic hypoglycemia was confirmed with a spontaneous hypoglycemia and laboratory blood glucose at 0.41 g/l, a concomitant insulinemia at 6.4 µUI/ml (≥ 3), C-peptide levels at 2.01 ng/ml (≥ 0.6) and absence of sulfonylurea. Localization was assessed by a pancreatic MRI concluding to a 10 mm tumor in the head of the pancreas, with low-signal intensity on T1-weighted images and high-signal intensity

on T2-weighted images. A complementary investigation by an endoscopic ultrasound identified 11 * 13 * 8 mm tumor in the head of the pancreas. The patient was operated on at 17 weeks of gestation. The tumor was removed by enucleation during an open surgery. Histologic and immunohistochemical reports concluded to a 15 mm well differenciated neuroendocrine tumor with no angioinvasion. Immediate post-operative follow up was marked by a pancreatic fistula persistent during 5 weeks, treated by drainage. In long-term follow-up, she no longer had hypoglycemia and gave birth at 40 weeks of gestation to a healthy girl weighting 4 kg.
Conclusion
This case highlights a rare clinical presentation of an insulinoma. The confirmation of the diagnosis is through the same biologic investigations than the non-pregnant population. The delay between diagnosis and treatment should be short in order to prevent foetal hypoglycemia.

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AEP438

Insulinoma: a challenge for a diagnosis

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Introduction
Insulinoma is the most frequent endocrine tumor of the pancreas and a diagnosis challenge in all cases of spontaneous hypoglycemia. The confirmation of hypoglycemia is the first step of the diagnosis before initiating the complementary investigations to confirm the insulinoma and determine its localization. The aim of this study was to investigate the diagnosis of insulinoma in a setting of organic hypoglycemia.
Methods
We performed a retrospective study of 38 adults in patients presenting with spontaneous hypoglycemia over a 19-year period. Hypoglycemia was confirmed when blood glucose levels were inferior to 0.45 g/l, insulinemia and C-peptide were elevated if respectively superior to 3 µUI/ml and 0.6 ng/ml.
Results
Ten patients were included with a confirmed hyperinsulinic hypoglycemia, with a sex ratio of 3/7. The mean age was 41 ± 15 years. Neurogenic and neuroglycopenic symptoms were present respectively in 9 and all cases. Fasting hypoglycemia was present in 6 cases, after physical activity in one case and at any time in 3 cases. Hypoglycemia was obtained spontaneously in 6 cases with mean hypoglycemia at 0.27 g/l, mean insulinemia at 118.6 µUI/ml and mean C-peptide at 32.01 ng/ml. Hypoglycemia was obtained after a supervised fast test in 4 cases, with hypoglycemia obtained after a mean of 3 hours. Mean hypoglycemia was 0.28 g/l, mean insulinemia was 29.8 µUI/ml and mean C-peptide was 5.13 ng/ml. Sulfonylureas weren't detected in all patients. In imaging investigations, abdominal ultrasonography was normal in the 6 patients it was performed on. Abdominal CT scan was performed in 8 patients and found a tumor in 3 cases. Abdominal MRI was performed in 7 patients, was normal in 3 cases and found a tumor in 4 cases. Endoscopic ultrasound was performed in 8 patients, was normal in 3 cases and found a tumor in 5 cases. It found a tumor in the 4 patients with a tumor in the MRI with a patient whose tumor was only diagnosed with endoscopic ultrasound. The tumors confirmed by CT scan weren't found by other imaging means. CT scan and endoscopic ultrasound were enough to found the localization in the 8 patients with confirmed localization before surgery.
Conclusion
The diagnosis of insulinoma is easily confirmed when the hypoglycemia is confirmed and allowing all biology investigations. The challenge remains in the localization as no imaging procedure was enough on its own to confirm localization, and even with all procedures, localization wasn't found in 2 cases, confirming therefore the difficulty of pre-operative investigations.

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AEP439

A case report of cerebral salt wasting incorrectly diagnosed as the syndrome of inappropriate antidiuretic hormone secretion

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Cerebral salt wasting (CSW) occurs as the result of injury to the central nervous system and is most commonly found among those who have experienced a traumatic brain injury (TBI). Although incidence is varied, it has been reported to be as high as 30% within the patient population presenting to hospital with a TBI. CSW causes hyponatremia with concurrent hypovolemia and increased sodium within urine despite normal renal function. Because of its rare nature, CSW is often misdiagnosed as the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Misdiagnosis of CSW occurs at increased rates within healthcare setting wherein the condition is rarely encountered – as with the current case who presented to a district general hospital. This can have a deleterious impact upon patient outcomes, as the conditions require the introduction of treatment regimens that are the opposite of each other. SIADH calls for fluid restriction, while CSW and its accompanying hypovolemia require sodium and fluid repletion. The following case report details an 81-year-old male patient who presented to a district general hospital following a fall that included trauma to the head and subsequent cerebral haematoma. Incorrectly diagnosed with SIADH, his condition continued to decline (including sodium levels as low as 124 mmol/l and a postural hypotension-induced syncopal episode) despite receiving appropriate treatment for his initial diagnosis. Following a consultation with an endocrinologist, his diagnosis was changed from SIADH to CSW and treatment with > 3 l/day with IV normal saline (0.9% solution) was administered. The patient was also advised to eat and drink as normal. After two days on this regimen, his sodium levels increased to 131 mmol/l and an increase in blood pressure alleviated his postural hypotension. After 27 days in the hospital, the patient achieved normal sodium levels and was discharged with advice to monitor his sodium levels via monthly monitoring with his general practitioner. At follow-up, the patient had maintained healthy sodium levels and an MRI of his head revealed resolution of the cerebral haematoma. Despite CSW and SIADH both causing hyponatremia, their etiologies hold important differences and, consequentially, their treatment requirements should be considered mirror images of each other. In order to effectively diagnose and treat patients with either CSW or SIADH, the awareness of both conditions must be increased among healthcare professionals.

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AEP440

Myasthenia during multiple autoimmune syndrome: About two observations

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Introduction
Multiple autoimmune syndrome (MASI) is a rare entity, defined by the presence of at least three autoimmune diseases in the same person. We report two specific observations of myasthenia gravis in the context of an SAIM3.
Observation 1
A 58-year-old man initially presented bilateral ptosis, difficulty chewing and swallowing, dysphonia and fatigability. Myasthenia gravis was suspected due to the aggravation of this complaints with effort and confirmed by prostigmine test and EMG which showed a post-synaptic block in the neuromuscular junction. The diagnosis of hypothyroidism was suggested by mucocutaneous infiltration and constipation and confirmed by a TSH elevated to 100IU/ml with a low FT4 of 5 pmol/l. It was hypothyroidism secondary to Hashimoto's thyroiditis with highly positive antithyroglobulin and Anti thyroperoxydase antibodies. The onset of melanoderma and hypotension suggested adrenal insufficiency, confirmed by low basal cortisolemia at 53 ng/ml and insufficient response to synactene 250g to 150 ng/ml after optimal thyroid hormone substitution. Anti-adrenal Antibodies were negative. The cervico-thoracic CT scan ruled out the presence of a thymoma. The diagnosis of SAIM type 3 was retained. The patient was trated by Mestinon, Cortef and Levothyroxine. The evolution was favorable.
Observation 2
A 14 year old patient, initially hospitalized for ptosis, asthenia and thermophobia. Clinical examination showed bilateral ptosis, ophthalmoplegia with limitation of lateral and vertical movements. The diagnosis of myasthenia gravis was made by a positive prostigmine test: correction of the deficiency within a few minutes after VILI injection of an ampoule of prostigmine. The electro-neuro-myogram was in favor of the diagnosis of myasthenia gravis. Anti-acetylcholine receptor antibodies were positive. Clinical examination of the patient also showed weight loss, fine tremors of the extremities, tachycardia and glare. The diagnosis of hyperthyroidism was confirmed

by an elevated FT4 of 27.8 pmol/l (8.6–25 pmol/l) and a braked TSH of 0.001 mU/l. This hyperthyroidism was related to Hashimotoxicosis guiven the positivity of anti thyroglobulin and anti thyroperoxydase antibodies. Signs of hypocorticism such as asthenia, weight loss, melanoderma and hypotension were objectified. Addison's disease was confirmed by low baseline cortisolemia at 37.4 ng/ml and positive adrenal antibodies. The patient was treated with prostigmine 240 mg/dr, cortef 15 mg/dr and radioactive iodine for her hyperthyroidism with good evolution.
Conclusion
The association of the different autoimmune diseases reflects the presence of a common genetic ground on which environmental factors determining clinical aspects are grafted.

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AEP441

Association of Hadju Cheney syndrome with adrenal insufficiency in a diabetic patient: A rare association

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Introduction
Hadju Cheney syndrome (HCS) is a rare progressive and debilitating genetic disorder that is characterized by a high degree of phenotypical pleiotropy. We report the first clinical case of a 44-year-old patient with HCS, diabetes and adrenal insufficiency (AI).
Observation
A 44-year-old patient with a history of myocardial infarction at the age of 33 and diabetes for 2 years on oral antidiabetic drugs is admitted for switching to insulin therapy. On examination, he had short stature, facial dysmorphism, early tooth loss with diffuse acroosteolysis on standard radiograph. The biological assessment showed a normal phosphocalcic balance. Bone densitometry showed diffuse osteoporosis. The renal ultrasound and the cardiac ultrasound were without abnormalities. Faced with the characteristic polymalformative syndrome, the diagnosis of HCS has been made and the genetic study looking for a mutation in the NOTCH2 gene is underway. In addition, the patient presented repeated episodes of hypoglycemia during his hospitalization with an inappropriate cortisolemia at the time of the hypoglycaemia, which allowed us to retain the diagnosis of AI very probably of central origin. The patient was put on hydrocortisone.
Discussion
HCS is a rare genetic skeletal syndrome. The diagnosis of this syndrome was made in our patient based on the characteristic clinical features and imaging findings in hands, feet and skull. Recently it has been shown that restricted range of mutations in the terminal exon of NOTCH 2 causes this syndrome. There has been no report about the linking of HCS and DM, although several studies addressed the pancreas and Notch signaling. Discussing the type of diabetes in our patient was therefore a bit difficult, we ruled out type 1 diabetes as well as mitochondrial diabetes. Type 2 remains the most likely with rapid recourse to insulin therapy. In addition, cranial dysplasia can be the cause of pituitary insufficiency which could explain the adrenal insufficiency in our patient. However, there was no other pituitary insufficiency.
Conclusion
Until this case, there has been no reported case of HCS with DM and AI. The present case indicates that there may be a link between HCS and DM in regard to the mutation of NOTCH2. Confirmation awaits further studies of the relationship between insulin secretion and NOTCH2 signaling.

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AEP442

Corticosteroids – 70 years of balancing between good and bad

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When in September 1948 the 'Compound E' was first synthesized and successfully administered as intramuscular injection to a woman with rheumatoid arthritis, hardly that anyone could imagine what profound impact it will have on medical research and practice. In a span of just two years, in 1950, the fascinate drug was renamed to Cortisone and brought from laboratory to broad clinical use. Seventy years later, it is still hard to find a medical field where corticosteroids are not present due to several roles they play in the human body. Corticosteroids are the cornerstone of therapeutical approach in wide spectrum of antinflammatory and autoimmune-based diseases and one among ten most commonly prescribed and over-the-counter drugs. However, from the very beginning to nowadays, the limiting factor regarding their use are side effects. Back to 1948, the reports are saying that after a couple months of continuous therapy with cortisone, the first patient was admitted to psychiatry clinic for comprehensive assessment and treatment of psychotic episodes. Description of side effects along with development of new cortisone derivates in order to minimise toxicity and improve potency shaped the next decades in corticosteroid timeline. The occurrence and magnitude of corticosteroid side effects is time and dose-dependent, following either linear or threshold dose-response pattern. Their extensive use in chronic conditions along with awareness about disadvantages triggered highly innovative research and expansion of new preparations for local administration. Prescribing corticosteroids via inhaled, topical dermal, intra-articular, epidural, intranasal or periocular route, particularly when used at high doses, allows us to target specific problem, diminish system resorption and consequently side effects, ranging from mild suppression of hypothalamic-pituitary axis to life-threatening infections. Corticosteroids inspire and teach. While search for corticosteroid preparations with even better risk-benefit profile continues, their use in chronic inflammatory and autoimmune diseases requires rationality in determining the optimal therapeutical regimen, convenient tapering schedule and often a skilled balancing between desired and side effects.

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AEP443

Monitoring of patients on high-dose long-term steroids in a rheumatology outpatient service

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Introduction
Corticosteroids play an essential role in the management of many rheumatic diseases. However, corticosteroids are associated with many adverse effects, including hyperglycaemia, dyslipidaemia, and osteoporosis. These adverse effects are dose related and patients on high dose, long term steroids (defined as > 5 mg oral prednisolone and treatment duration > 3 weeks) are at greatest risk. NICE guidelines on corticosteroids recommend monitoring of HbA1c, triglycerides, and potassium for all patients on long term steroids1. Regarding osteoporosis risk, it is recommended that all adults who are expected to be on prednisolone ≥ 5 mg/day (or equivalent) for over 3 months have bone mineral density assessed three-yearly[2].
Aims
To examine whether Hba1C, potassium, and lipid profile are monitored amongst rheumatological patients on steroids, and to assess whether these patients have had bone mineral density assessed within the previous 3 years by means of dual energy X-ray absorptiometry (DEXA).
Materials and methods
This retrospective audit examined the records of 442 patients attending rheumatology clinics in Mater Misericordiae University Hospital, Dublin, Ireland over a 4-week period in November 2020.
Methods and results
Fourteen percent (n = 62) of patients were on high dose long term steroids. Seventy-one percent (n = 44) were female, 29% male (n = 18), with a median age of 63 years. The most common conditions encountered were rheumatoid arthritis (22% n = 14), giant cell arteritis (21% n = 13), polymyalgia rheumatica (18%, n = 11), systemic lupus erythematous (6% n = 4), large vessel vasculitis (5% n = 3), mixed connective tissue disease (5% n = 3) Bechet's (5% n = 3) and others (18% n = 11). All patients were on prednisolone and the mean dose was 8.7 mg. The median duration of treatment was 24 months. Ninety seven percent of patients (n = 60) had potassium checked within the preceding 12 months. Fifty percent (n = 31) had triglycerides checked, 52% (n = 32) had Hba1C checked. The average Hba1C level was 42.4 mmol/mol. Forty three percent (n = 14) had Hba1c in the range of 42–47, while 16% (n = 5) had a Hba1c ≥ 48. The majority of patients (69%, n = 43) had undergone DEXA scanning, with an average recorded T score of –1.47.
Conclusions
Corticosteroids have a significant role to play in the management of many rheumatic conditions. Prescribers need to be aware of the many associated adverse effects and monitor for the presence of these effects accordingly.

1. NICE guidelines: Corticosteroids. June 2020; 2. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Liu *et al*. Allergy, Asthma & Clinical Immunology 2013.

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AEP444

ABSTRACT WITHDRAWN

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AEP445

Vitamin D deficiency in young adults and the question of the need for early replacement for the primary prevention of osteoporosis

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Introduction
Low concentrations of vitamin D are associated with decreased calcium absorption, negative calcium balance, and compensatory growth of parathyroid hormone, resulting in excessive bone resorption. The first step in preventing osteoporosis is to ensure a proper diet, especially calcium and vitamin D intake.
Aim of the study
The aim of this study was to determine the concentration of 25-hydroxyvitamin D3 (25-OH-D3) in Eastern Croatia in subjects aged 18 to 25 years at the end of winter and to examine whether there is a difference according to gender and compare the results with reference values.
Subjects and methods
The study was conducted on a sample of 59 subjects, with an average age of 23 years, of which 27 were men (45.8%) and 32 women (54.2%). Blood was drawn and centrifuged at 3.000 rpm for 10 minutes. After centrifugation, serum was collected, and the sample was analyzed by liquid chromatography combined with mass spectrometry (LC-MS/MS).
Results
The mean concentration of 25-OH-D3 was 16.36 ng/ml (SD 5.68; range 4.90 to 28.60). Men had a statistically significant higher concentration compared to women (18.96 vs. 14.16 ng/ml, p 0.01). The concentration was lower than the reference value (20 to 100 ng/ml). Only 28.8% of subjects (44.4% men and 15.6% women) had values greater than 20 ng/ml.
Conclusion
As many as 71.2% of young adults had vitamin D deficiency at the end of the winter period. Women had statistically significant lower concentrations. The observed deficit indicates the need to determine the optimal intake of 25-OH-D3 for the purpose of osteoporosis prevention. It is necessary to conduct research on a larger number of examinees over a longer period with monitoring of outcomes.
Keywords: calcifediol, vitamin D deficiency, young adults, liquid chromatography-mass spectrometry, osteoporosis

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AEP446

An audit of Multiple Endocrine Neoplasia type-1 (MEN-1) surveillance

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Introduction
Multiple Endocrine Neoplasia type-1 (MEN-1) is an inherited autosomal dominant condition with a high degree of penetrance characterized by tumour occurrence in the form of pancreatic neuroendocrine (pNET), parathyroid and anterior pituitary gland tumours, among others. Treatment for MEN-1 associated endocrine tumour, particularly pancreatic, is more challenging than in those without MEN-1, given its multicentric nature and aggressive behaviour. Hence early detection through targeted surveillance is paramount.
Aim
The aim of the audit is to compare our surveillance of MEN-1 patients and benchmark against published guidelines.
Methods
We performed a search for patients with a diagnosis of MEN-1 using our hospital electronic records (notes, laboratory and radiology) and collected data retrospectively. We looked at the radiological and biochemical surveillance and their frequency.
Results
A record of 15 patients with a diagnosis of MEN-1 was found (males 4/15 (27%) and females 11/15 (73%). 13/15 (87%) had annual calcium profile and one at 3 years. For parathyroid hormone (PTH) 11/15(73%) had annual measurements, 3/15(20%) had 3 yearly profile. Screening frequency for fasting gut profile for 1 year, 2 years, 3 years were 9/15(60%), 2/15(13%) and 3/15(20%), pancreatic cross-sectional imaging were 7/15 (47%), 2/15 (13%) and 2/15(13%) respectively. The majority of patients had plasma prolactin and insulin-like growth factor 1 (IGF-1) checks annually 11/15 (73%) and 3/15 (20%) once every 3 years. For pituitary MRI surveillance: 10/15 (67%) were screened within the recommended 3–5 years timeline while 33% had longer interval between scans.
Conclusions
Overall our audit shows good compliance with existing MEN-1 guidelines, with our cohort of patients being regularly screened for the development of primary hyperparathyroidism, pNET and pituitary tumours. To improve this further our MEN-1 patients are now being reviewed in specialised clinics.
Reference
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AEP447

Attitudes of physicians towards the guideline-recommended LDL target levels in diabetic dyslipidemia

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Aım
The aim of this study is to investigate the attitude of physicians, who are specialized in internal medicine, endocrinology, nurology and cardiology, on LDL target levels and antilipidemic treatments in Turkey.
Methods
This study outlines attitudes of physicians towards the guideline-recommended LDL target levels in diabetic dyslipidemia. An invitaiton to fill a questionnaire on demographic and profession characteristics as well as attitudes towards the guidelines. 564 physicians filled the questionairre.
Results
42.2% of the physicians participating in the survey are between the ages of 30–39 and 0.9% of them are over 70. 27.1% of them have been working as a physician for 5–10 years and 12.9% for 15–20 years. 55% of the physicians' profession are internal medicine, 27.1% endocrinology, 10.1% cardiology and 7.8% neurology. 95.2% of the physicians stated that they had been taking the guideline recommendations as reference and TEMD(Turkey Endocrinology and Metabolism Association) and ACC/AHA(American College of Cardiology/American Heart Association) guidelines were the most considered guidelines. While the majority agrees that LDL level is a risk factor for cardiovascular disease, 0.9% of the physicians are not sure and 0.7% of them disagree. 13% of the physicians disagree with the view of 'routine statin therapy should be initiated in high risk type 2 diabetic patients'. Although guidelines recommend keeping LDL below 55 mg/dl with high dose statin therapy in type 2 diabetic patients with cardiovascular disease, 8% of physicians do not agree with this recommendation. 30.2% of the physicians aim the LDL level < 55 mg/dl for the patients with type 2 diabetes accompanied by progressive atherosclerotic cardiovascular disease. 55.8% of those physicians are specialized in internal diseases. Only 9.3% of physicians aims LDL level < 55 mg/dl for the patients with type 2 diabetes accompanied by chronic renal failure. 40.3% of them are specialized in internal diseases. 28% of the physicians do not agree with the suggestion that statin therapy should continue for life.

Conclusions
Although physicians affirm that they follow the guidelines, LDL target level recommendations in current guidelines are not seem to be adopted. The guidelines recommend low LDL target levels, while physicians keep target levels higher.

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AEP448

Biological activity of thrombopoietin receptor agonists: development of *in vitro* functional and binding assays

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Introduction
Nowadays thrombopoietin receptor agonists (TPO-RAs) represent a promising approach for the patients with immune thrombocytopenia (ITP). Usage of two licensed TPO-RAs, romiplostim and eltrombopag, provide efficient support of ITP patients´ platelet count and, as a consequence, better control of disease. Both agents have an acceptable toxicity profile, but there are several another disadvantages in terms of usage of these drugs such as cost (especially for romiplostim), daily dosing (for eltrombopag) and specific adverse events. That´s why discovery of new TPO-Ras or development of similar products of existing TPO-Ras are emergent approaches to improve the life quality of ITP patients. The non-clinical development plan of both similar and new TPO-Ras should contain sensitive and specific *in vitro* pharmacology assays. Using two known TPO-Ras (recombinant human thrombopoietin (rhTPO) and romiplostim) in this study we have performed validation of the two *in vitro* assays to provide robust functional and binding data.
Methods
Romiplostim-TPO-R binding affinity was monitored with BLI technique using Octet RED96 instrument (ForteBio, Pall). In this study recombinant human thrombopoietin receptor with a C-terminal 6-His-tag (R&D Systems Inc.) was immobilized to anti-penta-HIS biosensors. Kinetic binding constants of romiplostim-TPO-R were determined through global fits using ForteBio Data Analysis. Association and dissociation rates were simultaneously fit to 1:1 ligand binding model to determine the affinity constant (KD) value. To evaluate functional effects of rhTPO murine 32D cell line expressed human TPO-R was developed. After transfection and during the development of stable and functional 32D-hTPO-R cell line clonal selection was performed. Presence of human TPO-R was determined using fluorescence-activated cell sorting analysis, Western blot analysis was used to evaluate TPO-R phosphorylation after rhTPO stimulation. Functional characterization of generated 32D-hTPO-R was performed in rhTPO-induced proliferation assay based on the CellTiter-Glo Luminescent Assay (Promega Corp.). EC50 values were analysed to measure functional proliferation response.
Results
In binding assay KD of romiplostim-TPO-R interaction was in 0.1228–0.134 nM range. In proliferation assay in 32D cells stable expressed functional human TPO-R for rhTPO EC50 was determined at 688 pg/ml. Both assays were validated in terms of main parameters such as linearity, specificity, precision. Acceptable degrees determined.
Conclusions
In this study our data demonstrated that binding and functional assays were well validated to receive robust data. Thus, *in vitro* pharmacology assays mentioned above can be used for the purpose of similar and new TPO-Ras drug development.

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AEP449

Parameters of successful telephone endocrinology consultation during covid-19 pandemic

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Objective
The COVID-19 pandemic is an unseen international emergency causing major challenges in medical care delivery. Patients with some chronic endocrine disorders (obesity, type 2 diabetes, probably also hypertension, corticosteroid excess) have higher rates of acute COVID-19 complications and death. Due to the changes in outpatient management there is a clear danger of inadequate clinical support for endocrinology patients. The decision for face-to-face or remote consultation should be based on patient assessment. In our study, we aimed to identify parameters that define the success of a telephone endocrinology consultation.
Methods
By telephone, we performed a prospective study of 100 authors' consecutive patients of our institution's outpatient endocrinology clinic, scheduled for a regular visit. Thyroid and diabetic patients were not included. It was done during 2020 covid-19 pandemic from September to November. We defined a successful consultation as one leaving both a patient and a doctor with the overall feelings of success and satisfaction about its contents and way of interpersonal interaction (successful/unsuccessful). We collected data on patients' sex (M/F), age (20–40, 40–60, 60 + years), education (primary, secondary, higher), first or follow-up consultation, clinician's general assessment of the level of disease control (insufficient, sufficient), duration of consultation (less than 5, 5–15, more than 15 minutes). For statistical analysis, we performed chi-squared test based on the categories above using SPSS. Values of $P < 0.05$ were considered statistically significant.
Results
In 76% of our patients, a telephone consultation was considered successful. 56 females were included. 44 patients were older than 60, 48 were 40–60 years old. Sex, age, clinician's assessment of disease control and duration of consultation were not linked to the success of consultation ($P > 0.05$). Higher education and a previous face-to-face consultation were associated with success. 48 patients accomplished secondary and 22 higher education: χ^2 (2) 6.93, p 0.041. 31 patients had first and 69 follow-up consultation scheduled: χ^2 (1) 5.33, p 0.022.
Conclusion
In more than three quarters of our patients, a telephone consultation was assessed as successful by both a patient and a doctor during covid-19 pandemic. The success was associated with higher education level and previous face-to-face contact. Telephone consultations seem to be successful in most endocrinology patients while also being safe. In the future, the role of telephone consultations in outpatient setting should be better defined, especially in patients with higher risk of covid-19.

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AEP450

Role of estradiol and progesterone in fragmented sleep of castrated rats

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Sleep is disturbed in both healthy and pathological aging, so it is essential to consider the role of ovarian hormones in both processes. Studies supporting the natural function of E2 (or elevated FSH) in fragmented sleep are inconsistent because when non-human animals have been used, they have mainly been male. Given this background, this study focused on determining the role of different estradiol and progesterone doses in the intermittent arousals of castrated rats maintained by two-month in controlled-conditions. These arousals were also determined in castrated rats without treatment and in sham-operated rats as experimental controls. The treatment scheme consisted of weekly increasing the dose of E2 and/or P4 to these females. The quality of sleep of the controls and the experimental evaluated by counting the animals' number of awakenings during the sleep cycle. This procedure was performed daily for five consecutive weeks, using video cameras. The results showed a significant difference between the number of awakenings of the ovariectomized rats and the sham-operated rats during the study weeks. The number of awakenings in the castrated rats treated with E2 and/or P4 gradually decreased as the hormonal doses were increased. In such a way, in the fifth week, the awakenings fell below those in sham-operated. E2 -treatment showed an effect from the first week with the first dose, and in the fifth week, it displayed a frankly anesthetic activity. Progesterone began to show activity on the third week, but it showed an anesthetic effect with the highest dose in the fifth week. However, both steroids combined showed significant activity, reducing the number of awakenings from the third week, without achieving the anesthetic effect seen with the steroids separately at the fifth week. These results suggested estrogens and progesterone-combination regulated the number of awakenings of the castrated rats since the third-week treatment. Plots of dose-response of these experiments indicated

that estradiol and progesterone effects were performing by different action mechanisms.

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AEP451

The (epi)genetic basis of gender incongruence

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In mammals, the gonads and the brain develop from bipotential organs that will differentiate into female or male organs, during a critical period of development. This process begins with the production of testosterone by the testes, which will be converted into estradiol in the brain, by the aromatase. While the end is defined by the moment when the inhibition of androgens (in males), or treatment with estrogens (in females), stops having an effect on brain dimorphism. But in humans, biological sex and brain sex are not always coincident. Thus, transgender females are born with male genitalia. Their sex is male, but their gender is female. In contrast, transgender males are born with female genitalia. Their sex is female but their gender is male. These people generally show gender incongruence (GI), due to the incongruence between sex and gender.
The origin of GI is complex, where neurological, hormonal and genetic factors play an important role. One of the current hypotheses suggests that GI could be related to a different sexual differentiation of the brain, not concordant with gender. But other processes are also involved. Thus epigenetics, specifically DNA methylation, can alter the chromatin structure, modifying the access of transcription factors to the promoter regions, modulating gene expression. Thus, 16 trans people were compared with 16 cis people, with the same geographic origin, ethnicity and sex. Methylation analysis was performed on blood, using the Infinium Human Methylation 850K BeadChip. The changes in methyloma were analyzed with the Partek Genomics Suite program. When we compared methylome of cis and trans populations with the same sex assigned at birth, we found significant differences in 71,515 CpGs that passed the criterion FDR p <0.05 (28.5% located in islands). When we compared cis men vs. trans women we found 20 CpG islands that passed both criteria (FDR p<0.05; fold change ≥ ± 2). The most significant CpGs were related to genes: *WDR45B*, *SLC6A20*, *NHLH1*, *UBALD1* and *PLEKHA5*. With respect to populations assigned female at birth, when we compared cis women vs. trans men, we found 4 CpGs that passed both criteria. The results of enrichment tests yielded significant over-representation for the categories of biological process, cellular component and molecular function ontologies: negative regulation of gene expression, positive regulation of catalytic activity, ribonucleotide binding, RNA binding, among others.

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AEP452

Growth hormone treatment in turner syndrome: How is the statural growth after one year?

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Introduction
Turner syndrome is a rare condition that affects only females. It results when one of the X chormoses is missing or partially missing. It can cause short height, ovarian failure, heart defects and other complications. It is an indication for growth hormone treatment. The aim of our study is to evaluate the statural growth over one year in turnerian patients treated with growth hormone.
Materials and methods
We conducted a retrospective study on 7 Turnerian patients admitted in the endocrinology department and treated with growth hormone. The results were collected and processed using the SPSS operating software V21.
Results
The prevalence of Turnerian patients treated with growth hormone was 36.8% of all Turnerian patients. The mean age of patients at diagnosis was 9.6 ± 4 years, and impuberism was noticed in all patients. At the beginning of growth hormon treatment, the mean height of the patients was 114.6 ± 9.8 cm, the mean standard deviation (SD) score for height was –2.8 SD ± 0.91 for the normal curve, and normal in the Turner curve. The median difference in bone age from chronological age was 33 months (from 12 months to 81 months). The mean dose of growth hormone at the initiation of treatment was 0.8 mg/day, giving an average of 0.04 mg/kg/day. After one year of treatment: The mean height was 120 ± 9 cm, the mean standard deviation score was –2.6 SD ± 1 in the normal curve, and normal in the Turner curve. The mean gain was 6 ± 2 cm, The median difference in bone age from chronological age was 8 months, (from 2 months to 48 months). IGF1 at one year of treatment was normal according to pubertal stage for all patients and no adverse effects of growth hormone treatment were detected during this period.
Discussion and conclusion
In our study, growth hormone treatment allowed an average statural gain of 6 cm over one year. Safety was assessed in all patients. Our results are in agreement with literature data regarding the interest of growth hormone treatment in Turner syndrome, allowing the optimization of the statural gain, especially when the treatment is started as early as possible.

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AEP453

The association of angiotensin converting enzyme inhibitors and receptor blockers with COVID-19 severity and mortality

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Background
The available data on the effect of Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs) use on COVID-19 infection are both insufficient and controversial. The present study was conducted to investigate the effect of a history of ACEI/ARBs use on the severity and mortality of COVID-19 infection.
Methods
This study recruited 147 patients with confirmed COVID-19. The relationship between the severity of the disease was then assessed with a history of ACEIs/ARBs use, diabetes, ischemic heart disease, hypertension and Glomerular Filtration Rate (GFR). The effect of a history of ACEIs/ARBs use, GFR ≤ 60 (mL/min), a history of hypertension, a history of ischemic heart disease, diabetes, LDH ≥ 500 U/l, and lymphocyte count ≤ 1500 on COVID-19-related deaths was also assessed.
Results
The results showed a significant relationship between a history of ACEIs/ARBs use before infection and COVID-19 severity and mortality. The severity of the disease also had a significant relationship with a history of smoking, diabetes, hypertension, ischemic heart disease, and GFR. Moreover, the mortality rate had a significant relationship with GFR ≤ 60 (mL/min), diabetes, LDH ≥ 500 U/l, and lymphocyte count ≤ 1500.
Conclusion
The present study showed that a history of ACEIs/ARBs use before COVID-19 infection significantly increased severity and mortality of COVID-19 infection. This result can help modify health policies during the COVID-19 pandemic.

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AEP454

Acute pancreatitis in a covid-19 patient

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Acute pancreatitis (AP) is an inflammatory disorder of the pancreas, most commonly caused by gallstones and heavy alcohol consumption. The diagnosis is established with at least 2 of the following criteria: abdominal pain; increased serum lipase/amylase levels greater than 3 times the upper limit of normal value; or characteristic findings on contrast computed tomography (CT). Since the beginning of the severe acute respiratory syndrome coronavirus (SARS-CoV-2) pandemic, a few studies have reported a potential pancreatic injury related to SARS-CoV-2 infection. We are presenting a case of acute pancreatits in a pacient without any relevant risk factors other than a COVID-19 infection. A 74-year-old male with previous history of dyslipidemia and type 2 diabetes mellitus was hospitalized with general malaise, headache and nausea that had last for one week. Chest radiography showed bilateral beginning opacities, and results from testing of transcription polymerase chain reaction assay were positive for SARS-CoV-2. Severe pneumonia developed, with progressive dyspnea and hypoxic respiratory failure that required high-flow oxygen supplementation. We prescribed tocilizumab (anti-interleukin-6 receptor antibody) and corticoids, and so his oxygen requirements declined over the next several weeks, with gradual resolution of his pulmonary symptoms. On day 16, our patient reported diffuse abdominal pain without signs of peritoneal irritation. The blood test showed high levels of leukocytes (30.6×10^3 µl). The patient presents progressive worsening of abdominal pain with distension, so an abdominal CT is requested. The image showed acute pancreatitis with multiple associated necrohemorrhagic collections. Conservative medical treatment is decided, including bowel rest, intravenous fluids therapy, antibiotics and analgesia. After two days, the patient presented bilious vomiting and paralytic ileus, so he is treated with prokinetics, nasogastric tube, and rectal tube in turns. We also channeled drum for parenteral nutrition. The patient evolved favorably, being able to progress to enteral nutrition and later to oral nutrition, which he tolerated. Hydrolyzed supplements, phosphate and potassium are added. The patient was discharged and a follow-up CT scan was performed one month later, observing a decrease in collections. COVID-19 pathogenesis is thought to be mediated by angiotensin-converting enzyme-2 (ACE-2) receptor on the host cells, which are highly expressed in the pancreatic islets. Though the exact mechanism of AP by SARS-CoV-2 infection is unknown, the cytopathic effect or systemic inflammatory responses to the virus are thought to be responsible. Physicians should consider this possibility sooner or later in the course of COVID-19 illness.

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AEP455

Profil of vitamin D in patients with idiopathic short stature: About 62 cases

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Introduction
Idiopathic short stature is a condition in which the height of the individual is more than 2 standard deviation below the corresponding mean height for a given age, sex and population, in whom no identifiable disorder is present. The aim of this study is to describe the vitamin D profile of patients followed up for idiopathic short stature in the endocrinology department of Mohamed VI University Hospital Center.
Materials and methods
We have collected 62 patients admitted in the Endocrinology Department of Mohammed VI University Hospital of Oujda, for the management of idiopathic short stature. The data were collected and processed using SPSS software V21.
Results
The average age of the patients was 11 ± 3 years, with a sex ratio M/F of 1.48. The mean height of our patients in admission was 128 ± 20 cm and the average weight was 26 ± 8 kg. The average standard deviation score was 2.7 ± 0.7 for height and 2.3 ± 0.9 for weight. The median difference in bone age from chronological age was 45 months (from 9 months to 144 months). The insulin growth factor 1 (IGF1) was low relative to pubertal stage in 12.9% of patients. Bone X-rays were performed in all patients and did not reveal any abnormalities. A propranolol-glucagon test was performed in 78.8% of patients and an insulin hypoglycemia test was performed in 16.1% of patients. No growth hormone deficiency was detected. The mean vitamin D value was 20 ± 8 ng/ml, in 62.9% of patients the vitamin D value was in the range 10–30 ng/ml, in 1.6% of patients it was less than 10 ng/ml, and in 9.7% it was greater than 30 ng/ml. The reminder of the phosphocalcic lobaratory test was normal in all patients.
Conclusion
The results of our study highlighted the value of vitamin D dosing in the context of idiopathic short stature, in order to detect any deficiency which may affect our children's growth.

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AEP456

Carney complex – a rare cause of Cushing's syndrome

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Introduction
The Carney Complex (CNC) is a rare, autosomal dominant, multiple endocrine neoplasia. It involves multiple endocrine glands, cardiac and skin myxomas, mammary fibroadenomas and mucocutaneous pigmentation. Cushing's syndrome, due to primary pigmented nodular adrenocortical disease (PPNAD), is described in 25% of the cases.
Case report
Woman, 21-year-old, was refered for secondary amenorrhea. Medical history significant for depressive syndrome and thrombophlebitis at 18-year-old. Medication: quetiapine 100 mg id. Family history: mother (52-year-old), DM type 2, hypertension and corticotropin-independent adrenal Cushing syndrome submitted to unilateral adrenalectomy, at 48 years old (histology: diffuse adrenal hyperplasia). Physical exam: BMI 18.7 kg/m^2, acne, facial erythrosis, hirsutism, purple striae, without mucocutaneous pigmentation. Biochemicaly: ACTH < 5 pg/ml (9–52), serum cortisol 14 µg/dl (5–25), urinary free cortisol (UFC): 345 µg/24 h (10–80) and serum cortisol after overnight dexamethasone suppression test 13.6 µg/dl. Adrenal glands on CT with normal morphology and contours. Genetic test positive for variant c.63C > Ap. (Tyr21 *) in heterozygosity in the PRKA1A gene. Diagnosis of Carney complex and Cushing's syndrome by PPNAD were made. Genetic testing of the mother identified the same mutation. No others manifestations associated with CNC were found. While waiting for bilateral adrenalectomy the patient started ketoconazole, 200 mg bid, with improvement of the signs and symptoms of hypercortisolism. On the last appointment the patient had no acne, her menstrual cycles were regular and she was feeling more energized. Biochemical: serum cortisol 9.3 µg/dl, UFC: 47 µg/24 h. Her mother's follow-up was started in our department.
Conclusion
CNC is rare multiple endocrine neoplasia with challenges in diagnosis. In the presence of Cushing's syndrome and PPNAD, CNC's diagnosis, although rare, should be considered, since bilateral adrenalectomy is essential for therapeutic success. Family screening, and management of other manifestations, are part of the follow-up and treatment of patients with Carney Complex.

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Pituitary and Neuroendocrinology

AEP457

A rare case of pituitary apoplexy likely combined to hypophysitis in an old man with SARS-CoV-2 pneumoniae

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Introduction
Neurological complications related to COVID-19 are described. The pituitary expresses ACE which is known as the entrance for Sarscov2 through binding to viral S-protein. Pituitary apoplexy (PA) is due to the sudden hemorrhagic infarction of pre-existing pituitary tumors or the gland itself and its symptoms and radiological findings can be similar to acute hypophysitis (AH) caused by viral infections.

Subjects and methods
We report a recent case of an 84-year-old caucasian male admitted to emergency department for sudden intense frontal headache for one day. The patient had been discharged three weeks earlier for SARS-CoV-2 pneumonia. He had type 2 diabetes mellitus and ischemic heart disease on acetylsalicylic acid therapy. At admission, an episode of atrial fibrillation occurred for which anticoagulation with enoxaparin was started.
Results
The nasopharyngeal swab for the SARS-CoV-2 virus RNA was positive, neutrophilic leukocytosis with marked increase of inflammation indexes were revealed, head CT scan showed a sellar mass in contact with the lower profile of the optic chiasm without sign of bleeding and chest CT showed bilateral sub-pleural densities with crazy-paving patterns compatible with late-stage SARS-CoV-2 pneumonia. Enoxaparin therapy was confirmed. The headache persisted with photophobia, nausea and vomiting. Later, third cranial nerve deficit with bilateral ptosis, ophthalmoplegia and anisocoria occurred followed by hypotension and confusion so that a cerebral magnetic resonance imaging (MRI) with contrast agent revealed the presence of necrotic-hemorrhagic regression in enlarged sellar tissue referable to PA in pituitary adenoma. Cortisol was < 5 mg/dl. Enoxaparin was interrupted and hydrocortisone was started followed by dexamethasone. Other anterior pituitary hormones were low and thyroxine was started. A second MRI was unchanged while a third MRI three weeks later showed change of pituitary lesion likely referable to combined AH. Accordingly, inflammation markers decreased after dexamethasone was started and the clinical conditions improved with partial recovery of ptosis and complete headache resolution.
Conclusions
PA as well as AH are very rare conditions. In this case a concomitant PA in an unknown macroadenoma and a likely AH have been found coexisting in a patient with SarsCov2 pneumoniae. We speculated on what connections between the two events might be present. Some triggering factors are recognized in PA, including anti-coagulation therapy as in our case. Moreover, SarsCov2 infection can induce reversible AH. Pituitary must be considered as a target organ in patients with Covid-19 for the rare though possible development of apoplexy or hypophysitis.

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AEP458

Pituitary apoplexy lead to disappearance of adenoma; two case reports

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Introduction
Pituitary apoplexy is a rare endocrine and neurosurgical emergency. It corresponds to the occurrence of an hemorrhage or infarction in the pituitary gland, or most often within a pituitary adenoma. The usual presentation associates sudden headaches, visual disturbances, altered consciousness and endocrine disorders wich are dominated by corticotropic insufficiency. We present two cases of pituitary apoplexy, the first one complicating an underlying pituitary adenoma, the second one revealing the adenoma, where both cases have progressed well under conservative treatment, and the surprise is that in the two cases the adenoma has totally disappeared.
Case 1
70-year-old man has a nonfunctioning pituitary adenoma 25 mm, with Hypopituitarism, presented in emergency department with complaints of 1 day of fatigue, vomiting, fever 39.4°c, visual disturbances, and severe retroorbitar headache; BP was 200/70 mmhg; scored at 9 on the Glasgow scale; pituitary MRI done on D4 is compatible with apoplexy. the ophthalmological examination finds oculomotor paralysis, with reduced acuity, diplopia, ptosis in the right eye, without impairing the visual field. The evolution under conservative treatment was spectacular; marked by the recovery of consciousness after 24 h, ophthalmologic improvement from D7; total regression of the adenoma on MRI at 3 months; and even a restoration of the corticotropic function at least partial;an insulin hypoglycemia test could not be done due to age and unbalanced diabetes.
Case 2
33-year-old female, without a known pitutary lesion, presented to the emergency department in april 2019 with sudden onset of severe headache without other features. she had history of generalized weakness, cycle disorders for the last 2 years; headaches and infertility for the last year. Ophthalmic evaluation revealed bitemporal upper quadrantanopia, normal acuity and no papilledema. CT of head on day 3 and MR imaging on day 4 confirm the apoplexy of a pituitary adenoma. the hormonal exploration found an corticotropic insufficiency, with low prolactin, as well as central diabetes insipidus. The clinical outcome was favorable under conservative treatment; in MRI of control there is no adenoma.
Conclusion
The neurosurgical approach should be favored in the event of impaired consciousness or visual disturbances, worsening or not relying at corticosteroid therapy which must be started in all cases. The apoplexy can be a form of spontaneous healing of adenomas; although monitoring remains necessary.

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AEP459

Cushing's disease presenting as pituitary apoplexy: Challenges of diagnosis and treatment

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Background
Pituitary apoplexy (PA) is a rare clinical syndrome, usually occurring in the pituitary adenoma due to a sudden bleeding and/or infarction. PA is usually seen in nonfunctional pituitary adenomas, but it can also be seen in ACTH secreting macroadenomas. The most common symptoms PA, which complicates 2 to 12% of pituitary adenomas, are severe and sudden headache, visual disturbances, or eye paralysis, and endocrinological abnormalities. PA is diagnosed by computed tomography or magnetic resonance imaging. Formerly considered as an urgent neurosurgical condition and treated only surgically, now PA is sometimes treated conservatively.
Clinical case
The 33-year-old woman was sent to the emergency department for persistent severe right-sided headache, nausea, vomiting, and impaired vision. Temporobasal subarachnoid hemorrhage on the right side, and aneurysm rupture was suspected on computed tomography (CT) of the brain. Patient was referred to ophthalmologist – right eye blindness and temporal hemianopsia in left eye were diagnosed. An additional MRI scan revealed a tumor in the sella turcica area. Patient was transferred to Vilnius University hospital Santaros Klinikos Center of Neurosurgery. Head CT angiography (CTA) was done to exclude intracranial vascular aneurysm. Subarachnoid hemorrhage, a large (24 × 15 × 26 mm) mass, significant pressure on the right segment of the right internal carotid artery (ACI) and dislocated optic chiasm were found. Blood samples showed increased ACTH, cortisol, and glucose levels (AKTH – 190 nmol/l, cortisol – 1068 nmol/l, glucose – 10 mmol/l), prolactin concentration was normal. During physical examination wide purple striae in the skin of the abdomen and arms, hirsutism, and cushingoid body appearance were noticed. The patient was never consulted by endocrinologist before. She underwent right pterional craniotomy and pituitary tumor removal. The final pathological diagnosis was necrosis and hemorrhage in the pituitary adenoma with probable ACTH expression and grain. Patient's right eye vision after surgery did not recover and she developed panhipopituitarism. A replacement treatment with glucocorticoids, levothyroxin and sex hormones were given.
Conclusion
The presented clinical case shows how unnoticed and undiagnosed Cushing's disease led to a pituitary adenoma apoplexy with various complications such as blindness in one eye and panhypopituitarism. Awareness of physicians of Cushing's disease symptoms could have allowed earlier diagnosis of the disease and avoided complications caused by apoplexy.

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AEP460

Pituitary tuberculosis: A clinical challenge

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Introduction
Cerebral tuberculomas are a rare form of tuberculosis due to the hematogenous spread of Mycobacterium Tuberculosis (MT). Pituitary localization is exceptionally uncommon with total reported cases in the literature fewer than a hundred. Symptoms and radiologic features are

nonspecific, leading sometimes to misdiagnosis. We report the rare case of a patient diagnosed with a primary pituitary stalk tuberculosis.
Observation
A 37-year-old woman was referred to our department for a suspected diabetes insipidus. A CREST syndrome treated by oral corticotherapy (10 mg of Prednisone) and benzodiazepin (120 mg of Diltiazem) marked her past medical history. She presented with a recent polyuria-polydipsia syndrome with about 10liters/day. No menstrual disorders were reported. Pituitary MRI showed a marked thickening of the pituitary stalk with nodular enhancement suggestive of granulomatosis. A water deprivation test confirmed the central diabetes insipidus with a rise in urine osmolarity after desmopressin administration and low arginine vasopressin (AVP) levels (< 0.5 pmol/l). The etiological diagnostic procedure begins with the search for possible other lesions suggestive of histiocytosis, sarcoidosis, tuberculosis or other etiologies elsewhere in the body that could be more easily biopsied, particularly because the biopsy of the stalk is difficult, harmful and often not contributive. We performed neck, thorax, abdomen, and pelvis CT scan, measurement of serum markers such as B2 microglobulin, angiotensin converting enzyme, anticytoplasmic antibodies and salivary gland biopsy. Tuberculin skin test (TST) showed a positive response with a skin reaction of 12 mm (> 10 mm). The pathological proof of the pituitary tuberculosis was thus obtained indirectly considering high tuberculosis endemicity in Tunisia, raw milk consumption and positive TST. Our patient was put on anti tuberculosis treatment and desmopressin substitution. Follow up MRI (3 months after tuberculosis medication stopped) showed complete resolution of the granuloma but with diabetes insipidus persistence.
Discussion and conclusion
Pituitary tuberculosis is an uncommon form of intra-cranial tuberculosis. Isolated pituitary tuberculosis in extremely rare and difficult to diagnose. The case we studied showed the difficulties encountered in the diagnosis of a thickened pituitary stalk.

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AEP461

A rare case of acromegaly developed in a patient with multicentric Castleman disease and complete disappearance of lymphadenopathies after treatment with Lanreotide Autogel

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Introduction
Multicentric Castleman disease (MCD) is characterized by highly vascularized multiple lymph node enlargements throughout the body. MCD is generally treated with systemic cytotoxic chemotherapy, with its attendant risk for toxicity. Studies suggest the presence of growth hormone receptors (GHR) in lymphatic tissues of patients with Castleman disease. However, the effect of somatostatin analogs for the treatment of MCD is not reported so far. Herein we present a case of MCD who was diagnosed with acromegaly and treatment with long-acting somatostatin analog Lanreotide Autogel resulted in the complete disappearance of lymphadenopathies.
Case
A 32-year-old female patient with multiple abdominal lymphadenopathies underwent abdominal explorative laparotomy for a mass of 42 × 42 × 31 mm diameter in the right lower abdominal quadrant. Immunohistopathological analysis of paraffin-embedded tissue blocks was consistent with lymphatic tissue that was widely positive for Kappa and Lambda light chains, and also positive for IgG, IgM, CD-34, CD-138, and CD3/CD-5. CD-10 was positive in germinal centers. The result was consistent with MCD. Due to the presence of facial appearance, acral enlargement, and macroglossia, the patient was investigated for acromegaly. Insulin-like growth factor-1 (IGF-1) was 643 ng/ml (normal age and sex-matched values 71–234 ng/ml). Serum nadir growth hormone (GH) during a 75 gr oral glucose tolerance test (OGTT) was 13.8 ng/ml. A 16 × 15 mm macroadenoma was found on pituitary MRI. She had no clinical and laboratory results consistent with POEMS syndrome. The patient underwent transsphenoidal adenomectomy and the result of the immunohistopathological analysis was consistent with a GH secreting adenoma that was positive for GH and negative for prolactin. However, 3 months after surgery, treatment with a long-acting somatostatin analog Lanreotide Autogel was started once every 28 days, due to the high serum levels of IGF-1 and nadir GH on OGTT. Nevertheless, 6 months after remission of acromegaly assessed by the normalization of serum age and sex-matched IGF-1 and random GH levels, a contrast-enhanced abdominal CT demonstrated a complete disappearance of intra-abdominal lymphadenopathies.
Discussion
MCD has a less favorable outcome and is generally treated with systemic cytotoxic chemotherapy. However, recent studies suggested a high expression of the GHR in lymphatic cells of the patients with Castleman disease. Therefore, we believe that the complete disappearance of the lymphadenopathies in the index patient is probably due to the antiproliferative and apoptotic effects of somatostatin analogs. Further prospective studies are required to assess the effect of somatostatin analogs in patients with MCD.

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AEP462

Cardiac remodeling in patients with childhood-onset craniopharyngioma – Results of HIT-Endo and Kraniopharyngeom 2000/2007

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Hypothalamic obesity caused by childhood–onset craniopharyngioma results in long–term cardiovascular morbidity. Knowledge about clinical markers and risk factors for cardiovascular morbidity is scarce. A cross–sectional study on transthoracic echocardiographic parameters was performed to determine the associations with clinical and anthropometric parameters in 36 craniopharyngioma patients. BMI correlated with the thickness of interventricular septum in diastole (IVSd) ($r = 0.604$, $P < 0.001$) and left ventricular diastolic posterior wall in diastole (LVPWd) ($r = 0.460$, $P = 0.011$). In multivariate analyses on risk factors for cardiac remodeling, sex hormone replacement therapy, BMI and male gender were positively correlated with increased left ventricular internal diameter in diastole (LVIDd), R2 = 0.596, F = 10.323, $P < 0.001$. BMI and insulin resistance were selected as significant independent determinants of IVSd, produced R2 = 0.655, F = 29.441, $P < 0.001$. Due to wide range of disease duration, 17 pediatric and 19 adult patients were analyzed separately. In the adult subgroup (age at study ≥ 18 years), BMI correlated with IVSd ($r = 0.707$, $P = 0.003$), LVPWd ($r = 0.592$, $P = 0.020$) and LVIDd ($r = 0.571$, $P = 0.026$). In the pediatric subgroup (age at study < 18 years), no correlation between TTE parameters and BMI was observed. Only LVIDd correlated with disease duration ($r = 0.645$, $P < 0.001$). All cardiac functions were within the normal range, indicating no association with functional impairments.
Conclusions
Cardiac remodeling in patients with craniopharyngioma correlated with the degree of hypothalamic obesity, disease duration, sex hormone replacement therapy, male gender and insulin resistance. As echocardiography has limited sensitivity in patients with obesity, further research on more sensitive techniques for cardiac diagnostics in craniopharyngioma patients is warranted.

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AEP463

Epidemiology of acromegaly in south-eastern Norway

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Objective
In order to improve therapeutic outcomes for patients with acromegaly, new treatment algorithms have been developed over the last decades. Valid epidemiological data of acromegaly in Norway is lacking. The overall aim of this study was to investigate incidence, prevalence and mortality of acromegaly in South-Eastern Norway, and to investigate effects of new treatment algorithms.
Design and method
Patients with acromegaly from South-Eastern Health region of Norway (56% of the total Norwegian population) diagnosed between 1999–2019 were included in a register-based cohort ($n = 262$). For every patient 100 age and sex matched controls from the general population were obtained

(n = 26200) and combined with individual data from the national cause of death registry. Mortality was assessed by Kaplan-Meier analysis, cox regression and hazard ratios (HRs).
Results
Mean age at diagnosis was 48.7 years (CI: 95%: 45.9–49.4) and did not differ between men and women (P = 0.811). The mean annual incidence rate was 4.7 (95% CI: 4.2–5.3) cases/10^6 persons and the point prevalence in 2019 was 83 cases/106. During the study period, 14 acromegaly cases died, five from cancer, three from cardiovascular disease and six from other causes. Overall mortality risk was elevated (HR: 2.79 (95% CI: 1.64–4.75). For patients diagnosed in period 1999–2005 and 2006–2012 the HR for mortality was 2.86 (95% CI: 1.35–6.05), and 2.96 (95% CI: 1.31–6.66). For the patients diagnosed in 2013–2019 this was 1.87 (95% CI: 0.26–13.50)). IGF-1 levels at diagnosis did not clearly influence mortality (HR: 0.59 (95% CI: 0.31–1.14)).
Conclusion
In South-Eastern Norway, the mortality in patients with acromegaly is elevated compared to the general population and comparable to results from other population-based studies in the Nordic countries and Europe.

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AEP464

The duration of postoperative steroid replacement therapy may not have a predictive role for recurrence risk of Cushing's disease

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Objective
In patients with Cushing's disease (CD), normal pituitary corticotrophs are suppressed by excessive and persistent cortisol secretion in responce to autonomous ACTH secretion by tumour. Therefore, patients exhibit signs and symptoms of ACTH deficiency shortly after resection of tumour and need steroid replacement therapy (SRT) until hypotalamo-pituitary-adrenal (HPA) axis recovery. We aimed to evaluate whether duration of SRT can serve as a predictive factor for disease recurrence in patients who underwent transsphenoidal surgery (TSS) and developed hypocortisolemia in early postoperative period.
Material-method
This retrospective study consists of thirty eight CD patients, aged 18–65 years who underwent TSS between 2003–2016 at University of Health Sciences Turkey, Faculty of Medicine, Istanbul Sisli Hamidiye Etfal Health Training and Research Hospital. Morning serum cortisol levels measured within first five postoperative days were < 5 μg/dl in 34 and < 10 μg/dl but with clinical features of adrenal failure in 4 patients. All patients were followed up with SRT and re-evaluated for HPA axis recovery every 3 months after withdrawal of SRT for at least 24 hours. HPA axis recovery was determined if morning serum cortisol was ≥ 18 μg/dl or if serum cortisol levels exceeded 18 μg/dl after ACTH stimulation. Patients with recovered HPA axis were assessed for disease recurrence in follow-up periodically. High 24 hour urinary free cortisol excretion, high midnight salivary cortisol and failure of cortisol suppression < 1.8 μg/dl after dexamethasone suppression tests were defined as markers for recurrence. Two groups according to disease status were designed as recurrence and remission groups and compared for early postoperative serum cortisol and duration of SRT.
Results
Remission and recurrence groups consisted 27 and 11 patients, respectively. The follow-up period was significantly high and age at presentation was significantly low in recurrence group. Duration of SRT didn't significantly differ between both groups.

Table 1. Data of patients in recurrence and remission groups. (P-value < 0.05 was determined as significant)

	RECURRENCE	REMISSION	P-value
	mean ± SD	mean ± SD	
Age at presentation (years)	38.5 ± 10.7	49 ± 12.3	0.026
POSTOPERATIVE			
Morning serum cortisol (μg/dl)	3 ± 2.1	3.1 ± 1.9	0.595
Follow-up duration (month)	76.4 ± 41.1	35.8 ± 24.5	0.001
SRT duration (month)	17.4 ± 19.9	12.6 ± 9.7	0.948

Conclusion
Although postoperative morning serum cortisol can be used for assessment of surgery success, how long the patient need SRT may not necessarily predict the recurrence risk. But if we lenghten the follow-up period in both groups, SRT may gain a significance in prediction of recurrence.

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AEP465

Hypothalamic-pituitary-adrenal axis activity in patients with primary polydipsia and healthy volunteers

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Background
The pathophysiology of primary polydipsia, a disorder with increased fluid intake, is poorly understood. A dysregulation in the hypothalamic-pituitary-adrenal axis (HPA) is speculated and arises mainly from research in patients witch a schizophrenia spectrum disorder but data is contradictory. The aim of this study was to investigate markers of HPA axis activity in patients with primary polydipsia compared to healthy controls.
Methods
In this exploratory analysis data from 34 patients with primary polydipsia and 20 healthy volunteers of two different prospective studies with the same study design were combined. The main outcomes were differences in circadian rhythm of serum and salivary cortisol, 24-hour urinary free cortisol, and cortisol levels before and after ACTH stimulation between patients with primary polydipsia and healthy volunteers.
Results
34 patients with primary polydipsia (68% female) aged 29.5 years (IQR 26.0, 38.8) with a median body mass index (BMI) of 23.1 kg/m^2 (IQR 20.7, 25.5) were included in the analysis. Circadian rhythms of serum cortisol levels (P = 0.9), urinary free cortisol levels (P = 0.17), and serum cortisol upon ACTH stimulation (P = 0.77) were similar between patients with primary polydipsia and healthy volunteers. Circadian rhythms of salivary cortisol levels were significantly lower in patients with primary polydipsia as compared to healthy volunteers with an estimated difference of –3.7 nmol/l (95%-CI –5.5, –1.8 nmol/l, P = < 0.001).
Conclusion
Our results suggest no difference in HPA axis activity between patients with primary polydipsia and healthy volunteers. The observed difference in salivary cortisol levels may be linked to the increased amount of water consumed by patients with primary polydipsia rather than altered stress response. Our results improve the psychopathological understanding increased fluid intake.

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AEP466

Study of the brain system for motor control in prader willi syndrome

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Background
Prader Willi syndrome (PWS) is a genetic disorder with a broad clinical expression. Severe hypotonia with feeding difficulties during early infancy and delayed motor development are very characteristic. At older ages, common motor features in the PWS phenotype include decreased muscle strength, deficiencies in motor coordination and sequencing, gait disturbances and dyspraxic manifestations, with no clear pathophysiological mechanism yet identified. The motor symptoms in PWS may be, in part, the result of the same alteration(s) in the brain system involved in motor control.

Objective
We aimed to examine the brain's motor system in PWS using functional magnetic resonance imaging (fMRI) with motor activation paradigms.
Methods
Twenty-three adults with PWS (12 women, age mean ± SD, 30.6 ± 10.1 years) participated in the study. Twenty-three age- and sex-matched healthy participants served as a control group. fMRI testing involved the performance of three manual tasks of different motor complexity: (i) repetitive flexion-extension of one hand; (ii) bimanual anti-phase repetitive flexion-extension movements; and (iii) repetitive sequence of fingers-to-thumb opposition with the right hand. Behavioral measurements of overall motor function were also registered by evaluating hand grip strength using a Jamar dynamometer, functional mobility and risk for falls as assessed by the Timed Get Up and Go (tGUG) test, and a quantitative measure of balance using the Berg balance scale. Whole-brain activation maps were compared between groups and correlated with behavioral measurements.
Results
As expected, participants with PWS showed significantly lower scores than controls on all the behavioral measures of motor function. Performance of the motor tasks engaged cortical and subcortical neural elements typically involved in motor processing, including bilateral primary sensorimotor and premotor cortices, the supplementary motor area, the basal ganglia and the cerebellum. No significant between-group differences were found for the simplest task (repetitive flexion-extension of one hand). However, the more complex tasks (alternate flexion-extension of both hands and fingers-to-thumb opposition movements) evoked significantly decreased activation in patients with PWS in dorsal premotor cortices, the supplementary motor area, and the cerebellum. A significant negative correlation (i.e., poorer performance, lower brain activation) was found between scores in the tGUG test and brain activation during coordinate hand movements in bilateral sensorimotor cortices in the PWS group.
Comment
Our study provides novel insights into the neural substrates of motor control in PWS by demonstrating reduced motor cortical activation during motor coordination.

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AEP467

The GLP-1 receptor agonist dulaglutide reduces fluid intake in primary polydipsia: A randomised controlled trial

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Background
Primary polydipsia, characterized by excessive fluid intake, carries the risk of water intoxication and hyponatremia, but treatment options are scarce. Glucagon-like peptide-1 (GLP-1) reduces appetite and food intake. In experimental models, they also play a role in thirst and drinking behavior. The aim of this trial was to investigate whether GLP-1 receptor agonists reduce fluid intake in patients with primary polydipsia.
Methods
In this randomised, double-blind, placebo-controlled, 3-week crossover-trial, 34 patients with primary polydipsia received weekly dulaglutide (Trulicity) 1.5 mg and placebo (0.9% sodium chloride). During the last treatment week, patients attended an 8-hour evaluation visit with free water access. The primary endpoint was total fluid intake during the evaluation visits. The treatment effect was estimated using a linear mixed-effects model. In a subset of 15 patients and 15 matched controls, thirst perception and neuronal activity in response to beverage pictures were assessed by functional MRI.
Findings
Patients on dulaglutide reduced fluid intake by 490 ml [95%-CI –780, –199], $P = 0.002$, from 2950 ml [95% CI 2435, 3465] on placebo to 2460 ml [95% CI 1946, 2475] on dulaglutide (model estimates). This corresponds to a relative reduction of 17%. 24-hour urinary output was reduced by –943 ml [95%-CI –1473, –413], $P = 0.001$. Thirst perception in response to beverage pictures was higher in patients with primary polydipsia versus controls and lower on dulaglutide versus placebo, but functional activity was similar between groups and treatments.
Interpretation
GLP-1 receptor agonists reduce fluid intake and thirst perception in patients with primary polydipsia and could therefore be a novel treatment option for these patients.

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AEP468

The diagnostic and predictors of postoperative diabetes insipidus

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Objectives
To assess diagnostic and prognostic markers of permanent and transient postoperative diabetes insipidus.
Patients and methods
The study included 152 patients undergone endoscopic endonasal transsphenoidal surgery aged from 18 to 65 years with median 40 [31; 52] years. Seventy three patients had Cushing disease, 66 – acromegaly, 4 – prolactinoma, 9 – hormonally inactive adenoma, 1 – Nelson syndrome, 1 – TSH-oma. Patients were monitored for clinical presentation, fluid balance, serum electrolytes, plasma and urine osmolality, copeptin level.
Results
By the end of follow-up period, permanent DI (pDI) has developed in 15 patients (15.5%), transient (tDI) – in 34 (35.1%), 47 patients did not have any disturbances (48.5%, ND) and 1 patient (1%) had SIADH. The onset was seen on the 5th median day [1; 9.5] after surgery for the pDI and on the 1th median day [1; 4.5] for tDI; median for tDI's duration was 30 days [1.5; 195]. Thirst and dry mouth were significantly more frequent in patients with pDI and tDI in comparison with patients without disturbances (OR 61.9 (10.1; 382.2), OR 25.3 (5.3; 121.5), $P < 0.001$; OR 22.0 (4.6; 104.8), OR 30.7 (7.8; 121), $P < 0.001$), just like water intake and daily urine were increased ($P = 0.003$, ŕ=0.009 and $P = 0.002$, ŕ=0.007, respectively). When assessing the blood osmolality level, no significant differences were found, however, the blood sodium level was significantly higher in patients with tDI compared to patients without disorders (145_{pDI} [142; 148], 146_{tDI} [144; 150], 144_{ND} [141; 147] – $P = 0.008$). In patients with pDI and tDI the indices of urine osmolality (0.296 [0.163; 0.36]$_{pDI}$, 0.282 [0.163; 0.36]$_{tDI}$, 0.652 [0.465; 0.929]$_{ND}$) and urine specific gravity (1.002 [1.0; 1.01]$_{pDI}$, 1.003 [1.001; 1.008]$_{tDI}$, 1.01 [1.005; 1.02]$_{N}$D) were significantly lower compared to patients without disturbances ($P = 0.015$, $P = 0.001$; $P < 0.001$, respectively) and sodium urine indices were significantly higher (50 [28; 74]$_{pDI}$, 56 [33; 73]$_{tDI}$, 109 [72; 127]$_{ND}$ – $P = 0.005_{pDI\ vs\ ND}$, $P = 0.001_{tDI\ vs\ ND}$). When assessing the copeptin level, there were no significant differences between pre- and postoperative levels, but patients with a pDI had a sharp decrease in its level (median 10.1 [8.3;11] pmol/l before and 5.1 [4.9;6.2] after the intervention).
Conclusions
Clinical presentation, fluid balance, serum electrolytes, plasma and urine osmolality do not represent reliable diagnostic or prognostic markers of postoperative DI and its outcomes, but copeptin levels are a promising marker for further study.

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AEP469

The usage of aripiprazole as a single agent in the treatment of hyperprolactinemia associated with diogenes syndrome- a novel approach

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Introduction
Hyperprolactinemia is a condition in which a person has higher-than-normal levels of the hormone prolactin in the blood. It is a relatively common condition encountered in the world of endocrinology. It is often seen as a side-effect with usage of anti-psychotics. Treatment options when symptomatic usually constitute dopamine agonist therapy, the common agents being Cabergoline and Bromocriptine. The uniqueness of this case is attributed to the usage of low-dose Aripiprazole as a novel agent in the treatment of hyperprolactinemia associated with Diogenes syndrome (DS).

DS is a behavioural disorder, mostly seen in elderly population, characterized by self-neglect, domestic squalor, apathy, compulsive hoarding and lack of shame regarding one's living condition.
Case details
We report the case of a 77-year-old woman, not known to psychiatric services and on no anti-psychotic treatment, was subsequently diagnosed with Diogenes syndrome (DS). As part of workup prior to commencing antipsychotic therapy, she was found to have prolactin levels of 11146 (0–495 mU/l). Rest of her pituitary profile was unremarkable. She described none of the common features associated with hyperprolactinemia. Her clinical features of excessive hoarding, extreme self-neglect and lack of insight into her symptoms were consistent with DS. Brain imaging was done which revealed a Macroprolactinoma. Following this endocrinology opinion was sought and treatment with low dose Aripiprazole 10 milligrams as a single agent was started with the aim of improving her mental state in conjunction to her prolactin levels. Over the next 8 weeks, prolactin levels decreased to 476 accompanied by a steady improvement in her mental state.
Conclusion
We propose the utility of low dose Aripiprazole as a single agent for the treatment of hyperprolactinemia in comparison to conventional dopamine agonists or as adjunctive therapy in psychiatric settings. Aripiprazole exhibits partial agonistic activity on Dopamine (D2) receptors and serotonin receptors which renders it useful in the treatment of psychiatric disorders and improvement of hyperprolactinemia, accompanied by the advantage of having a low side effect profile. Literature review depicts limited evidence and reports of Aripiprazole being used as a single agent to treat hyperprolactinemia as opposed to significant number of studies where it has been used as adjunct therapy. Of note, frontal lobe dysfunction has been postulated to account for Diogenes syndrome, however on the other hand, the involvement of Pituitary lesions especially prolactinomas, has not been well documented.

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AEP470

Nonfunctioning pituitary adenomas: What can we do? What we did

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Nonfunctioning pituitary adenomas (NFAs) have no symptoms of hormonal overproduction and can be asymptomatic or have severe symptoms due to mass effects. The aim of our study was to assess clinical features and therapeutic outcomes in patients with clinically NFAs. We retrospectively collected data of 175 patients from 3 hospitals of Buenos Aires. Mean age: 51 years (r:13–90), 52% women, mean follow-up: 7.37 years. At diagnosis, clinical presentation was: visual field defects (VFD) 42%, headache 24%, incidentaloma 23%, hypopituitarism 8%; tumor size: macroadenomas 94% (17% giant adenomas). Surgery was performed in 132 patients (75%), transsphenoidal approach in 78%. The remaining patients were closely followed up. Radiotherapy was performed after surgery in 22%. Operated patients had larger tumors (31 ± 11 vs 18 ± 9 mm, $P < 0.000$), more VFD (80 vs 40%, $P < 0.000$) and hormonal deficiencies (70 vs 42%, p:0.002) compared with non-operated patients; no age differences between the groups. In operated patients, tumor type: gonadotroph 63%, null cell 26%, silent GH 3%, silent PRL 2%, plurihormonal 1% and silent ACTH 1%. Ki67 was available in 49%: < 3%: 77%, between 3–10%: 23%; positive P53 in 23%, positive cytokeratin in 85%. After surgery: 16% of patients presented empty sella, tumor size reduction was > 50% in 30%, the remaining had < 50% tumor reduction. VFD improved in 42%, no change in 49% and worsened in 9%. Hormonal axes improved in 12%, no change in 50%, added deficiencies: 37%. Of 132 operated patients, 86 underwent only 1 surgery, 46 had more surgeries. In non-operated patients tumor size was stable in 82.5%, reduced in 12.5% and increased in 5%; VFD had no changes in 92.5%, improved in 7.5%; hormonal deficiencies had no changes in 95%, improved in 5%. Comparing operated and non-operated patients, the first showed more improvement in VFD (47 vs 18%, P:0.03) and tumor size (80 vs 12.5%, $P < 0.000$). Operated patients, had significantly more hormonal deficiencies (40 vs 0%, P:0.001). No correlation was found between VFD and age or sex. Kaplan–Meier analysis showed no significant differences in progression between operated and non-operated patients.
Conclusions
In patients with NFAs, surgery was the first therapeutic option, radiotherapy was performed in only 22%. Operated patients presented improvement in VFD but added hormonal deficiencies. Close follow-up of non-operated patients was preferred in smaller tumors.

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AEP471

Association between fibroblast growth factor-21 and carotid intima media thickness in patients with acromegaly

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İntroduction
The aim of this study was to evaluate the association between fibroblast growth factor-21 (FGF-21) levels and carotid intima media thickness (CIMT) in acromegalic patients in relation to the atherosclerotic complications.
Metarials and methods
The study goroup included 70 acromegalic patients. According to the disease activity, patients cathegorized inti 2 groups: controlled and active acromegaly. Seventy-two patients were recruited to the control group. FGF-21, GH, IGF-1, lipids, glucose, insuline levels were assesed. Patients with acromegaly and control subjects were evaluated for their body mass index (BMI) (weight/height squared). CIMT was measured with a B-mode ultrasound.
Results
Median FGF-21 levels were significantly higher in control group compared to acromegaly group (472.5 vs. 192.5 pg/ml, $P < 0.001$, respectively). Acromegalic patients had higher CIMT than controls (0.63 ± 0.15 mm, 0.44 ± 0.08 mm; $P < 0.001$). FGF-21 levels and CIMT were not significantly different between controlled and active acromegaly patients ($P = 0.34$; $P = 0.24$, respectively). Although, there was no correlation between FGF-21 levels and CIMT in acromegalic patients ($P = 0.44$); a positive correlation was found between High-density lipoprotein (HDL) cholesterol and FGF-21 level ($P = 0.02$). In multiple regresyon analysis, HDL-C was the only determinant of FGF-21 (β coefficient = 0.604, $P = 0.02$). Regarding CIMT in multiple regresion analysis, fasting plasma glucose (β coefficient=0.461, $P = 0.02$), LDL (low-density lipoprotein) cholesterol (β coefficient = –1.295, $P = 0.04$), and systolic blood pressure (β coefficient=0.511, $P = 0.04$) were the influencing factors.
Conclusion
Acromegaly is associated with increased mortality due to cardiovascular complications. Data on serum FGF-21 levels in acromegaly were limited and conflicted. We found lower FGF-21 levels in acromegaly group than controls, despite high CIMT in these group. There was no association between FGF-21 levels and CIMT. This result may be associated with the improving effects of growth hormone on liver fat where the main regulation of FGF-21 take place. We found that glucose intolerance, lipid dysregulation, and hypertension were the factors influencing CIMT in acromegaly.
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AEP472

Age and sex differences among patients with acromegaly

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Introduction
Acromegaly is a chronic, slowly progressing disease caused in most cases by growth hormone (GH)- producing pituitary neuroendocrine tumors (PitNETs). This rare disorder is associated with a spectrum of various clinical manifestations and treatment outcomes differ between patients. The aim of this study was to evaluate the impact of age at the onset of symptoms and sex on clinical features, comorbidities, biochemical status at the diagnosis, and the severity of disease.
Methods
This is a one-centre cohort study conducted in 2019 among consecutive adult patients with acromegaly and no family history of PitNETs. Baseline data regarding biochemical and radiological status were collected retrospectively, whereas information concerning diagnostic delay, age at the onset of symptoms, menarche, voice break were collected during a routine visit in the outpatient clinic. Statistical analysis was performed in two subgroups depending on sex and in three subgroups depending on age at the diagnosis.
Results
101 consecutive patients were interviewed in the outpatient clinic (60 women, 41 men) with mean age at the diagnosis 46 years (range 19–75). Male patients presented hypogonadism more frequently than female patients (54.1% vs 25.5%, $P < 0.05$) whereas the differences between sexes in the occurrence of hyperprolactinemia and macroadenomas were not statistically significant. The occurrence of hypogonadism positively correlated with tumour size and negatively correlated with remission of the disease after the first surgery. Baseline IGF-1 level above the upper limit of age-adjusted normal range level and ACTH level were higher in men than in women(529.1 ± 277.7 vs 399.8 ± 250.6 ng/ml and 53.9 ± 28 vs 38.3 ± 23 pg/ml, respectively). Both basal and nadir GH did not differ between sexes. Among younger patients (≤ 40 years) hyperprolactinemia, hypogonadism and macroadenomas were discovered more frequently at the time of diagnosis than in the middle-aged (41–59 years) and in the elderly (≥ 60 years) ($P < 0.05$). Contrarily, arterial hypertension, nodular goitre and diabetes mellitus or glucose intolerance were more common among elderly patients with acromegaly than in younger age groups ($P < 0.05$).
Conclusion
According to our results, the course of disease in acromegaly is influenced by patient's gender and age at the onset of symptoms. These differences should be considered when treating patients with acromegaly.

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AEP473

Panhypopituitarism without pituitary ischemia after hantavirus infection

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Introduction
Hantaviruses are a group of viruses causing hemorrhagic fever with renal failure syndrome (HFRS). HFRS is a disease characterized by bleeding, thrombocytopenia, increased vascular permeability, and acute renal failure. Hypopituitarism associated with HFRS often results from necrosis in the pituitary gland caused by ischemia or infarction. HFRS may be difficult to diagnose due to its unclear clinical features. In this report, we present a patient who developed panhypopituitarism with preserved pituitary function following HFRS.
Case presentation
A 43-year-old male patient presented to the emergency service due to the complaints of body pain, nausea, vomiting, diarrhea. On physical examination, the temperature was 38 °C and the diagnostics tests indicated kidney failure and thrombocytopenia (Table 1). The patient was diagnosed as having HFRS since the patient was positive for both hantavirus and Ig M/G and also had a suspicious history of contact with rodents. The patient was referred to our endocrinology clinic due to the development of hypotension, hypoglycemia and hyponatremia during medical treatment. The patient was also diagnosed with panhypopituitarism. The patient was initiated on methylprednisolone 3×20 mg therapy. After the completion of this therapy, levothyroxine 50 mg was added to the treatment and its dosage was gradually increased to 75 mg. Upon the improvement of clinical and laboratory findings, the steroid therapy was reduced and maintenance treatment was initiated with hydrocortisone 2×10 mg. Magnetic resonance imaging (MRI) revealed a normal pituitary gland in terms of both size and appearance. The patienet was initiated on intramuscular testosterone propionate (IM) 250 mg every 3 weeks due to the presence of hypogonadism.At a 6-month follow-up, pituitary MRI showed a normal pituitary gland in terms of size and appearance, and the patient is still being followed up in our endocrinology outpatient clinic due to panhypopituitarism.
Conclusion
Panhypopituitarism is an extremely rare complication that may arise following HFRS. Clinicians should keep this complication in mind even in patients with normal pituitary MRI findings and should promptly initiate replacement therapies to reduce morbidity and mortality.
Keywords: panhypopituitarism, hantavirus

Table 1. Laboratory findings

	Value	Reference range
GH (µg/l)	0.08	< 3
IGF-1 (mg/ml)	22	58–215
FSH (IU/l)	1.01	1.27–19.26
LH (IU/l)	< 0.2	1.24–8.62
T. Testosterone (µg/l)	< 0.1	1.98–6.79
Prolactin (µg/l)	1.78	2.64–13.13
Cortisol (ug/dl)	1.25	35–430
ACTH	< 5.00	0.19–0.71
TSH (mIU/l)	0.26	0.41–6.8
sT3 (ng/l)	1.22	2.0–4.4
sT4 (ng/dl)	0.6	0.93–1.7

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AEP474

Pulmonary thromboembolism-caused acute severe euvolemic hyponatremia complicated by COVID-19 infection: A case report

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Introduction
Hyponatremia is frequently encountered in clinical practice. Euvolemic hyponatremia (Syndrome of Inadequate Antidiuresis, SIAD) represents diagnostic and management challenge regarding etiology unraveling, its gradual acute substitution, and later causal treatment.
Case report
A 68-year-old woman was admitted to the Emergency unit with acute psychosis. On examination, there were no focal neurological signs. On admission, she had severe euvolemic hyponatremia (repeated serum sodium level of 101 mmol/l), while other laboratory parameters were within normal range, except for mild normocytic anemia. Further investigations confirmed the diagnosis of segmental pulmonary thromboembolism as a possible cause of SIAD, after other causes were excluded (malignancy, drugs, CNS diseases…). Hyponatremia was corrected carefully with hypertonic saline infusion and fluid intake restriction. The patient recovered from psychosis immediately with a gradual increase in serum sodium levels and its normalization. She was treated with low molecular weight heparin followed by oral anticoagulant therapy. After three weeks of treatment, the patient's medical history was complicated by asymptomatic SARS CoV-2 infection, and the patient was transferred to a COVID treatment determined hospital. Even though she has belonged to the high-risk group regarding the clinical outcome of COVID-19, her chest X-ray was normal. During hospitalization, her sodium level remained in the reference range (138–142 mmol/l) on unrestricted fluid intake.

Conclusion
This case should alert a clinician regarding the possibility of reversible psychosis in a patient presenting with acute severe hyponatremia caused by pulmonary thromboembolism. Her condition was further complicated by a COVID-19 infection, from which she recovered with no additional complications. Even in the cases with life-threatening hyponatremia (101 mmol/l), complete recovery of patients could be obtained by simultaneous careful correction of hyponatremia and management of its possible cause.
Keywords: hyponatremia, hypertonic saline, pulmonary thromboembolism
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AEP475

Recovery of reproductive function under indomethacin treatment in a woman with langerhans cell histiocytosis: A case report

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Introduction
Langherans Cell Histiocytosis (LCH) is a rare disease due to a neoplastic proliferation of Langerhans-type cells. Hypothalamic-pituitary (HP) involvement may occur in 20–40% of the patients, presenting with diabetes insipidus (DI) and/or anterior pituitary dysfunction. Typically, such abnormalities are permanent and unresponsive to systemic treatment of LCH. We report the case of a young woman with pulmonary and HP localizations, and significant endocrinological improvement during indomethacin treatment leading to a spontaneous, premature multiple birth.
Case report
A 26-yr old female, smoker, was diagnosed with pulmonary LCH due to respiratory symptoms, that improved after stopping smoking. Six years later, she presented polyuria (up to 8000 cc/24 h), leading to the diagnosis of DI, due to LCH localization on the pituitary stalk. Desmopressin therapy was started, up to 180 mg/day. In the same year, she stopped estrogen-progestin contraception, with a 7-months secondary amenorrhea. Endocrine investigation revealed a normoprolactinemic hypogonadotrophic hypogonadism with GH deficiency and normal thyroid and adrenal functions. Stimulation with GnRH (100 mg) showed a mild and late response and she was put on hormone replacement therapy (HRT). A few months later, indomethacin was started (up to 50 mg three times a day) and the doses of desmopressin was progressively reduced to 60 mg/day. HRT was discontinued because the patient wanted to have a baby but amenorrhea recurred, despite a clear increase in estrogen secretion and basal and GnRH-induced gonadotropin secretion. Medically assisted procreation failed three times even though she progressively recovered irregular menses. One year after the last attempt, at the age of 38, she had a spontaneous pregnancy and delivered two healthy premature monozygotic twins (at 33 weeks). Indomethacin was withdrawn at the beginning of pregnancy. She breastfed for two months and resumed menstruation.
Discussion
Little is known about the recovery of pituitary function after systemic treatment of LCH, with only a few reports of spontaneous DI recovery and a single case of gonadotroph deficiency recovery 3 years after the last course of glucocorticoids. In our case the improvement of DI and recovery of reproductive function occurred during indomethacin treatment.
Conclusion
To the best of our knowledge this is the first report of significant endocrinological improvement occurring during indomethacin treatment, which has recently shown to be effective in bone localizations through the inhibition of prostaglandins production. This observation indicates that HP dysfunction may be reversible and supports further studies to evaluate the potential role of indomethacin in this localization.
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AEP476

Growth Hormone (GH) treatment in adults with Prader-Willi Syndrome (PWS) restores plasma kisspeptin to normal levels

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Background
Central kisspeptin action is well known in reproductive regulation; however, its peripheral action is not well understood. Most studies reveal that kisspeptin signaling influences energy and metabolic status.
Objective
To compare serum kisspeptin levels 1) between adult patients with PWS, obese subjects matched for age, sex and BMI and healthy subjects; 2) in adult patients with PWS before and after treatment GH.
Methods
Twenty seven GH-deficient adult patients with PWS (15 women, 30 ± 9.4 years), 27 obese subjects and 22 healthy subjects were studied. We determined anthropometric, glucose homeostasis parameters, body composition by DEXA and serum kisspeptin levels in all subjects at baseline and after 12 m of GH treatment in the PWS group.
Results
At baseline, there were no differences in serum kisspeptin levels between groups, although healthy group showed the lowest levels (PWS: 141.7 ± 21.0 pg/ml; obese: 141.5 ± 31.7 pg/ml; healthy: 127.7 ± 27.8 pg/ml, $P = 0.136$). Kisspeptin levels correlated with body fat mass ($r = 0.373$, $P = 0.008$). In the PWS group, after one year of GH therapy, lean body mass increased in 2.1% ($P = 0.03$), total fat mass decreased in 1.6% ($P = 0.005$) and serum kisspeptin dropped significantly ($P = 0.027$) to levels similar to healthy subjects (129.6 ± 29.8 pg/ml, $P = 0.816$).
Conclusions
In GH-deficient adults with PWS, one year of GH therapy effectively improves body composition and restores serum kisspeptin to normal levels. Further studies are necessary to elucidate the physiological mechanism of the relationship between changes in kisspeptin and body composition.
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AEP477

Body composition and nuchal skinfold thickness in pediatric brain tumor patients

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Background
Obesity, cardiovascular disease (CVD), and relapse/progression have impact on prognosis in pediatric brain tumor (BT) patients.
Methods
In a cross-sectional study, we analyzed nuchal skinfold thickness (NST) on MRI follow-up monitoring as a parameter for body composition (BC) and CVD in 177 BT patients (40 WHO grade 1–2 BT; 31 grade 3–4 BT; 106 craniopharyngioma (CP)), and 53 healthy controls (HC). Furthermore, BMI, waist-to-height ratio (WHtR), caliper-measured skinfold thickness (cSFT), and blood-pressure (BP) were analysed.
Results
CP patients showed higher BMI, WHtR, NST and cSFT when compared with BT and HC. WHO grade 1–2 BT patients were observed with higher BMI, waist circumference and triceps cSFT when compared to WHO grade 3–4 BT patients. NST correlated with BMI, WHtR, and cSFT. NST, BMI and WHtR had predictive value for CVD in terms of increased BP. In multivariate analysis, only BMI was selected for the final model resulting in an odds ratio of 1.25 (1.14–1.379). In CP patients with hypothalamic involvement/lesion or gross-total resection, rate and degree of obesity were increased.

Conclusions
NST could serve as a novel useful parameter for assessment of BC and CVD risk in BT patients.

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AEP478

Uncured acromegaly, the dark side of the moon: a cross- sectional study

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Introduction
Although surgical treatment of acromegaly is the treatment of choice in most patients, a wide therapeutic arsenal is available. Medical treatment can be indicated as primary treatment, complementary and even as pre-operative treatment.
Objectives
To determine the prevalence of uncured acromegaly and the prevalence of controlled disease within this group. To clinically, biochemically and histologically characterize uncured acromegalics. To analyze the predictive factors for non-cure in acromegaly.
Material and methods
Retrospective study of adult patients with uncured acromegaly under follow-up in the Neuroendocrinology Unit of a tertiary hospital in Madrid during the period 2000–2020. Non-cure criteria were considered: elevated IGF-1 according to age and sex and random GH ≥ 1µg/l and/or post OGTT 75 gr ≥ 0.4 or ≥ 1µg/l, according to the analytical method used. Controlled disease criteria were considered: normal IGF-1 according to age and sex and random GH < 2.5µg/l. Continuous variables were expressed as mean and standard deviation and categorical variables as absolute values and percentages. Univariate and multivariate logistic regression models were analyzed to determine predictors of non-healing, significant $P < 0.05$.
Results
Of 97 adult patients with acromegaly, 52.7% ($n = 51$) did not meet cure criteria, of these, 46.5% ($n = 40$) after sphenoidal surgery. 56.9% were women, age 61 ± 18.7 years, BMI 28.4 ± 5 kg/m^2, IGF-1 956.2 ± 677.1µg/l and GH 30.0 ± 42.7µg/l. 75% presented pituitary macroadenoma, 82.1% with extrasellar extension. 50% were somatotropinomas and the rest secreted GH+PRL (35%), GH + PRL + TSH (10%) and PRL (5%). 84.6% and 41.7% had positivity for Ki67 (72.7% < 3% and 27.3% 3–10%) and p53, respectively. 94.1% ($n = 48$) received medical treatment, 20 patients in monotherapy (12 SSAs, 7 carbergoline and 1 pegvisomant) and 28 patients in combined therapy (12 SSAs + cabergoline, 6 SSAs + pegvisomant, 1 pegvisomant + cabergoline and 9 triple therapy). In total, 92% met criteria for controlled disease, 100% of those treated with SSA and pegvisomant in monotherapy and 85.7% with cabergoline in monotherapy (directly proportional to the dose), and 89.2% of those receiving combined therapy. 35.7% also received RT, with 93.3% controlling the disease. Predictive factors of non-cure after surgery were pituitary macroadenoma, initial GH and IGF-1 values and co-secretion of GH + PRL and GH + PRL + TSH.
Conclusions
The surgical remission rate exceeds 50%. Almost all patients who are not cured achieve control of the disease with pharmacological treatment. Medical treatment should be individualized according to the presence of pituitary macroadenoma, co-secreting hormone pituitary adenomas, initial levels of GH and IGF-1 and the clinical and hormonal evolution of the patient.

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AEP479

Metabolic profile in patients with prolactinoma before and on dopamine agonist therapy

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Background
Prolactinomas are the most frequent type of hormone-secreting pituitary adenomas. Prolactin(PRL)-receptor mediates intracellular signaling pathways that contribute to weight gain, dyslipidemia, impaired fasting glucose (IFG), type 2 diabetes mellitus (T2DM) and cardiovascular disease, parameters that improve along with PRL level control on dopamine agonist (DA) therapy.
Aim
To assess metabolic disturbances in prolactinomas at diagnosis and during follow-up.
Methods
Fifty-seven patients with prolactinomas (aged 50.2 ± 17.6 years, 37 M:20 W median PRL 838.45 mg/l) were retrospectively assessed for weight, lipids, fasting glycemia, blood pressure, cardiovascular events. Evaluation was made at baseline, at 6, 12 and 24 months after DA treatment (1–7 mg/week cabergoline/7.5–30 mg/day bromocriptine). Nadir PRL on therapy was 0.2 mg/l. Serum PRL was measured by chemiluminescence.
Results
At the time of diagnosis, 27.3% were overweight and 52.7% obese. Weight excess was significantly more prevalent in men (89.2%) vs. women (55), $P < 0.01$ and in macroprolactinoma (83.7%) vs. microprolactinoma (37.5%), $P < 0.01$. Nine subjects had central hypothyroidism, 46 central hypogonadism and 5 panhypopituitarism. Initial BMI (29.8 ± 5.4 kg/m^2) significantly decrease both at 6-months (29.1 ± 4.6 kg/m^2, $P = 0.04$) and 24-months (28.9 ± 5.6 kg/m^2, $P = 0.01$). Maximum decrease in BMI (0.7 kg/m^2) occurred at 6-months, despite the fact that only 63.2% had achieved disease control. At the time of diagnosis, 65.3% had dyslipidemia. Initial cholesterol level was 208.3 ± 40.7 mg/dl and significantly decreased both at 6-months (185.1 ± 39.6 mg/dl, $P < 0.01$) and 24-months (183.5 ± 44.04 mg/dl, $P < 0.01$). Significant decrease was also observed in LDL-cholesterol and triglyceride levels from 127.3 ± 38.9 mg/dl and 165.3 ± 135.3 mg/dl at baseline to 106.2 ± 28.8 mg/dl($P = 0.05$) and 133.1 ± 77.4 mg/dl($P = 0.01$) at 6-months and to 106.9 ± 31.4 mg/dl and 115.5 ± 72.8 mg/dl, respectively at 24-months ($P < 0.01$). HDL-cholesterol levels were similar at 6-months, but significantly lower at 24-months compared to baseline (42.3 ± 9.9 mg/dl vs. 49.1 ± 44 mg/dl, $P = 0.04$). Nine of 37 dyslipidemic patients (24.3%) received statin. Arterial hypertension (26.31%, $n = 15$) and chronic coronary syndrome (CCS) (10.5%, $n = 6$) prevalence was similar at the time of diagnosis and at 24-months: 29.8% ($n = 17$) patients with hypertension and 12.3% ($n = 7$) patients with CCS. At baseline, 21.8% ($n = 12$) had IFG and 5.3% ($n = 3$) DM. At 24-months evaluation, the prevalence of IFG and DM was 7.3% ($n = 4$) and 3.6% ($n = 2$), respectively.
Conclusion
Two years dopamine agonists treatment improved metabolic parameters in prolactinoma patients, with weight loss, decrease in total and LDL-cholesterol and triglycerides. Long term follow-up, larger studies are necessary to assess cardiovascular risk of patients with PRM, in order to stratify therapeutic intervention and to reduce associated mortality.

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AEP480

What should be the optimal testosterone level to improve the symptoms of hypogonadism in male macroprolactinomas?

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Objectives
Male prolactinoma patients mostly have hypogonadotropic symptoms. While treatment with dopamine agonists (DAs; such as bromocriptine or cabergoline) leads to recovery of sexual glands, it can lead to impulsive control disorders as an undesirable side effect. The aim of this retrospective study is to determine the level of testosterone that eliminates symptoms, provides fertility and does not cause this undesirable side effect regardless of prolactin (PRL) level in macroprolactinomas with long-term follow-up.

Material and Methods
Twenty-seven male patients with macroprolactinoma followed in outpatient Pituitary Clinic were included to the study. There were 16 macro (≥ 1–2.8 cm), 7 large macro (≥ 2.9–3.9 cm) and 4 giant (≥ 4 cm) adenomas. From medical records PRL, LH, FSH, Testosterone (T) were evaluated and a timeline was created to analyze the progress regarding symptoms of hypogonadism and infertility. At each visit, their answers to hypogonadism symptoms and fertility questions were evaluated. PRL and T levels in the period when they were asymptomatic and fertile were recorded. Fertility-induced T levels were compared with age-matched thirty-three controls. Patients with children prior to admission were excluded from fertility statistical analysis.
Results
The mean age of patients was 38.8 ± 11.8 years, and 41.6 ± 10.2 years in the controls. The average delay in diagnosis was 4.3 years. Mean PRL, basal tumor diameter and shrinkage were 2846 ± 3415 ng/ml, 27.2 ± 10.2 mm and 63.4%, respectively. Basal T levels were 1.6 ± 1.0 ng/ml for patients and 4.4 ± 1.5 ng/ml for controls ($P < 0.001$). Mean T level in asymptomatic period was significantly lower than controls (3.2 ± 0.4 ng/ml vs. 4.4 ± 1.5 ng/ml, respectively, $P = 0.002$), and at this time mean PRL was slightly elevated than normal as 27.2 ng/ml. Mean maximum dose of bromocriptine and cabergoline were 11.1 ± 5.1 mg/daily and 1.7 ± 0.6 mg/weekly, respectively. The patients were followed up for an average of 8.3 ± 4.8 years. Fertility was achieved in 6 of the patients who desired fertility, and there was no difference between the T levels of these patients and the controls (3.7 ± 0.8 ng/ml vs. 4.4 ± 1.5 ng/ml, $P = 0.38$). When fertility was achieved mean PRL level was 26.9 ± 23 ng/ml. The highest T levels of the patients under therapy was not significantly different from controls (4.9 ± 1.6 ng/ml vs. 4.4 ± 1.5 ng/ml, respectively). Mean PRL level accompanying these T levels was 12.1 ± 15.2 ng/Ml.
Conclusion
The slightly elevated PRL should not be taken into account in these patients under treatment, when symptoms disappear, or fertility is restored. Therefore, patients should be carefully questioned in terms of their complaints at each visit and the dose of DA should not be increased unnecessarily to avoid possible adverse serious side effects.

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AEP481

Pituitary function after transsphenoidal surgery including measurement of basal morning cortisol as predictor of adrenal insufficiency

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Introduction
Patients with pituitary adenomas undergoing transsphenoidal surgery require pre- and post-surgery examination of pituitary hormones. There is currently no consensus on how to evaluate the adrenal axis post-surgery. The aims of this study were to investigate factors that may predict postoperative adrenal insufficiency (AI) and to investigate the overall effect of transsphenoidal surgery on the pituitary function.
Methods
One-hundred-and-forty-three consecutive patients who had undergone transsphenoidal surgery for pituitary adenomas were included. Data on tumour size, pituitary function pre-surgery, plasma basal cortisol measured within 48 hours post-surgery and pituitary function 6 months post-surgery were collected. Patients with AI prior to surgery, perioperative glucocorticoid treatment, Cushing's disease and no re-evaluation after 1 month were excluded ($n = 93$) in the basal cortisol analysis.
Results
Low plasma basal cortisol post-surgery, tumour size and previous pituitary surgery were predictors of AI (all $P < 0.05$). A basal cortisol cut-off concentration of 300 nmol/l predicted AI 6 months post-surgery with a sensitivity and negative predictive value of 100%, specificity of 81% and positive predictive value of 25%. New gonadal, thyroid and adrenal axis insufficiencies accounted for 2%, 10% and 10%, respectively. The corresponding recovery rates were 17%, 7% and 24%, respectively
Conclusion
Transsphenoidal surgery had an overall beneficial effect on pituitary endocrine function. Low basal plasma cortisol measured within 48 hours after surgery, tumour size and previous surgery were identified as risk factors for AI. We recommend measurement of basal cortisol post-surgery to secure glucocorticoids to patients at risk of AI and to avoid unnecessary glucocorticoid treatment.

Table 1. Association between basal cortisol and adrenal axis six months post-surgery

Basal cortisol level	Sufficient	Insufficient	Total	Cut-off limits	Specificity	Sensitivity	NPV	PPV
0–99 nmol/l	2	2	4	100 nmol/l	96%	67%	98%	50%
100–199 nmol/l	2	0	2	200 nmol/l	92%	67%	98%	33%
200–299 nmol/l	5	1	6	300 nmol/l	81%	100%	100%	25%
300–399 nmol/l	9	0	9	400 nmol/l	62%	100%	100%	14%
400–499 nmol/l	4	0	4	500 nmol/l	53%	100%	100%	12%
500–599 nmol/l	4	0	4	600 nmol/l	45%	100%	100%	10%
> = 600 nmol/l	21	0	21					
Total	47	3	50					

Grouping plasma basal cortisol levels according to sufficiency vs. insufficiency of the adrenal axis assessed by Synacthen-test six months post-surgery. PPV = Positive predictive value. NPV=Negative predictive value.

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AEP482

Factors that contribute to dopamine agonist resistance of prolactinomas

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Introduction
Prolactinomas are the most common hormone-secreting pituitary tumours encountered in the clinic. They are usually treated with dopamine agonists (DA): bromocriptine (BRC) and cabergoline (CAB), which are highly effective in the majority of cases. DA resistance is the failure to achieve normal levels of prolactin and, or reduction of the adenoma with at least 50%.
Aim
to assess the prevalence of the known factors that contribute to DA resistance (male gender, younger age at diagnosis, large tumours, the invasiveness of the tumour) among patients that do not respond to medical treatment.
Materials and methods
222 patients with prolactinoma were retrospectively assessed for treatment responsiveness. Gender, age of the diagnosis, serum prolactin levels, the dimensions of the pituitary adenoma were compared in responsive and resistant patients. Prolactin was measured by chemiluminescence and tumour volume and extension by computed tomography scan or MRI.
Results
there were 188 patients responsive to DA therapy and 34 resistant ones. There is no significant gender differences between the 2 groups (M:F = 83:105 in responsive group vs. 16:18 in resistant group, n = ns, chi square test). Resistant patients tend to be younger (30.5 ± 12.5 years) than responsive ones (35.6 ± 13.6 years), P = ns. Serum median prolactin was similar in responsive patients (650 ng/ml) and in resistant ones (462 ng/ml). Median maximum diameter was also similar (2.1 cm vs.2.12 cm).
Conclusions
In our series, there were no significant differences regarding gender, age at diagnosis, initial prolactin levels or tumour volume between patients responsive or resistant to DA therapy. Attention should be payed to histological and genetic differences between these patients.

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AEP483

Electrolyte disturbances in hospitalized patients with COVID-19

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Introduction
SARS-CoV-2 has caused a global outbreak of coronavirus disease 2019 (COVID-19). It is known that this virus binds angiotensin-converting enzyme 2 (ACE2) of the renin-angiotensin system, which may exert substantial effects on sodium and potassium metabolism. Viral pneumonia and respiratory distress are well known etiologies for hyponatremia due to syndrome of inadequate secretion of antidiuretic hormone, and can worsen clinical course of the disease and outcomes.
Aim
To investigate the prevalence of electrolyte disturbances (hyponatremia, hypokalemia) in patients with COVID-19.
Materials and methods
We examined medical records of 153 patients, which were hospitalized for inpatient treatment of COVID-19 infection from May to June 2020. Study group included 75 men (49%) and 78 women (51%), median age 60 years [Q1 47; Q3 73], BMI 28.7 kg/m^2 [25.0; 32.9]. All patients were diagnosed with pneumonia due to SARS-CoV-2 with median percent of lung involvement 28.5% [15.3; 44.7]. Median SpO2 was 94% [92; 97], and median NEWS score was 3 [2; 6]. There were 10 lethal cases. 14 patients at admission received diuretic therapy.
Results
On admission, the median natremia was 137 mmol/l [135; 139], hyponatremia (Na < 135 mmol/l) was detected in 25% (95% CI 18–32%), profound hyponatremia (Na < 130 mmol/l) – in 4.6% (2–9%), hypernatremia (Na > 145 mmol/l) in 0.6% (0–4%) of patients. Median potassium levels were 3.8 mmol/l [3.5; 4.2], hypokalemia (K < 3.5 mmol/l) was detected in 17.6% (12–25%), hyperkalemia (K > 5.1 mmol/l) in 2.6% (1–7%) of patients. Diabetes mellitus (DM) was observed in 15% of patients and was associated with lower Na levels 135 mmol/l [132; 136] vs 137 mmol/l [135; 139] in patients without DM (P = 0.003, Mann-Whitney test), and not with K levels. Na and K levels at admission were not associated with diuretic use by patients.
Conclusions
Our data suggests that hospitalized patients with COVID-19 infection have the high prevalence of impairment of sodium and potassium homeostasis, up to 32% and 25% respectively.

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AEP484

Spontaneous remission of cushing's disease – a case report

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Adrenocorticotropic hormone (ACTH) adenomas causing Cushing's disease (CD) have been recognized as an aggressive and invasive subtype of pituitary adenomas. Remission of CD without surgical or medical treatment is an extremely rare occurrence. Moreover, a clinically relevant peculiarity of these tumors, though rarely observed, is their ability to modify their clinical expression from a silent form to CD or vice versa, the latter even more unexpected. We describe the case of a 51-year-old woman referred to our clinic from the Gastroenterology Department in November 2018 with typical signs and symptoms of Cushing's syndrome. The laboratory tests supported an ACTH dependent Cushing's syndrome, with a high-normal ACTH and a high-dose dexamethasone suppression test with a more than 50% reduction of plasma cortisol, suggesting CD. Though initial, the brain MRI could not reveal a pituitary tumor, 10 months later a 6 mm pituitary microadenoma was described upon follow-up MRI. She was treated with metyrapone as part of the PROMPT study (a prospective multicenter, open-label, phase III/IV study). After a 12 weeks period of titration to achieve normal urine and serum cortisol levels, the patient entered the 6-month extension period during which she received 1500 mg of metyrapone daily, with significant clinical and biochemical (as defined by mean urine free cortisol (UFC) ≤ upper limit of normal) improvement. The treatment was stopped on 15 December 2019, according to study protocol and the patient was reevaluated 5 and, respectively, 6 months later. Surprisingly, she appeared much improved, though she did not receive any treatment to counteract hypercortisolism during this period. She had lost 18 kilograms and we could note the disappearance of cushingoid features as well as a remission of diabetes mellitus and arterial hypertension. These findings were further supported by the hormonal evaluation that excluded an active CD. Moreover, the pituitary-adrenal axis was normal (cortisol 8 a.m. = 6.9 μg/dl, ACTH = 29.3 pg/ml, 24-hour UFC = 152.3 μg/24 h), whereas the pituitary MRI revealed no pituitary mass as well as no signs of hemorrhage or infarction. There were no clinical and biochemical signs of recurrence 12 months later, in December 2020, either. This spontaneous remission from CD is puzzling and there seems to be no explanation for it. However, though regrowth of the pituitary adenoma and recurrence are even less encountered than spontaneous remission in CD, careful lifelong follow-up is mandatory in this patient.

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AEP485

Hypopituitarism in systemic diseases

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Introduction
Hypopituitarism is a rare condition defined by loss of pituitary function due to involvement of hypothalamus and/or pituitary gland by infiltrative diseases mainly sarcoidosis and Langerhans cell histiocytosis (LCH). Central diabetes insipidus is the most frequent manifestation of LCH (10–50%) and rarely in neuro-sarcoidois. Herein, we describe 2cases of hypopituitarism due to neuro-sarcoidosis and LCH.
Case 1
A 38 year-old man was admitted in endocrinology department to be explored for central diabetes insipidus. MRI imaging showed multifocal osteolytic lesions in maxillary and mandibular bones, thick pituitary stem and disappearance of the T1 hyper signal from the post pituitary gland. The patient presented normal renal function, normal levels of ACTH and thyroid-stimulating-hormone as well as serum electrolytes (sodium: 137 mmol/l, potassium: 3.8 mmol/l; calcium: 8.8 mg/dl). Mandibular-bone-biopsy and histological findings confirmed the diagnosis of LCH with multi-system bone and post-pituitary involvement. The patient received corticosteroid in combination with vasopressin through the nasal route. He also underwent surgical resection of maxillary lesion and dental prosthesis. Evolution was marked by persistence of diabetes insipidus requiring continued substitution with vasopressin. 3 years later, he presented bilateral mixed hearing loss due to secondary chronic medial otitis and dyspnea. Thoracic CT showed diffuse micro-cystic lesions in the lung parenchyma. High doses of steroids, vinblastine and vasopressin were started. He was lost from sight for 4 years, he stopped treatment except vasopressin. He had persistent deafness. Biological assessment was normal. Radiological assessment showed the same pulmonary, mastoid and mandibular lesions observed 4 years ago. The patient was considered in remission.
Case 2
A 49 year-old women was presented in internal medicine department in 2006 with cutaneous lesions (erythematosis lesions/nodules) in the upper member and the trunk. She suffered from short breath and cough. CT scan showed bilateral hilar lymphnodes enlargement with interstitial lung lesions. Pulmonary function test revealed low static lung volumes with low DLCO. Skin and lymph nodes biopsies revealed granulomas without caseum necrosis. Hormonal evaluation demonstrated decreased thyroid-stimulating hormone secretion with decreased thyroid hormone. Pituitary magnetic resonance imaging revealed thickening of pituitary stalk. Treatment of central hypothyroidism by thyroid hormone replacement was administered. Corticosteroids at the doses of 0.5 mg/kg/day were prescribed for 4weeks followed by progressive tapering with total duration of 4 years.
Conclusion
Central diabetes insipidus canbe related to several etiologies. Rare causes must be kept in mind, especially infiltrative diseases such as sarcoidosis or histiocytosis. Systemic clinical presentation guides usually the diagnosis.

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AEP486

A successful surgical outcome in thyrotropin-secreting pituitary macrodenomas

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Background
TSHomas are a rare cause of hyperthyroidism, and account for 0.5 to 3% of pituitary tumours. Incidence=0.15 per million per year. Prevalence=1 per million. Our limited experience of this condition can result in diagnostic and treatment challenges. Here we describe a case treated surgically lead to successful outcomes
Case
35 years old female referred to our service with secondary amenorrhea for the last two years. Amenorrhea Started after her delivery. She was on oral contraception pill before her pregnancy. She had associated increased tiredness, anxiety and palpitations. She has no medical or family history of endocrinopathy. Not on any regular medications. Clinically euthyroid. No eye disease or goitre, visual fields intact to confrontation. Initial bloods revealed high free T4 and T3 with inappropriate normal TSH level. Repeated bloods in different assay showed same results. Considered to be close to a state of syndrome of inappropriate secretion of thyroid-stimulating hormone. Accordingly investigations send looking for TSHoma Vs TSH resistance hormone. Sex hormone binding globulin, Alpha-glycoprotein subunits were both elevated suggestive of TSHoma. Thyroid releasing hormone test done showed flat response. Magnetic resonance imaging showed a macropituitary tumor.Started on larenotide however she could not tolerate it, surgery performed subsequently, histology confirm TSHoma. Few weeks later her thyroid function normalized and her symptoms improved including period become regular.
Conclusion
Surgery remains the first-choice treatment for TSHoma. If surgery is successful, recurrence is rare. Our case showed an excellent outcome in typical case of TSHoma, respond very well to the surgical intervention. Surgical option is the first line, however surgical failure can be seen in 40 percent of cases.

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AEP487

Case report: Girl with short stature with no response to growth hormone treatment

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Introduction
Growth hormone deficiency (GHD) is a rare disorder and severe forms of GHD may have a genetic basis. Familial isolated growth hormone deficiency (IGHD) is classified into 4 types, type IA being the most severe form. These patients present with severe growth failure with undetectable growth hormone (GH) concentrations and about 50% tend to develop antibodies on GH treatment.(1, 2, 3) The appearance of anti-GH antibodies may not be a regular finding even among members of the same family. There have been reported cases when these antibodies have disappeared after a few years. (4, 5).
Case report
We present the case of a young female patient who was referred for endocrinological evaluation for short stature at the age of 1 year. She came from a family with a very short mother (height of 145 cm) without an endocrinological evaluation and a sister treated with somatropinum for severe GHD for 9 years, with a good height response to treatment. The patient presented with severe short stature, height of 62 cm (–5.17 standard deviations, SD), with normal weight (body mass index (BMI) 16.64 kg/m^2). The paraclinical exam showed undetectable GH, low values of insulin growth factor 1 (IGF1), normal 25 hydroxyvitamin (25OHD), normal thyroid and adrenal function. Dynamic growth hormone evaluation showed unstimulated levels. Pituitary MRI (magnetic resonance imaging) showed adenohypophyseal hypoplasia. Based on the evaluation she was diagnosed with severe GHD and received treatment with somatropinum 0.23 microg/kg bw/day. At the six months reevaluation we found a height of 63.3 cm (–6.11 SD) and a BMI of 15.62 kg/m^2. The response to treatment was considered inadequate and an IGF1 generation test was performed without a significant increase of IGF1. The most probable explanation was the presence of GH antibodies, but the test was not available. She was followed for 1 year, but the height parameters were not improved (at the age of 2.5 years, height of 64.8 cm, -6.94 SD)
Conclusions
In patients with familial IGHD the response to somatropinum treatment could be affected by the appearance of anti-GH antibodies. Although these antibodies can disappear after few years, in cases with disabilitating short stature the lack of treatment can have a severe impact on the well being and the development of the patients. Although mecasermin might be an alternative in these cases, their approved indications can limit the access to treatment.

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AEP488

Pituitary surgery in northern ireland: A twenty year retrospective population based analysis

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In Northern Ireland, the sole tertiary referral centre for pituitary disease which includes neurosurgery and endocrinology for ~1.9 million people, is based in the Royal Victoria Hospital, Belfast. A retrospective study has been commenced to examine clinical, biochemical, histopathological and radiological data for all patients operated on across an approximately 20 year period in Northern Ireland. Ethical approval was obtained from the Northern Ireland Biobank (study number NIB18–0282). We present preliminary clinical and histopathological data on this Northern Ireland pituitary surgery population cohort. To date, a total of 704 pituitary samples have been identified between 2000 to mid 2019, an average of 35.9 surgeries per year. During this time there were maximum two operating pituitary surgeons. There were 20 procedures for 17 paediatric patients, with the most common diagnosis being craniopharyngioma (n = 6). A total of 684 procedures for 633 adult patients were undertaken, of which 285 patients were female and 348 were male. Average age of the entire adult cohort at resection was 53.3 years (SD ± 15.1 years), with average resection age 50.6 years for female and 55.5 years for male. 591 surgeries were completed for pituitary neuroendocrine tumours (PitNETs) (86%), diagnosed on the basis of combined clinical, histopathological and radiological assessment. The majority of these procedures were undertaken for non-functioning PitNETs (n = 390, 66%). Other operated PitNET pathologies included acromegaly/gigantism (n = 112, 19%), Cushing's disease (n = 60, 10%), prolactinoma (n = 20, 3%) and thyrotropinoma (n = 7, 1%). Only two samples could not be completely characterized. There are seven patients known to have AIP mutations in this surgical cohort (1% of all patients). Other more frequent pathologies requiring surgical intervention or biopsy included craniopharyngioma (n = 27), Rathke's cleft cyst (n = 17) and hypophysitis (n = 7). Rare diagnoses included paraganglioma (n = 1), meningioma (n = 1) and Non-Hodgkin's B cell lymphoma (n = 1). There were two perioperative deaths (mortality rate 0.3%), both secondary to postoperative haemorrhage. In summary, from the beginning of the year 2000 to mid 2019 this Northern Ireland tertiary referral centre has averaged appoximately 36 adult pituitary procedures per year, the majority of which were undertaken for PitNETs (86%). Establishment of a pituitary database spanning nearly two decades will provide a valuable research resource suitable for integration with novel tissue based analysis and will assist in clinical service improvement to enhance our understanding of pituitary disease, particularly in Northern Ireland.

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AEP489

Disease activity is associated with depression and anxiety in cushing's syndrome during COVID-19 pandemic

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Purpose
To assess the depression and anxiety and their relationship with disease activity in patients with Cushing's syndrome (CS) in the COVID-19 pandemic.
Material and methods
This is a cross-sectional study including 54 patients with CS (48 female/6 male). Beck Depression Inventory-II (BDI-II), State Trait Anxiety Inventory (STAI)-State, STAI-Trait were used to evaluate, scores and severity of depression, the current state of anxiety, and general anxiety, respectively. Patients with active CS (n = 10) were recorded as group 1, those who were still receiving glucocorticoid replacement therapy after surgery (n = 14) as group 2, and those in remission (n = 30) as group 3. The groups were compared in terms of parameters that could affect anxiety and depression scores. Correlation analyses were also performed.
Results
BDI-II scores were higher in group 1 than group 3 (P = 0.002), and STAI-State scores were higher in group 1 than group 2 (P = 0.03) while STAI-Trait scores and the other parameters were similar between the groups. Moderate and severe depression were detected in 60% of group 1, 25% in group 2, and 16% in group 3. High state anxiety was seen in 70% of patients in group 1, 50% in group 2, and 57% in group 3. There were positive correlations between BDI-II scores and disease activity (r = 0.438, P = 0.001), and STAI-State scores and disease activity (r = 0.297, P = 0.029).
Conclusion
Increased depression and state anxiety during the pandemic in patients with active CS suggested that psychiatric disorders may increase in those with a higher risk of severe COVID-19 disease.

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AEP490

Third month MRI predicts macroprolactinoma reduction after cabergoline therapy

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Background
Transsphenoidal surgery is in general the preferred first-line treatment for patients with macroadenomas except for prolactinomas, which is mainly indicated when the treatment with dopamine agonists (DA) fails. However, in those patients resistant to DA (i.e. volume reduction < 50% in the follow-up) this strategy delays the surgical procedure.
Objective
To identify predictors of DA resistance in order to select patients who may benefit from early surgery.
Methods
We retrospectively analysed a database of a tertiary reference centre searching for patients diagnosed of prolactinoma after 2010 (when medical records were computerized) and with active follow up in the last five years. The adenoma volume was analysed by MRI before 3 and 12 months of treatment. We used spearman rank to investigate if our main outcome: (volume reduction of ≥ 50% after 12 months of treatment with DA therapy), was influenced by several variables including age, gender, prolactin levels, DA doses and adenoma volume reduction at 3–4 month of treatment.Finally we tested by logistic regression which variables predict better the main outcome.
Results
A total of 185 prolactinomas where included: 124 (67.0 %) were microadenomas and 61 (33.0%) were macroadenomas. We excluded 28 patients with incomplete data or diagnosed before 2010 and 6 patients that underwent surgery in first line. Finally, 27 patients meet de inclusion criteria; mean age [44.4 years; CI 95%: (37.8–59.8)].), of whom 10 were women (37.0%) and 17 were men (63.0%). Mean follow up [67.5 months; CI 95%: (52.5.0–82.7)]. Ten (37.0%) patients (8 males: 80.0%) underwent surgery after more than one year of DA because a lack of tumour reduction. The volume reduction at the first MRI (3–4 months) was the unique valuable predictor: [OR: 1.16 (IC 95% 1.02–1.32)]. A cut off tumour volume reduction ≥ 35% by the first 3–4 months of DA therapy predicted subsequent volume reduction > 50% in the first year with an AUC 0.95 [CI: (0.76–0.99)].
Conclusion
The tumor shrinkage in the first 3–4 month after starting treatment with DA is the best predictor of future volume reduction resistance. These results could help in decision-making regarding the management of macroprolactinomas.

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AEP491

The role of cannulated prolactin test in females of reproductive age presenting with isolated mild persistent hyperprolactinaemia on random sampling

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Introduction
Current guidelines recommend a single elevated prolactin measurement drawn without excessive venepuncture stress as sufficient for diagnosing hyperprolactinaemia. However, previous studies have demonstrated that the cannulated prolactin test is more reliable at eliminating stress-induced hyperprolactinaemia, thus avoiding unnecessary additional investigations. We routinely perform morning serial prolactin sampling immediately after brachial vein cannulation followed by repeat sampling at 30 and 60 minutes of rest, to rule out stress-induced hyperprolactinaemia.
Objectives
This retrospective study aimed at evaluating the incidence of stress-induced hyperprolactinaemia in females of reproductive age referred to our hospital with isolated mild hyperprolactinaemia on repeat random testing in the community. We investigated any correlation between presenting symptoms and diagnosis of true hyperprolactinaemia and the incidence of pituitary abnormality on MRI.
Methods
All adult female patients, aged between 18–53 years, undergoing cannulated prolactin testing at our Endocrine Unit between 2016 and 2020 were included. Exclusion criteria: presence of macroprolactinaemia, chronic kidney disease, genetic predisposition syndromes, previous diagnosis of pituitary tumours and those with abnormal thyroid biochemistry.
Results
55 patients were eligible, with an average age of 33 years. The mean level of referral prolactin was 979 mIU/l (min: 511, max: 3022, normal range < 496 mIU/l). 40% of patients presented with menstrual disturbances and 32% had galactorrhoea. 58% of patients had a normal prolactin level on cannulated testing, thus confirming stress-induced hyperprolactinaemia. Those with true hyperprolactinaemia were more likely to report galactorrhoea (48% vs. 21%, P < 0.05). 15/32 (47%) patients with stress-induced hyperprolactinaemia were asymptomatic (vs. 26%, P < 0.05). 52% of patients with true hyperprolactinaemia harboured an abnormality on pituitary MRI. Those with a lesion were younger (mean age 30 years vs. 40 years in those with normal MRI, P < 0.05). There was no statistically significant difference in baseline prolactin or symptomatology between the group with normal MRI finding and those with abnormal MRI. Notably 2/5 asymptomatic patients with true hyperprolactinaemia had a microadenoma evident of MRI.
Conclusion
The cannulated prolactin test reliably diagnosed stress-induced hyperprolactinaemia in our select cohort of female patients of reproductive age. Whilst asymptomatic patients are more likely to have stress-induced hyperprolactinaemia, 40% harbour a microprolactinoma if diagnosed with true hyperprolactinaemia on cannulated prolactin testing.

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AEP492

GH and IGF-1 discrepancies in acromegaly patients after pituitary surgery – an observational single-center study

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Introduction
Treatment of choice in acromegaly is transsphenoidal resection of GH-secreting pituitary adenoma. Its efficacy ranges from 28% to 83% depending on tumor size and location. Random GH < 1 μg/l or nadir GH in OGTT < 0.4 μg/l and normal IGF-1 are found to be the evidence of effective

surgery. However, some patients diagnosed with acromegaly remission after surgery present discordant GH and IGF-1 results.
Aim
Purpose of this study was to assess the frequency of discrepancy between GH and IGF-1 levels and identify parameters that might affect its occurrence.
Material and methods
Fourty seven patients (19 males, 40.4%) with acromegaly remission after pituitary surgery were included in the study. Random GH and IGF-1 measurements 3, 6, 12, 24 and more than 24 months after surgery were analyzed in terms of discrepancies. GH measurements in OGTT 3 months after surgery and later, if random GH > 1 μg/l, were performed. We defined discrepancy either as random GH > 1 μg/l or nadir GH > 0.4 μg/l in OGTT and normal IGF-1 or GH below levels listed before and elevated IGF-1. Clinical factors such as: sex, age, age at diagnosis, diagnosis delay, BMI, weight, tumour size, GH and IGF-1 at diagnosis and carbohydrate metabolism were analyzed in patients with and without GH and IGF-1 discrepancies. None of the patients required pharmacological treatment of acromegaly after surgery.
Results
The percentage of patients with GH and IGF-1 discrepancies was the smallest 3 months after surgery (42%), then increased 6 months after surgery (71%) and finally decreased over time (60% after 12 months, 55% after 24 months and 52% more than 24 months after surgery). The most frequent type of discrepancy was slightly elevated IGF-1 and random GH < 1 μg/l or nadir GH < 0.4 μg/l in OGTT (over 70% of patients with discordant GH and IGF-1 results within the first year after surgery). IGF-1 tended to decrease over time. Age, age at diagnosis, diagnosis delay, BMI, weight, tumor size, GH and IGF-1 at diagnosis were similar in patients with and without discrepancies ($P > 0.05$). A tendency to higher percentage of males in group with discrepancies was observed, 55% vs 30%, $P = 0.08$.
Conclusions
Discrepancy between GH and IGF-1 are common in patients with acromegaly remission after surgery affecting 42% to 71% of patients depending on time after surgery. Patients with GH and IGF-1 discrepancies should be observed, although the frequency of discrepancies decreases over time. Men may be more likely to present GH and IGF-1 discrepancies after effective adenomectomy.

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AEP493

Growth hormone treatment for adults with Prader-Willi syndrome: A meta-analysis

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Background
Features of Prader-Willi syndrome (PWS) overlap with features of growth hormone (GH) deficiency, like small hands and feet, short stature, increased body fat and low muscle mass and strength. In children with PWS, GH treatment improves physical health, cognition and quality of life (QoL). GH treatment is standard of care in PWS children, but in adults this is not the case. A systematic review and meta-analysis was conducted to provide a concise overview of the current knowledge on GH treatment in adults with PWS.
Methods
The databases Medline, Embase and Cochrane Central Register of Controlled Trials were sought for studies on the efficacy or effectiveness of GH treatment for adults with PWS. Randomized controlled trials (RCTs) and non-randomized (un)controlled trials (NRCTs) that reported data for adults with PWS who received GH treatment for at least six months were selected. Data on body composition, body mass index (BMI), cardiovascular endpoints, bone, cognitive function, QoL and safety were extracted.
Results
Nine RCTs and 19 NRCTs were included. Body composition improved during GH treatment with an increase in mean (95% CI) lean body mass of 1.72 kg (0.33–3.10 kg) for 258 person-years of follow-up, and a reduction of mean (95% CI) fat mass of –1.94% (–3.30% to –0.57%) for 223 person-years of follow-up. BMI, low-density lipoprotein levels and bone mineral density did not change during GH treatment. GH treatment was safe for both GH naïve adults with PWS and for adults previously treated with GH.
Conclusion
GH treatment is safe and improves body composition in adults with PWS. As poor body composition plays a key role in the high cardiovascular morbidity of adults with PWS, these data suggest that GH treatment might reduce long-term cardiovascular complications in this vulnerable patient group.

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AEP494

Cabergoline treatment for non functioning pituitary macroadenomas

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Introduction
Cabergoline seems to be a promising and effective medical treatment for the more agressive Non Functioning Pituitary Adenomas (NFPAs) by reducing or keeping tumor's size stable long-term. Here we present the experience of our center
Methods
We studied 7 patients with NFPAs attending our clinic the last 10 years (median period 42 months, range 12 to 114 months), in whom cabergoline was started due to threatening tumor rise approaching the optic chiasm. Five patients had prior pituitary surgery (transsphenoidal, and 2/5 an additional transcranial) for aggressive adenomas compressing the optic chiasm, histological and immunohistochemical findings negative for intact pituitary hormone expression and significant residual tumor or tumor regrowth post surgery. The other 2/7 had macroadenomas approaching the optic chiasm. We evaluated tumor's mass (cm), tumor's volume (cm^3), visual fields and pituitary function before and twenty-four months after the initiation of cabergoline. Tumor shrinkage > 25% from the baseline is considered significant, although even stabilization or reduction of the tumor at least 10% is consindered very important.
Results
Mean age of the patients was 67.29 ± 8.97 years old and mean cabergoline dose was 2.1 ± 0.95 mg/week. Mean tumor volume at baseline was 8.78 ± 6.73 cm^3 and on cabergoline 8.19 ± 6.50 cm^3 and 7.87 ± 6.56 cm^3 at six and twenty-four months respectively. 2/7 patients (28.57%) had no change on tumor volume during the study period. At six months in 2/7 (28.57%) a volume reduction less than 10% (4.76%, 3.57%) was observed and in 3/7 (42.85%) a reduction more than 10% (19.23%, 15.98%, 18.51%). After twenty-four months from baseline in 1/7 patient (14.28%) there was a volume reduction less than 10% (7.42%), in 3/7 (42.85%) a reduction more than 10% (15.98%, 15.58%, 23.55%) and in 1/7 patient (14.28%) a reduction more than 25% (61.69%). All patients had a remarkable improvement on visual fields defects. Hormonal hypersecression and side effects were not noted.
Conclusion
Our data indicate that cabergoline could be beneficial for aggressive NFPAs. However long-term trials with more participants are needed for more reliable and accurate conclusions.

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AEP495

Efficacy and safety of cyberknife stereotactic radiosurgery in acromegaly

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Objective
Active acromegaly is associated with increased mortality. While surgery is the mainstay of treatment, it is not always curative. In selected cases, CyberKnife stereotactic radiosurgery (CK SRS) can be used as adjuvant treatment in patients with persistent disease.
Design
This is a retrospective review of the biochemical and imaging characteristics for patients with active acromegaly treated with CK SRS at St.Bartholomew's Hospital, between 2014–2019.
Methodology
Biochemical response was measured using serum IGF-1 levels, calculated as a percentage of the upper limit of normal (% ULN). Levels were recorded prior to treatment, at 6–12 months post-treatment and at the most recent follow-up visit. Anterior pituitary hormone deficits were assessed before and after treatment. Tumour size was followed up with MRI.
Results
A total of 10 patients (7 male, mean age 36 years [± 12.6, SD]) with active acromegaly were treated with CK SRS, delivered as a single session. Nine patients were treated following failure to attain biochemical remission with transsphenoidal surgery (TSS). One patient had primary CK SRS, having declined TSS. Two patients had previously received conventional fractionated external beam radiotherapy. The median maximal tumour diameter preceding therapy was 6 mm (IQR 5.2–10.5 mm). Cavernous sinus invasion was reported in 2 cases. The median radiation dose prescribed was 23 Gy (IQR 20–24 Gy). At the time of treatment, 4 patients were on dopamine agonist, 4 patients on somatostatin analogue and 2 patients were on pegvisomant. The mean follow-up period was 31.6 months (± 13.5 months, SD). The median IGF-1 % ULN was 146% pre-treatment (IQR 126.5–208.5), 109% at 6–12 months (IQR 76.5–131%) and 71% (IQR 59–91%) at last follow-up. By the last follow-up visit, 5 patients required additional treatment, 2 patients had no change in treatment, 2 patients underwent dose reduction and 1 patient was off medication. The mean radiological follow-up using MRI was 16.6 months (± 15.9 months, SD). No cases showed tumour enlargement. Before treatment, 6 patients had evidence of anterior pituitary hormone deficits. One patient with pre-existing hypogonadism developed secondary hypothyroidism post-treatment. Side-effects included headache (7 patients), blurred vision (1 patient), fatigue and nausea (1 patient). Two patients reported no side-effects. There were no new visual fields defects, cranial nerve palsies, cerebrovascular events or secondary tumours.
Conclusion
CK SRS appears safe and effective in selected patients with acromegaly, when there is failure to attain biochemical cure with surgery and in patients intolerant or resistant to medical treatment.

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AEP496

Pituitary apoplexy: Clinical features, management and outcomes-a retrospective study

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Introduction
Pituitary apoplexy (PA) is a rare medical emergency caused by acute haemorrhage and/or infarction within a pituitary or usually pituitary tumour. Typically, PA is characterised by severe headache, visual fields defects, decreased visual acuity, cranial nerve palsies and hypopituitarism. However, many patients present with mild or ambiguous signs and symptoms or even PA is an incidental radiological finding.
Aim
To evaluate clinical presentations, pituitary function and management of patients diagnosed with PA. Patients and methods: We conducted a retrospective analysis of medical records of patients diagnosed with PA between 2015 and 2020 at the Department of Endocrinology of the Bielanski Hospital. Diagnosis of PA was based on clinical presentation, hormonal and imaging results.
Results
Forty-three patients were identified, with women predominance (56% female), and mean age of patients 42 yrs. (SD 17.2, range 16–79). Precipitating factors such as pregnancy/labour, surgery, dopamine agonist treatment were identified in 44% of cases. Diagnosis of pituitary tumour was established prior to PA in 11 cases (26%), during PA in more than half of cases (53%), but in as many as 21% of patients, the tumours were discovered with a suggestion of past apoplexy. Majority of PA cases (81.4%) underwent conservative management (75% of symptomatic patients) and only 18.6% required surgical intervention (due to severe headache and visual defect). Most of the pituitary lesions (63%) were identified as non-functioning pituitary adenomas. The remaining tumours were: prolactinomas (16%), Rathke cleft cysts (12%), GH- secreting adenomas (5%). There were 2 cases of Sheehan's syndrome. Fifteen patients (35%) were asymptomatic but their imaging results strongly suggested PA. In symptomatic patients, the most common symptoms at presentation were headaches (79%), visual field defects (32%) and decreased visual acuity (50%). Other symptoms included: diplopia, isolated acute cranial nerve palsies, dizziness and impaired consciousness. The most common anterior pituitary dysfunction was gonadotroph deficiency (57%), followed by ACTH, TSH and GH deficiencies (in 46%, 46% and 36% respectively). Panhypopituitarism was present in 1 case (4%). Two patients had a second incident of PA apoplexy during follow up and 2 patients were diagnosed with encephalitis or meningitis simultaneously. Regrowth of pituitary tumour was observed in four patients (9.3%).
Conclusions
Although PA can be life-threatening and sometimes requires neurosurgery, most cases can be managed conservatively. We found less proportion of patients with anterior pituitary deficiency. The risk of tumour progression after PA makes long-term follow-up necessary.

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AEP497

Kallmann syndrome due to a mutation in ANOS1 gene and monoallelic mutation in GNRHR gene

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Introduction
Hypogonadotropic hypogonadism (HH) is a rare disease. When associated with anosmia/hyposmia, it is called Kallmann syndrome (KS). Several mutations in different genes have been implicated in its pathophysiology, the most frequent being ANOS1/KAL1, FGFR1 and GNRHR genes. This heterogenicity can be explained by the increasing detection of more than one pathogenic variant in the genes responsible for causing the disease (oligogenism). The prevalence of this phenomenon is estimated to be 2.5–11.3%. Therefore, the classical paradigm of monogenic transmission of the disease has been challenged over the past years.
Case report
Male patient, 32 years old, referred to our endocrinology clinic because of decreased libido and erectile dysfunction. He had been diagnosed with hypogonadism at the age of 13 due to pubertal delay and anosmia. No history of testicular or head trauma. He was temporarily supplemented with testosterone. Past medical history included diabetes *mellitus* type 2, obesity and gastroesophageal reflux disease. Family history: hypogonadism in his brother and maternal cousin. In the physical examination: weight 98 kg, height 172 cm, arm-span 170 cm and body mass index 33 kg/m^2. Testicular volume of 10 ml with no masses or lesions. He had normal secondary sexual characteristics and no gynecomastia nor synkinesis. Blood results: total testosterone 0.5 ng/ml, free testosterone 0.84 pg/ml, LH 0.2mU/ml, FSH 0.6mU/ml, prolactin 3.5 ng/ml, TSH 1.56 µUI/ml, IGF-1 79.2 ng/ml, 60-minute cortisol (tetracosactide stimulation test) 34.7 µg/dl, HbA1c 7.8% and C-peptide 5.24 ng/ml. Renal ultrasound showed no genitourinary abnormalities. Pituitary MRI evidenced a small-sized gland, no sellar/parasellar masses and absence of olfactory bulbs and tracts. Bone densitometry showed no signs of osteoporosis. Genetic next generation sequencing identified the variant (Arg457Ter) in ANOS1 gene in *hemizygosity* and the variant (Gin106Arg) in GNRHR gene in heterozygosity. He was diagnosed with KS due to the mutation of ANOS1 gene and was treated with testosterone, showing clinical and analytical improvement.
Discussion
This is the first case described of HH due to a hemizygotic mutation in ANOS1 gene and the additional presence of a mutation in GNRHR gene, which is usually associated with an autosomal recessive form of non-anosmic HH. It has been proposed that the presence of more than one heterozygous mutation of genes normally associated with an autosomal recessive disease can act synergically to the pathogeny. In this case, however, we cannot affirm that the GNRHR mutation contributed to the disease, since the ANOS1 mutation is usually sufficient to cause the disease in males.

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AEP498

The role of endoscopic ultrasonography for localization of sporadic and men-1 syndrome associated insulinomas: Case series

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Introduction
The diagnosis of insulinomas is made biochemically. However, proper localization of insulinomas is essential before surgery. Non-invasive methods including magnetic resonance imaging (MRI), computed tomography, ultrasonography, glucagon-like peptide-1 receptor PET/CT, 68Ga-DOTATATE PET/CT, and invasive methods such as endoscopic ultrasonography (EUS) and selective arterial calcium stimulation test are used for preoperative localization. However, some of these methods are either expensive and may not be available in most centers, or highly invasive that requires particular expertise. Therefore, we aimed to evaluate the role of EUS in the localization of insulinomas.
Case series
This case series including 8 patients with biochemically proven insulinomas. The age, gender, MRI, EUS, and immunuhistopathological results of the patients are shown in Table-1. A mass on MRI was detected in only 2 of the 8 patients. However, EUS showed a mass in the pancreas of all patients. All patients underwent surgery according to the EUS results, and a diagnosis of insulinoma was made in all patients by immunohistopathological analysis. All patients achieved cure after surgery except a patient with MEN-1 disease who had multiple small insulinomas as well as a glucagonoma.
Discussion
More than 90% of insulinomas are benign, solitary, and < 2 cm. However, MEN-1 associated insulinomas may be multiple. The sensitivity of CT and MRI is between 33% -64% and 40% -90%. However, no mass could be found by CT or MRI in 25–30% of the patients. In our series, the mass could not be detected in 6 of the 8 patients by MRI while all of the insulinomas were localized by EUS. On the other hand, the sensitivity of EUS decreases in the presence of a large number of tumors and small tumors, as in cases with MEN-1 disease. Therefore, EUS should be performed in all cases suspected of sporadic insulinomas before any other invasive localization method, but in patients with MEN-1 disease, other invasive and non-invasive localization methods should be performed even in the presence of a tumor on EUS.

Patients	Gender/ Age	Presence of tumor on MRI (mm)	The tumor size on EUS (mm)	Histopathological results after surgery
1*	F/27	No	9	6 mm and 5 mm insulinomas and an 8 mm glucagonoma*
2	F/29	No	15	Insulinoma
3	F/33	No	15	Insulinoma
4	M/35	No	15	Insulinoma
5	F/44	No	14.5	Insulinoma
6	F/45	No	7	Insulinoma
7	M/55	20	22	Insulinoma
8	M/64	16	20	Insulinoma

*: MEN-1 syndrome

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AEP499

Ectopic cushing's syndrome: Report of 5 cases from a tertiary care center

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Introduction
Ectopic Cushing's syndrome (ECS) is a rare entity caused by ACTH secretion by a non-pituitary tumor. The management of these patients is challenging due to its low frequency and limited experienced. The objective of this study was to describe the patients with ECS treated in the Division of Endocrinology at the Ramón y Cajal University Hospital (Madrid, Spain) in the last six years.
Methods
Records of patients with ECS from 2016 to 2020 were retrospectively reviewed including clinical and biochemical data, imaging modalities to locate the non-pituitary source of ACTH production, management and follow up.
Results
The study group included 5 patients: two ECS secondary to bronchial carcinoid, one secondary to thymic carcinoma, one secondary to metastatic medullary thyroid carcinoma (MTC) and one occult ECS. Two were women and 4 men, median age of 44.6 (15.0–57.6) years at diagnosis. The specific clinical picture of Cushing syndrome developed in all patients with the exception of one patient with ECS due to bronchial carcinoid. Moreover, 2 patients presented hypertension, diabetes and obesity. Only the patient with ECS due to MTC had hypokalemia at diagnosis. The median urinary free cortisol and nocturnal salivary cortisol levels were 421.8 (30.6–47142) μg/24 h and 29.9 (3.4–2436) μg/dl, respectively, and the median plasma ACTH levels was 148.4 (46.1–929) pg/ml. The ectopic origin was confirmed by a combination of dynamic tests and imaging modalities. The tumor was identified in all patients except in one case, and 2 patients had metastatic dissemination. Primary treatment was surgery in 4 patients, one of them combined with chemotherapy and radiotherapy (thymic carcinoid), and medical treatment in 1 patient (occult ECS). Bilateral adrenalectomy was required in one patient. The medical treatments used to control hypercortisolism were ketoconazole in 3 patients and metopirone plus ketoconazole in one patient. After a mean follow-up of 67 months, 1 patient (MTC) died and 4 are still alive, 2 (bronchial carcinoid) cured and 2 (occult ECS and thymic carcinoid) with persistent/recurrent disease.
Conclusions
ECS is a rare disease caused by a wide spectrum of tumors with varied manifestations and associated increased morbidity and mortality. The most common tumor was bronchial carcinoid. Control of both tumor and hypercortisolism requires multiple treatment modalities, and surgery with removal of primary tumor was found to be the treatment of choice, if possible. Therefore, multidisciplinary management is recommended.

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AEP500

Cerebral infarction in childhood-onset craniopharyngioma patients – results of kraniopharyngeom 2007

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Background
Cerebral infarction (CI) is a known vascular complication following treatment of suprasellar tumors. Risk factors for CI, incidence rate, and long-term prognosis are unknown for patients with childhood-onset craniopharyngioma (CP).
Methods
MRI of 244 CP patients, recruited between 2007 and 2019 in KRANIOPHARYNGEOM 2007, were reviewed for CI. Risk factors for CI and outcome after CI were analyzed.
Results
Twenty-eight of 244 patients (11%) presented with CI based on reference assessment of MRI. One CI occurred before initial surgery and one case of CI after release of intracystic pressure by a cyst catheter. 26 of 28 CI were detected after surgical tumor resection at a median postoperative interval of one day (range: 0.5–53 days). Vascular lesions during surgical procedures were documented in 7 cases with CI. There was a trend ($P = 0.094$) towards higher initial presurgical tumor volume in CI patients compared with non-CI patients. No relevant differences with regard to surgical approaches

were found. In all 12 irradiated patients, CI occurred before irradiation. Multivariable analyses showed that hydrocephalus and gross-total resection at the time of primary diagnosis/surgery both were risk factors for CI. PFS was lower after CI (median survival=1.16 years) when compared with the subgroup of patients without CI (median survival > 5.62 years). After CI, quality of life (PEDQOL) and functional capacity (FMH) were impaired.
Conclusions
CI occurs in 11% of CP cases. Tumor size, degree of resection and increased intracranial pressure are risk factors, which should be considered in the planning of surgical procedures for prevention of CI.

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AEP501

Clinical features, diagnostic criteria and treatment outcomes in 40 patients with thyrotropin-secreting pituitary tumors

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Introduction
Thyrotropin-secreting pituitary adenomas (TSH-omas) are rare. For this reason each case of TSH-secreting pituitary tumor can help expand extensive clinical experience in world practice.
Materials and methods
We included 40 patients with TSH secreting pituitary adenomas. Hormonal profile: TSH (0.25-3.5 mIU/L), FT4 (9-20 pmol/l) FT3 (2.5-5.5 pmol/l) were measured by Architect i2000SR (Abbott Laboratories, Abbott Park, Illinois, U.S.A). MRI was performed on GE Optima MR450w 1.5T.
Results
Forty patients with TSH-omas were under observation in our center from 2010 to 2020. The median age was 46 [32; 57] with a predominance of female (31 cases) over male (9 cases). Clinical manifestations included cardiac arrhythmias (80%); neurological changes (60%), impairment of bone metabolism (51.35%) hypopituitarism (10%) visual impairment (10%). At the beginning of the observation, 17 patients had increased TSH, FT3 and FT4 levels; in 10 patients FT3 and FT4 only; 5 patients had elevated TSH and either FT3 or FT4, and in 8 — an increase in one of the hormones. Mean value of TSH was 4.28 [2.4; 6.4] mIU/L, FT4 — 23.03 [20.03; 29.37] pmol/l, FT3 – 7.2 [5.9; 10.09] pmol/l. Sex steroid binding globulin, C-terminal telopeptide and osteocalcin were elevated in 62.86%, 62.07% % and 48.15% of cases, respectively. In 75% of cases short-term octreotide treatment led to thyroid hormone normalization. On MRI macroadenomas were registered in 72.5% cases. In 1 case there was no pituitary adenoma on MRI. In 20 patients, diagnosis was finally confirmed by immunohistochemical examination. In 13 patients, the diagnosis verification was based on remission after surgical or medical treatment. In the remaining 7 cases, the diagnosis was made on clinical and laboratory data. Remission was achieved in 33 patients: 25 (75.76%) after neurosurgery, 3 received treatment with somatostatin analogues and 5 required somatostatin analogues after neurosurgery; 2 out of 7 patients who did not achieve full remission were lost for observation.
Conclusion
At the time of diagnosis 72.5% of patients had macroadenomas and 80% had cardiac arrhythmias, suggesting a long duration of disease. However less than 50% of patients had all tests elevated emphasizing the necessity of multiple hormone testing and complex diagnostic evaluation.

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AEP502

White blood cell count: A potential useful tool for suspected Cushing's syndrome

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Background
Suspicion of Cushing´s syndrome (CS) is usually suggested by non-specific clinical data. Chronic hypercortisolism associates changes in white blood cell count (WBC), essentially a higher count with relative lymphopenia. Our purpose is to investigate the prevalence of these findings among a local series of patients with Cushing's syndrome before and after the hypercortisolism revertion to assess the diagnostic value of these parameters in order to decide who must be evaluated for the disease.
Methods
Data from 34 patients, who underwent surgery for Cushing´s syndrome in our center from 2004 to 2020, were reviewed. The diagnosis of CS was made on the basis of standard clinic and analytical criteria. Urinary free cortisol (UFC), cortisol after 1 mg of dexamethasone (Nugent´s test), and morning cortisol concentrations were collected. WBC baseline parameters were gathered from the blood test preceding diagnosis and 1 month after surgery. We defined relative lymphopenia as <20.5% of WBC, and absolute lymphopenia as < 1300/µL, whereas relative neutrophilia encompassed neutrophils > 65% of WBC, and absolute neutrophilia > 5000/µL.
Results
26 out of the 34 patients were women, and mean age was 49.4 years (range 19-87). The mean baseline UFC levels was 494.8 ± 891.2 µg/24h, Nugent´s test was 24.6 ± 25.8 µg/dl and mean morning cortisol level was 27.2 ± 18.6 mcg/dl. 17 patients had CS due to adrenal causes, 13 were found a pituitary adenoma and 4 an ectopic ATCH production. 76% patients with CS had a relative lymphopenia (mean: 15%) and only 26.4% an absolute lymphopenia. In 82% and 91% patients we found a high absolute (mean: 7065 ± 4958/µl) and relative (mean: 73.8%) neutrophil count respectively. Only 2/34 patients did not have any WBC alterations. After treatment we found an improvement in all WBC lineages with only 11,7% of patients presenting relative lymphopenia (mean: 34%), 2,9% absolute lymphopenia (mean: 2927 ± 1720/µl), 44% absolute neutrophilia (mean: 5322 ± 6374 cel/µl), 11,7% relative neutrophilia (mean: 50%). Results also revealed a correlation between the WBC changes and the markers of CS severity, including UFC and morning serum cortisol.
Conclusions
WBC count may be a useful tool to suggest the evaluation for Cushing´s syndrome in patients with clinical unspecific symptoms like the association of diabetes and abdominal obesity. Specifically as a parameter with negative predictive value in the absence of any WBC alterations.

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AEP503

Screening of acromegalia among patients with endocrine and somatic pathology

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Introduction
The practice of screening for many chronic diseases, particularly endocrine pathology, is taking place all over the world. The relevance of screening increases significantly when we are talking about diseases with a torpid manifestation and absence of certain clinical symptoms in the debut. Such diseases include pathological conditions caused by pituitary hormone hypersecretion, in particular, acromegaly.
The aim
Of the study was to determine the informative value and specificity of the questions included in the acromegaly primary screening questionnaire on the basis of a comparative analysis.
Material and methods
A questionnaire for screening for acromegaly was developed, which in the final version included 11 questions representing the clinical and phenotypic signs of long-term hypersomatotropinemia. The evaluation was performed on a scale of points, with a maximum of 11 points. The survey was carried out in individuals from the 'risk group' who came to an outpatient visit to a general practitioner, therapist, cardiologist, endocrinologist for other reasons and in the presence of somatic and/or endocrine pathology (n=1660).
Statistical analysis
Variation statistics using the 'SPSS 19.0 statistical software' (IBM Corp., Armonk, NY, US).
Results
The maximum sum of points (11) in the questionnaire was found in 2 women in the older age group (over 65), which was 0.12% of the total number of respondents; 8 points in 4 women (0.24%); 7 points in 10 people (4 m/6 f) (0.61%); 6 points in 18 people (4 m/14 f) (1.10%); 5 points in 30 people (4 m/26 f) (1.84%). After in-depth clinical examination, 32 patients were examined to further verify the diagnosis. The examination revealed glucose intolerance in 9 patients (18.8%), diabetes mellitus type 2 in 5 patients (10.4%), hyperprolactinemia in 3 (6.3%) women aged 24 – 37 years, increased IGF-1 level in 2 patients (4.2%). Further examination revealed the

presence of pituitary microadenoma in 2 women with high level of blood prolactin. Two patients (1 m/1 f) aged 28 and 57 yrs old respectively with high IGF-1 levels were diagnosed 'acromegaly, tumor stage, active form'.
Conclusion
Screening in high-risk groups revealed hormonally active pituitary tumors (isolated prolactinoma (n = 2) and somatotropinoma (n = 2)) with a frequency of 0.15% per 1000. Such a rather high percentage of detected orphan pathology indicates the effectiveness of the proposed screening technique and the feasibility of its implementation in high-risk groups.
Keywords: acromegaly, primary screening.
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AEP504

Acromegaly: Knowing the enemy in order to win

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Introduction
Acromegaly is an uncommon chronic disease with an insidious course. Due to the high morbimortality it causes, its early diagnosis and treatment are priority. The three therapeutic pillars are surgery, pharmacological treatment and radiotherapy, alone or in combination.
Objectives
To clinically, biochemically and histologically characterize patients with acromegaly under follow-up in a tertiary hospital in Madrid since 2000.
Methods
Retrospective study including 97 adult patients diagnosed with acromegaly under follow-up in the Neuroendocrinology Unit of the Hospital Universitario La Paz, Madrid, during the period 2000-2020. Data were obtained by review of medical records. Continuous variables were expressed as mean and standard deviation and categorical variables as absolute values and percentages.
Results
Of the 97 patients with acromegaly, 96.7% (n=94) had a pituitary origin and 3.3% (n=3) had an ectopic one (bronchial, pancreatic and adrenal, 33% in each case). Mutations in GNAS and MEN1 genes were found, 1% in each case. 55% were women, age 61.53±16.5years, BMI 28.67±4.2kg/m2, annular circumference 20.4±1.5cm, GH 21.2±36.5µg/L and IGF-1 754.7±544.8µg/L. Only 58.6% were diagnosed during the first 5 years of disease. 76.3% were diagnosed by clinical manifestations secondary to hormonal hypersecretion, 15.8% by compressive clinical manifestations and 7.9% incidentally. 57.6% had pituitary macroadenoma, 36.5% had microadenoma, 2.4% had empty sella turcica and 1.2% had normal pituitary. 66.7% of the adenomas were densely granular, 58% somatropinomas, and 34.5% and 88.9% were positive for p53 and Ki67, respectively. 5.7% had pre-surgery hormonal deficits (4 patients with secondary hypothyroidism and 3 hypogonadotropic hypogonadism) and 48.9% had post-surgery hormonal deficits (22 patients with secondary adrenal insufficiency, 19 hypogonadotropic hypogonadism, 16 secondary hypothyroidism, 8 transient diabetes insipidus, 3 permanent diabetes insipidus, 2 transient SIADH, 2 biphasic response, 1 adult GH deficiency). Transsphenoidal surgery was the first line of treatment in 88.7% (n=86) of patients, achieving a cure rate of 53.4% (n=46). 13.3% were surgically reintervened and 26.5% also received RT. Of the 51 patients not cured, 94.1% (n=48) received medical treatment, achieving disease control in 92% of cases. The main comorbidities were: dysglycosis (53.6%), nodular thyroid disease (57.7%), left ventricular hypertrophy (69%), arterial hypertension (39.4%), osteopenia (34%) and obstructive sleep apnea-hypopnea syndrome (25%).
Conclusions
Timely diagnosis of early stage acromegaly remains a challenge in routine clinical practice. The best biochemical marker is IGF-1. In the hands of expert neurosurgeons, the treatment of choice remains transsphenoidal surgery. It is essential to integral approach associated comorbidities.
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AEP505

Increased anxiety and perceived stress in active acromegaly during the COVID-19 pandemic

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Aim
To examine and compare the anxiety level and stress perception of acromegaly patients with controlled and active disease in the COVID-19 pandemic.
Material and Method
49 (23 females/26 males) patients admitted to the outpatient clinic during the first month after the pandemic period were recruited in this cross-sectional study. State-Trait Anxiety Inventory (S-Anxiety for state scale, T-Anxiety for trait scale) and Perceived Stress Scale-14 (PSS-14) were used to evaluate the event-related current state anxiety, the general tendency to anxiety, and perceived stressful situations. Patients were divided into two groups as active (n=14) and controlled (n=35) disease groups compared to parameters affecting psychiatric distress.
Results
The active acromegaly group had significantly higher scores on all of the S-Anxiety (p=0.011), T-Anxiety (p=0.002), and PSS-14 (p=0.007) scores after controlling for age, gender, BMI, education years, marital and occupation status, disease duration, and disease-specific medical treatment status covariates. S-Anxiety (p=0.021), T-Anxiety (p=0.004), and PSS-14 (p=0.009) scores were found significantly higher in single patients than in married ones.
Conclusion
This study showed significantly increased anxiety and perceived stress levels during the pandemic, especially in the active and single acromegaly patients. Psychiatric symptoms should be carefully evaluated in the follow-up of acromegaly patients. The necessary psychological support should be provided to patients by focusing on these symptoms to improve patient management, particularly in a health-related stressful situation as the COVID-19 pandemic.
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AEP506

The association of z-score with early postoperative remission and characteristics of bone mineral density in patients with cushing's disease: Single center study

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Introduction
Various direct and indirect mechanisms by which glucocorticoid (GC) excess and elevated adrenocorticotropic hormone (ACTH) levels impairs bone metabolism have been described. In the literature, there are different factors described which affect the early outcome of pituitary surgery in patients with CD including preoperative ACTH levels and the clinical severity of the disease. Combining these data, we conducted a retrospective study to investigate the association of BMD Z-scores with early postoperative remission rate and clinical parameters of the patients with CD.
Method
Patients diagnosed with CD were retrospectively evaluated. After the exclusion of 230 patients, a final cohort of 87 CD patients were included. Early postoperative remission was defined as a morning cortisol concentration measured on the first day after surgery of less than 5 µg/dL. The diagnosis of BMD 'below the expected range for age' was defined as a Z-score ≤ -2.00 SD.
Results
No significant association was found between DXA results and early postoperative remission. There was also no significant difference in DXA results between eugonadal and menopausal groups. A significant negative correlation between preoperative morning cortisol level and BMD, T-score and Z-score of FT was shown, while there was a positive correlation between preoperative ACTH/Cortisol ratio and DXA results of L1-4 (Table 1).
Conclusions
To the best of our knowledge, this is the first study which investigates if the severity of bone loss is a predictive risk factor for the failure of transsphenoidal surgery for Cushing's disease and there was no statistically significant relationship between these two entities.

Table 1 – The Correlation Between DXA Results and Preoperative Cortisol, ACTH, ACTH/cortisol ratio and Size of the Adenoma

		L1-4			FN			FT		
		BMD	T	Z	BMD	T	Z	BMD	T	Z
Cortisol	r	-0.115	-0.122	-0.177	-0.119	-0.104	-0.159	-0.219	-0.237	-0.276
	p[a]	0.289	0.261	0.100	0.272	0.336	0.827	**0.041**	**0.027**	**0.010**
ACTH	r	0.181	0.163	0.123	0.116	0.078	0.024	0.105	0.039	-0.21
	p[a]	0.094	0.130	0.255	0.285	0.473	0.827	0.335	0.720	0.845
ACTH/ Cortisol	r	0.280	0.258	0.257	0.199	0.156	0.126	0.249	0.206	0.160
	p[a]	**0.009**	**0.016**	**0.016**	0.065	0.150	0.244	**0.020**	0.055	0.139
Size of the adenoma	r	0.144	0.120	0.099	0.086	0.026	-0.001	0.109	0.060	0.002
	p[a]	0.182	0.270	0.361	0.430	0.808	0.993	0.316	0.584	0.983

ACTH: Adrenocorticotropic hormone, BMD: Bone mineral density, r: Correlation coefficient, F_N: Femoral neck, F_T: Total femur, L_{1-4}: Lumbar vertebrae 1-4, T: T-score, Z: Z-score; [a]Evaluated by Spearman's Rho correlation test

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AEP507

Treatment regimens affecting glucose metabolism and gastrointestinal hormones in acromegaly: A descriptive study

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Context
Active acromegaly is associated with impaired glucose metabolism, which improves upon treatment. Treatment options include surgery, medical therapy with somatostatin analogues (SSA) and Pegvisomant (PEG) and in few cases irradiation.
Objective
To describe the differential effect of various treatment regimens on the secretion of glucose, insulin, glucagon, glucagon-like peptide-1 (GLP1), and glucose-dependent insulinotropic polypeptide (GIP) in patients with acromegaly.
Methods
Descriptive study of data from 23 surgically treated, non-diabetic patients with acromegaly and 12 healthy controls. Participants underwent an oral glucose tolerance test (OGTT) and subsequently isoglycaemic intravenous glucose infusion on a separate day, both with continuous measurement of the above-mentioned hormones. Analysis: Baseline hormone concentrations, time-to-peak and area under the curve (AUC) on the OGTT-day. Groups were compared using ANOVA.
Results
The patients treated with SSA (N=15) had impaired insulin, glucagon, GLP1 and GIP-response (AUC, P=0.007), and numerical impairment of all other hormone responses (AUC, P>0.05)(Table 1). Patients co-treated with pegvisomant (SSA+PEG, N=4) had a numerically increased secretion of insulin and glucagon compared to patients only treated with SSA (N=11) (insulin AUC mean (SEM), SSA+PEG 49 nmol/l*min (8.3) vs SSA%PEG 25 (3.4), P>0.05); glucagon AUC, SSA+PEG 823 pmol/l*min (194) vs SSA%PEG 332 (69), P>0.05). GIP secretion remained significantly impaired, whereas GLP1 secretion was numerically increased with PEG (SSA+PEG 3088 pmol/l*min (366) vs mono-SSA 2401 (239), P>0.05) (Table 1). Similarly, the incretin-effect was numerically increased in SSA+PEG compared to SSA%PEG. No difference was found between patients treated with/without radiotherapy nor substituted or not with hydrocortisone.
Conclusion
SSA impaired the insulin, glucagon and incretin hormones secretion. Co-treatment with Pegvisomant seemed to counteract the somatostatinergic inhibition of the glucagon secretion and improved the insulin response to OGTT. We speculate that Pegvisomant exerts its action via GH-receptors on pancreatic δ-cells.

TABLE 1. Hormonal response to OGTT in healthy controls and patients receiving SSA with/without additional Pegvisomant.

	Controls	SSA%PEG	SSA+PEG	P
N	6	11	4	-
Glucose-AUC (mmol/l*min)	1352 (78)	1487 (62)	1508 (109)	0.1
Insulin-AUC (nmol/l*min)	62 (14)	25 (3)	49 (8)	0.006[a]
Glucagon-AUC (pmol/l*min)	946 (233)	332 (69)	823 (194)	0.01[a]
GLP1-AUC (pmol/l*min)	3972 (451)	2401 (239)	3088 (366)	0.007[a]
GIP-AUC (pmol/l*min)	11062 (2334)	2658 (356)	2237 (240)	0.0001[a]/0.001[b]
Incretin effect (%)	55.5% (7.7)	33.6% (47.4)	49.9% (13.9)	

Results are mean (SEM). Analyses by one-way ANOVA with post-hoc analysis. [a]SSA%PEG compared to controls, [b]SSA+PEG compared to controls

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AEP508

Female central hypogonadism with or without organic pituitary lesions: diagnostic value of LH and FSH basal levels

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Central hypogonadism (CH) is a syndrome that can be revealed in women with hypoestrogenic amenorrhea due to the lack of normal response of gonadotropins to the hypoestrogenemia. CH can be caused by organic lesion of the hypothalamo-pituitary region or has idiopathic character – without any structural background. This syndrome is often called 'hypogonadotropic hypogonadism', but LH and FSH levels within 'normal' laboratory range does not exclude CH because insufficiency of impulse secretion can appear despite normal basal secretion.
Patients and methods
46 women with idiopathic CH (18-45 y.o., BMI 16-25 kg/m2), 25 women with CH due to the organic lesions (18-45 y.o., BMI 17-37 kg/m2), 68 healthy cycling women (control group, 19-45 y.o., BMI 17-31 kg/m2). Organic causes of CH were as follows: congenital empty sella turcica and pituitary hypoplasia; pituitary adenomas and craniopharyngiomas presently or earlier (treated by surgery). LH and FSH levels were measured in all participants by chemiluminescent immunoassay; in healthy women tests were performed in early follicular phase.
Results
According to Mann-Whitney test, LH and FSH levels were significantly lower in patients of both groups than in control group (p<0.0001 in all cases). Moreover, LH and FSH were significantly lower in group of organic lesions than in group of idiopathic CH (p=0.0017 for LH and p=0.0014 for FSH). ROC-analysis showed that LH<2.36 ME/l with sensitivity 82.61% and specificity 94.12% and FSH<5.075 ME/l with sensitivity 73.91% and specificity 80.88% pointed to central genesis of hypogonadism without organic lesions. Similar analysis was performed for patients with CH due to the organic lesions: LH<1.8 ME/l with sensitivity 96.0% and specificity 98.53% and FSH<3.145 ME/l with sensitivity 92.0% and specificity 95.59% speaks in favor of CH due to the pituitary organic lesion.
Conclusion
In female patients with hypoestrogenic amenorrhea LH<2.36 ME/l and FSH<5.075 ME/l are pointing to central genesis of hypogonadism with high sensitivity and specificity; LH<1.8 ME/l and FSH<3.145 ME/l in case of those female patients can point to organic cause of central hypogonadism, and thus can be considered as indication for pituitary region MRI if it was not performed earlier.

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AEP509

Self-administration of long-acting somatostatin analogues in NET patients forced by the COVID-19 pandemic – does it affect the clinical outcome?

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Background
Somatostatin analogues (SSA) (octreotide and lanreotide) are recommended as a first line treatment of locally advanced or metastatic well-differentiated neuroendocrine tumors (NETs) with a good expression of somatostatin receptor (SSTR). Both of them are usually used in injection repeated every 4 weeks.
The study objective
Was to compare the way of SSA administration (injection performed by professional medical staff before epidemic period and self-administration of the drug forced by the COVID-19 epidemic restrictions) to progression free survival (PFS) in patients with locally advanced or metastatic NETs.
Materials and methods
88 patients in 2019 and 96 patients in 2020 with locally advanced or metastatic well-differentiated NETs (G1 and G2) treated in the Clinical Department of Endocrinology in Krakow, Poland, were included to the study. All patients had a good expression of SSTR type 2 assessed in functional somatostatin receptor imaging and were treated for at least 3 months with a stable dose of lanreotide Autogel 120 mg or 30 mg of octreotide LAR every 4 weeks. Prior to change of way of drug administration at the beginning of the COVID-19 epidemic period all of them were trained in regards to drug self-injections by the professional NET nurses. A retrospective analysis was performed, based on the medical documentation. Time to progression (TTP) was defined as the time beginning from the use of the first SSA dose to the time of progression confirmed by radiological examinations: computed tomography (CT) or magnetic resonance imaging (MRI).
Results
The rate of NET progression in the study group in 2020 was higher than in 2019 28,1% vs 18,2% (27 vs 18 cases), p=0,079. The analyzed groups did not differentiate in regards to age, follow-up period, performance status and tumor burden (assessed as liver, lymph nodes and bone involvement). The mean TTP was in 2019 56.8 months (range: 8-144) and in 2020 56.0 months (range: 6-152). In 2019 no progressions were diagnosed in patients with G1 tumors, whereas in 2020 the progression was observed in 7 patients with G1. The greatest increase in the incidence of progression was seen among patients with small bowel NETs.
Conclusions
The way of long-acting SSA administration: injection done by professional medical staff vs self-injection of the drug may significantly affect the risk of NET progression. The unequivocal confirmation of such a relationship requires further observation.

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AEP510

Is this just vitiligo? Nelson is hiding

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A 64-year old man presented to our endocrinology clinic with progressive lumbar pain that had developed two months earlier. He had undergone bilateral adrenalectomy for Cushing disease and two years later transsphenoidal resection for Nelson tumor. On physical examination, the patient had remarkable hyperpigmentation due to ACTH hypersecretion periorbital, peri-auricular and in the lower-neck region. These findings were clearly evident in his case due to the extensive facial vitiligo. Findings on bone scintigraphy were suggestive for metastatic lesions and biopsy confirmed our suspicion of bone-invasive pituitary carcinoma. The patient was referred to the oncology department as a candidate for immunotherapy but opted for palliative care because of his weakened general condition. This case highlights the fact that hypercortisolism induces a state of immunosuppression. After remission of Cushing's syndrome, rebound immunity frequently results in overt autoimmune diseases. This immunological phenomenon has been described in both ACTH-dependent and -independent cases.

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AEP511

Microprolactinoma and pregnancy. A case report and review of literature

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Introduction
Prolactinomas are the most common pituitary tumors and a common cause of infertility because of gonadal dysfunction, in young women. The treatment of choice is dopamine agonists, which can restore fertility and promote shrinking of the tumor in the majority of cases. Managing prolactinomas during pregnancy may be challenging. Treatment discontinuation is recommended once the pregnancy is confirmed in women with microprolactinoma. For microprolactinoma, the risk of symptomatic tumor enlargement during pregnancy is very low (<2%). Breast-feeding has no harmful effect on tumor growth. We present a case with microprolactinoma that had a good development of pregnancy and lactation period.
Case presentation
A 20-year-old female patient, was first diagnosed with left-sided, 8 mm cystic pituitary microprolactinoma 5 years ago. She began the treatment with Cabergoline 0.25 mg twice per week. Following a period of 3 years, she was periodically controlled with prolactin level and MRI. The adenoma size was constantly shrinking from 8 to 5 and then 2.6 mm. During this time, she was taking Cabergoline 0.25 mg twice per week. The last prolactin level was 1084,49 ng/mL (108,78 – 557,13) approximately twice normal level, Anti TPO 6,49 UI/mL (<34), TSH 3,11mUI/L. 5 days later, her pregnancy was confirmed, and Cabergoline was switched to bromocriptine 2.5 mg twice per day. She took the treatment for only one month and discontinued it because of arterial hypotension. The patient warned about the risk of tumor enlargement and alarming symptoms. She had clinical follow-up every 2-3 months. She didn`t complain of anything related to diseases' activity, and the pregnancy had no problem. She gave birth naturally at the right time a healthy boy. Her normal menstrual cycle begun 40 days postpartum. During the postpartum period and lactation, she did not take any medication, and prolactin levels were progressively decreasing from 61,5 to 49.6 and 30.04 ng/mL (6-29.9) during a time period of 11 months.
Conclusion:
Despite discontinuation of treatment once pregnancy has been confirmed, we didn`t notice any clinical progression of microprolactinoma during pregnancy, and no further examination was indicated. During the postpartum and lactation period, prolactin levels were progressively decreasing to normal, and no medication was needed.

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AEP512

When a common symptom leads to a rare diagnosis – prostate metastasis in the pituitary

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Common non-specific symptoms like fatigue can occasionally point towards a rare significant pathology. We report a similar case in which investigations for subtle symptoms revealed a serious unexpected diagnosis. A 76 year-old man presented to his GP for new onset mild fatigue. He had an underlying prostate cancer with no known metastases, treated only with hormonal therapy. This was under surveillance with urology team. GP sent off blood tests which showed a very low random serum cortisol (28nmol/L). Hence an urgent endocrine review and short Synacthen test (SST) was organised. SST showed secondary adrenal insufficiency. Baseline 9am ACTH = 41ng/L (>50ng/L) Baseline 9am cortisol = 116nmol/L (>420nmol/L) 60 min cortisol after Synacthen injection: 471nmol/L (>420nmol/L) The remaining pituitary hormonal profile showed secondary hypothyroidism (TSH=1.34mIU/L, T4=5.3mcg/dL) and raised prolactin (565 mcg/L). He was started on oral hydrocortisone after the above results whilst awaiting endocrine appointment. By the time patient attended the endocrine clinic in 3 weeks he was noted to be wearing a homemade eye patch over his left eye. On questioning he reported new diplopia and visual impairment for which he had consulted private optician who referred him to ophthalmologist. On examination there was with left oculomotor nerve palsy and bitemporal hemianopia. He was admitted in hospital from endocrine clinic and an urgent pituitary MRI was organised. This revealed a large sellar mass (1.8x2.2x3cm) with extension into the cavernous and sphenoid sinuses. These findings were consistent with a diagnosis of pituitary macroadenoma causing chiasm compression

and partial hypopituitarism. The final impression was non-functional pituitary macroadenoma causing compressive symptoms. He was urgently referred for trans-sphenoidal surgery. Trans-sphenoidal surgery proved to be complex leaving residual tumour and was complicated with post-operative diabetes insipidus with persistent visual impairment. Histology of pituitary tumour showed metastatic adenocarcinoma of prostatic origin. The patient later received radiotherapy. Unfortunately, surveillance imaging confirmed disease progression with enlargement of the remnant lesion and more extensive involvement of adjacent structures. Currently the patient is on palliative radiotherapy with full pituitary hormone replacement. Fatigue is a nonspecific common symptom. Low random cortisol is usually not expedited as an urgent test however in context of secondary hypothyroidism it should prompt urgent pituitary imaging especially in patients with history of prostate cancer. There have been only a handful of cases of prostate metastasis in the pituitary gland. This case reminds about rare metastatic presentations in pituitary gland.

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AEP513

Growth hormone deficiency in hypopituitary male patient with treated Cushing's disease

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Impaired growth hormone (GH) secretion occurs in patients with Cushing's disease (CD) as a result of cortisol excess. After a surgical treatment, eventually accompanied with radiation therapy, recovery of GH secretion is seen in only variable proportion of patients. According to some studies, it is recommended to perform assessment of GH secretion one to two years after surgical cure of CD. We report a case of a 40-years-old male admitted to the hospital because of sudden loss of consciousness. At the age of 15 years, he was diagnosed with CD and underwent transsphenoidal surgery with the removal of an ACTH-secreting microadenoma. His height at that time was 148 cm, GH was low, with loss of pulsatility. One year postoperatively he received hydrocortison replacement and desmopressin. Three years after, a patient was reevaluated, value of GH was still below reference range, provocative testing using an insulin tolerance test (ITT) was not performed because of epilepsy. According to hormonal testing and petrosal sinus sampling, CD recurrence was diagnosed and radiotherapy successfully applied. After that, a patient has not been motivated for a regular follow-up for almost 20 years. On admission, his height was 165 cm, weight 68 kg (BMI 25 kg/m2), signs of hypogonadism were present. Hormonal examination showed TSH 4.83 mIU/l (0.4-4.0 mIU/l), fT4 4.2 pmol/l (10.3-23.1 pmol/l), GH 0.1 ng/ml (0.0-1.0 ng/ml), IGF-1 5 ng/ml (109-284 ng/ml), IGF BP3 0.7 ug/ml (3.4-6.7 ug/ml), FSH 1.8 mIU/ml (0.7-11.1 mIU/ml), LH 1.6 mIU/ml (0.7-11.1 mIU/ml), cortisol in daily profile 3…2…2 nmol/l. Pituitary magnetic resonance imaging demonstrated an empty sella. Bone mineral density assessed by DXA scan was normal. According to hormonal status, hydrocortisone and thyroxine replacement therapy was started. For the next 5 years, a patient was not followed again. In March 2019, he had an acute myocardial infarction and stent implantation; ejection fraction was preserved. Two months later, on reevaluation, IGF-1 was 29.0 ng/ml (53.3-215 ng/ml), IGF BP3 0.712 ug/ml (3.3-6.7 ug/ml) and GH replacement was finally initiated. During the next months dose adjustment was made (current GH 0.6 ng/ml, IGF-1 227 ng/ml, IGF BP3 4.44 ug/ml). As a result, quality of life and lipid profile are significantly improved (cholesterol 4.48 vs 5.05 mmol/l before treatment, LDL 2.05 vs 2.85 mmol/l, HDL 1.5 vs 1.35 mmol/l). In conclusion, because of multiple long-term benefits, assesment of GH status and GH replacement therapy should be considered in patients with CD in remission.

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AEP514

Control of acromegalo-gigantism with lanreotide: About a case

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Introduction
Acromegalo-gigantism is a rare disease, occurring before the epiphyses weld, it causes a linear acceleration of growth in children and adolescents. Medical treatment with analogues of somatostatin (AS) well established can be used in cases where surgery is impossible or inadequate or in cases of surgical failure
Observation
This is a 14-year-old patient, followed for acromegalo-gigantism discovered at the age of 7. The patient has a height of 1.88 m (+3 SD), a Tanner stage G4P4 and features of acromegaly. The diagnosis was made in front of an IGF1 level at 791ng/mL (1.6 × normal) with pituitary MRI a pituitary macroadenoma of 16 × 11 × 11mm somatotropic on anathomopathologic pituitary examination with Ki-67 proliferation index < 1. The rest of the hypophysiogram was normal. The patient was operated on twice: in 2015 by the upper route and revision surgery by the transphenoidal route in 2017 associated with treatment with somatostatin analogues (octreotide 200 µg/day) were indicated for failure of the surgery. The course after surgery was marked by continued growth, an IGF1 level raised to 801 ng/mL (1, 6 × normal) and on pituitary MRI a residue of 11.7 × 7 mm. The patient is placed on lanreotide LP 120 mg/28 days with then reconciliation of the injections every 21 days.The course under treatment is marked by clinical improvement with slowing of the growth rate, normalization of the IGF1 level to 441ng/mL (115-489).
Discussion and Conclusion
Control of acromegaly with lanreotide is not always easysome are more sensitive than others, this is due to the involvement of specific genetic factors. The observation of our case highlights the difficulty of managing pituitary gigantism and the encouraging results of medical treatment with lanreotide.

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AEP515

Acromegaly revealed by pituitary apoplexy: A case report

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Introduction
Apoplexy is a rare, serious and acute complication of pituitary adenomas, revealed by tumor syndrome, visual disturbances and hormonal deficits in 60% of cases. We report a case in which the diagnosis of acromegaly was revealed by pituitary apoplexy.
Observation
45-year-old patient. The examination found a tumor syndrome made up of headaches, reduced visual acuity and vomiting which had evolved for 10 days before admission. The clinical examination reveals a rapid deterioration of the general condition associated with a dysmorphic syndrome evoking acromegaly. The hormonal assessment showed a thyrotropic, corticotropic and hyper-prolactinemia deficit with a level of IGF-1 at 486.6ng/ml (88-140) or 3.47 times the normal and on MRI a sellar process. 32 × 23 × 30mm with hemorrhagic component. The patient underwent a large adenoma excision by the transphenoidal route with simple postoperative consequences. The hormone replacement therapy was: hydrocortisone parenterally and then orally with levothyrox.
Discussion and conclusion
The revelation of acromegaly by pituitary apoplexy is exceptional. Our observation has as a particularity a favorable and rapid evolution of the pituitary apoplexy complicated by anterior pituitary insufficiency after hormonal substitution and simple postoperative consequences.

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AEP516

Rare case of pituitary apoplexy after SARS-COV-2 infection

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Pituitary apoplexy is a rare complication of a pituitary adenoma consisting in hemorrhage or infarctation usually in patients with preexisting comorbidities. SARS-COV-2 infection is a 'new' disease known to determine vascular impairment in some patients, although studies on this

particular issue are still rolling. We present the case of a 64 years old woman suffering from mild hypertension (well-controlled under sartans) who in may 2020 got the SARS-COV-2 infection and because of high fever (38,5 C) was hospitalized and placed on treatment with azitromicyne and antinflamatory treatment. 4 days later she develops severe headache with light visual impairment. The symptoms were considered to be in the context of the viral infection so no further investigation were made, but still the patient was placed on corticosteroids with good outcome. Three monts later she presents to our endocrinology department with severe asthenia, hypotension, generalized edema and constipation. She is immediately diagnosed with panhypopytuitarism and a pituitary IRM is being made which describes a pituitary adenoma with a hemorrhage zone of approximately 2 cm. Under treatment corticosteroids and thyroid hormones the evolution is good. The neurosurgical evaluation doesn't consider appropriate to undergo surgery at this time. 6 moths later the patient is in still in very good condition and the IRM reveals slight shrinkage of the tumor and some resorbtion of the hemorrhage area. The particularity of this case we consider to be the non-existence of comorbidities usually associated with pituitary apoplexy and also the late diagnosis of this life-threatening condition, mainly because of the low-experience with COVID manifestation and the general effect of the pandemic both on medical services and also on patients addressability during this period.

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AEP517

Septooptic dysplasia -a rare cause of congenital hypopituitarism

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Septooptic dysplasia is a clinically heterogeneous disorder characterized by optic nerve hypoplasia, pituitary hormone abnormalities and midline brain defects.clinical diagnosis requires the presence of at least two of the features of the classical triad. Here is male presented on endocrinology consult for the first time at the age of thirthy five. On clinical examination height and weight were normal, face hypogonadal, sparced facial and body hair, testicle hypotrophy, normocytic anemia, reduced bone mineral density. Hormonal analyses showed complete deficiency in pituitary hormones. On MRI study there was corpus callosum agenesis and partial agenesis of the septum pellucidum, empty sella and hypoplastic hypothalamus. Ophtalmology evaluation revealed temporal paleness of optic discs and nonspecific peripheral visual field defects without significat visual impairment. Septooptic dysplasia is rare cause of congenital hypopituitarism. Most patient present with two out of three features, among which hypopitutarism with midline brain defects, presented here, is the rarest combination. Hypopituitarism varies from one to more hormone deficiencies, and during time additional hormone deficinecies may develop. Some patient, like the one presented here, has normal height despite growth hormone defiency, paradoxical growth without growth hormone, attributed to insulin and other growth stimulatory factors.

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AEP518

Spontaneous remission in Cushing's disease: A case report

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Spontaneous remission of Cushing disease might be a phase of cyclic disease, but could also be explained by an ACTH-microadenoma infarction or hemorrhage. True remission must be differentiated from cyclic Cushing's disease with prolonged follow up. 63-years-old female patient was referred to endocrinologist's and presented with uncontrolled hypertension, type 2 diabetes, central obesity, hirsutism, swelling of the face and legs and a 'buffalo hump'. After additional investigation elevated ACTH (24.1pmol/l (n1.63-14.15)), basal cortisol (1187nmol/l (n147-726)) and high 24-hours urinary free cortisol 2236.4nmol/l (n138-524) were determined. Cortisol was not suppressed after low-dose dexamethasone suppression test. Pituitary MRI revealed 0.5x0.2x0.3cm hypointense zone in posterior pituitary. Petrosal sinus sampling was planned, but the patient was admitted to the emergency department with panniculitis in her limbs. After chest and abdominal CT scan 3.1x2.4cm tumor in left ventricle and 0.6cm hypointense tumor in the liver was detected. Patient case was discussed at multidisciplinary team and it was concluded that at that moment biopsy benefit would not outweigh the risks. Patient was treated with iv a/b. When inflammation markers decreased petrosal sinus sampling was performed. It confirmed pituitary source of ACTH production and right side lateralization which coincided with MRI data. During two months period from the first suspicion of pituitary microadenoma till the petrosal sinus sampling was performed, clinical symptoms of Cushing syndrome significantly decreased as well as hormone levels: basal cortisol level 1187->403.16nmol/l, ACTH 24.1->7.1pmol/l. Diabetes control significantly improved as well. The situation was interpreted as spontaneous remission and it was decided to continue active observation of the patient. However, 10 months later worsening of patient's status was observed. Basal cortisol increased dramatically (1354nmol/l) as well as ACTH level (26.4pmol/l). Pituitary MRI was repeated: there was 0.5x0.2x0.6cm hypointense zone in posterior pituitary and transphenoidal pituitary adenoma surgery was performed. Histopathological analysis confirmed chromophobic pituitary adenoma. A few weeks after surgery increasing cortisol levels were observed, due to subtotal removal of pituitary adenoma (confirmed with MRI). For peristent hypercortisolism control, treatment with metyrapone was initiated. After 5 months of treatment metyrapone was halted due to development of adrenal insufficiency. The patient is normocortisolemic for 6 months already, despite of the remnants of pituitary adenoma on MRI and is only under the active follow up at the department. Spontaneous remission in Cushing's disease is a very rare situation. There is still lack of data on pathophysiology, management and follow up strategies for this condition.

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AEP519

Primary hypothyroidism associated with empty sella turcica and hypopituitarism

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Introduction
The empty sella syndrome is a rare disorder characterized by a flattened pituitary gland leaving place to the cerebrospinal fluid to fill in the sella turcica.The diagnosis is radiological and it is often discovered during pituitary disorders. Generally patients suffer from hypopituitarism, and primary hypothyroidism is found to be a rare association.
Observation
Herein the case of a young woman who consulted at the age of 33 year-old for recent onset of diabetes mellitus. The patient had an important retardation regarding the pondero-statural development (Weight: 18.5 Kg, Height: 102 cm) with impuberism (S0,P0 Tanner stage). The evaluation of the hypophyseal function showed firstly; a primary hypothyroidism (TSH >100 µU/mL, TPO antibodies negative) with a thyroid atrophia on the cervical ultrasound, secondly an hypogonadotropic hypogonadism (FSH 28.4 mUI/mL, LH 2.11 mUI/mL, Estradiol 13.4 pg/mL, Prolactin 125 mUI/L), thirdly a corticotropic deficiency confirmed by an insulin induced hypoglycemia test and a low level of ACTH (7.72ng/L), and lastly, a complete GH deficiency. In front of this hypopituitarism, an hypothalamic- hypohyseal MRI revealed an empty sella turcica with a normal pituitary stalk. The procedure to follow was to treat the patient with hormonal replacement therapy, and her state significantly improved with a gain of 11 cm in a period of five months (Height: 113 cm).
Conclusion:
This clinical presentation of the empty sella syndrome is atypical and only few similar cases were found in the literature.Hence the importance of diagnosing it, in order to improve the knowledge of this syndrome and its different aspects.

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AEP520

The paradox of growth hormone therapy during the covid-19 pandemics – high serum igf1 and poor growth

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Affecting multiple aspects of every-day living, Covid-19 could be a stress-promoting event, and short-stature patients could be an at-risk population. The scope of our study is to assess whether the on-going pandemic could affect children's response to growth hormone therapy. This was a retrospective study that evaluated children on growth hormone treatment who presented for clinical visits between September 2019 and January 2021 at the Pediatric Endocrinology Department of Elias University Clinical Hospital. Eighty patients were included, (48 boys/32 girls), with a mean age of 10.95±2.99 years. They received growth hormone treatment for a number of conditions, but the predominant indication was GH deficiency (63.7% of patients). The parameters assessed were height, standard deviation scores (SDS) for height, standard deviations for height gained before the pandemics, in the first 6 months of the pandemics and at 1 year interval and acquired centimeters at these intervals. The gains in SDS for height decreased over time from 0.20±0.19 before the pandemics to 0.15±0.21 at 6 months and to 0.12±0.24 at the last evaluation, but the statistical significance was not achieved (p=NS). Also, gains in centimeters decreased from 3.76±1.3 to 3.51±1.27 and 3.25±1.51 at 6 and 12 months, respectively, with a statistically significant difference between the first and the last evaluation (p=0.006). The dose of growth hormone treatment did not differ significantly between evaluations (p=NS). At the first evaluation, 10% of patients had a decrease in SDS for height. The proportion of patients with inadequate response to treatment increased significantly at 12 months (18.8%) in comparison with baseline (p=0.004) and six months evaluation (13.8%, p=0.009). We observed that over the course of the study, the mean SDS of IGF1 grew from 0.60 +/- 1.48 before the pandemics to 0.65 +/- 1.28 at the first evaluation, and 0.96 +/- 1.37 at the second evaluation with a statistically significant difference between the 6 month and one year evaluation (p=0.012). Our data suggest that the response to somatropinum treatment might be decreased during the Coronavirus pandemic, independently of treatment doses and other factors affecting IGF-1 level. Stress-induced activation of the adrenal axis may be responsible of the decrease in growth observed by mechanism of peripheral insensitivity to IGF-1.

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AEP521

Outcomes and complications of endoscopic pituitary surgery: A single-center study

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Objectives
To present the results of our series of endoscopic surgery of PA, performed in a third level hospital by an experienced team.
Methods
Retrospective review of PA undergoing endoscopic surgery between 2011 – 2018 in our institution. Clinical variables and radiological characteristics and outcomes were collected at diagnosis, before surgery and for an average of 4.8 years of postoperative follow-up.
Results
121 patients with PA and endoscopic surgery were identified. Table 1 summarises baseline characteristics.

Table 1

Age at surgery (years)	57.8 ± 17
Sex (n male)	64 (52.9%)
Charlson Index score	2 (0-10)
Clinical presentation (at diagnosis)	
- Incidental	43 (35.5%)
- Hypopituitarism	65 (53.7%)
- Apoplexy	13 (10.7%)
- Compressive symptoms	51 (42.1%)
- Visual impairment	38 (31.4%)
Non-functioning adenoma	78 (35.5%)
Functioning adenoma	43 (64.5%)
- GH-secreting	26 (21.4%)
- ACTH-secreting	11 (9.0%)
- PRL-secreting	5 (4.1%)
- TSH-secreting	1 (0.8%)
Tumour characteristics	
- Tumour size	
- Macroadenoma	102 (84.3%)
- Maximum diameter (mm)	22.3 ± 11.0
- Extrasellar extension	92 (76.0%)
- Suprasellar	86 (71.1%)
- Sphenoidal	20 (16.5%)
- Cavernous sinus invasion	47 (38.8%)
- Knosp >3	28 (23.1%)

Data are n (%) values, mean ± SD or median (IQR).
Surgical evolution and post-surgical outcomes are shown in Table 2.

Table 2

Surgery indications	
- Functioning adenoma	41 (33.9%)
- Compressive symptoms	40 (33.1%)
- Large tumour size	30 (24.8%)
- Apoplexy	8 (6.3%)
- Resistance to medical treatment	2 (1.6%)
Complications:	
Intraoperative	4 (3.3%)
- CSF leak	1 (0.8%)
- Intracranial haemorrhage	2 (1.6%)
- Epistaxis	1 (0.8%)
Immediate postoperative (1st week	35 (28.9%)
after surgery)	13 (10.7%)
- DI	5 (4.1%)
- Infection	4 (2.8%)
- Epistaxis	3 (3.3%)
- CSF leak	10 (8.2%)
- Other	16 (13.2%)
Late postoperative	7 (5.7%)
- DI	2 (1.6%)
- Infection	1 (0.8%)
- CSF leak	6 (4.9%)
- Other	
Hospital stay (days)	7.3 ± 6.0
Postoperative status	
- Visual field improvement	25/38 (65,7%)
- Hormone excess normalization	22/43 (51,1%)
- Hypopituitarism	65 (53,7%)
- Macroscopic total resection	86 (71,1%)
- Absence of tumor rest (RM/TC)	82 (67,8%)
Final visit outcomes	
- Reintervention	19 (15.7%)
- Radiotherapy	14 (11.5%)
- Remission	76 (62.8%)
- Death	3 (2.5%)

Conclusion
Endoscopic pituitary surgery appears to be safe and effective when an experienced pituitary team is available.

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AEP522

Nonpituitary neoplastic mass lesions of the sellar region: Hematologic malignancies – A 16-year single-centre experience

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Introduction
Hematological neoplastic mass lesions of the sellar region are rare.
Aim of the study
To analyze a case series of patients with hematological malignancies affecting sellar region.
Patients and methods
A retrospective study of 1166 patients with sellar lesions diagnosed at Department of Neuroendocrinology over the 16-year period (2005-2020).The demographics, clinical presentation, laboratory features, radiological findings, histological diagnosis, course of treatment and outcomes are described.
Results
We identified five cases (0.4%) of sellar region lesions attributed to a hematological malignancy (all females, mean age 55.2±3.4years). The variety of hematological pathologies included: one patient with multiple myeloma (MM), one patient had acute myeloid leukemia (AML),while three other patients had lymphoma (intravascular large B cell lymphoma (IVL,n=1) or high-grade B cell non Hodgkin lymphoma (NHL,n=2/in one patient in leukemic phase). Three patients (except IVL and AML) presented with symptoms and signs suggestive for cavernous sinus infiltration (cranial nerve palsies and diplopia), one patient with NHL and large mass presented with visual field defects and one patient (AML) presented with diabetes insipidus (DI). Typically the duration of neurological and endocrine symptoms and signs was short. All patients were in poor general condition, with malaise, half of them with pronounced sweating and vomiting. All patients had elevated sedimentation rate and altered blood count (anemia, thrombocytopenia (n=4), thrombocytosis (n=1) and rapid progressive leukocytosis (n=1), while patients with lymphoma had elevated lactate dehydrogenase (LDH). On magnetic resonance, sellar mass was demonstrated in three patients while patient with IVL had empty sella. Patient with AML had loss of posterior lobe T1W hyperintensity. Two patients (IVL and NHL) presented with multiple anterior pituitary deficiencies and one patient (AML) had isolated DI. Hyperprolactinemia due to pituitary stalk compression occurred in 3 out of 5 patients (excluding IVL and AML). Two patients were operated by transsphenoidal approach (NHL and MM). All patients were treated with chemotherapy. Three patients had lethal outcome during treatment. Patient with IVL achieved long term remission with partial reversal of hypopituitarism. One patient with NHL is now treated with immunochemotherapy.
Conclusion
Suspicion of hematological malignancy in sellar region should be raised in patients with short duration of nonspecific symptoms, neurological signs (ophthalmoplegia), blood count alterations and LDH elevation, pituitary dysfunction and imaging features atypical for pituitary adenoma. Early diagnosis is crucial for timely initiation of hematological treatment aimed to induce disease remission and partial or full recovery of pituitary function.

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AEP523

Biliary ultrasound surveillance in patients with acromegaly treated with somatostatin receptor ligands: A large tertiary centre experience

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Background
Somatostatin receptor ligands (SRL) are commonly used in patients with acromegaly to control insulin growth factor 1 (IGF1) concentrations. Biliary sludge or gallstone formation are well-recognised biliary adverse events (BAE) from SRL therapy. Our current practice is to routinely monitor patients with acromegaly on SRL with ultrasound scanning (USS). Once BAE are detected, ursodeoxycholic acid (UDCA) therapy is initiated.
Objectives
This single centre retrospective study aimed to evaluate: 1) cholecystectomy rates in our cohort; 2) incidence of BAE and; 3) efficacy of UDCA therapy.
Methods
All patients with acromegaly treated with SRL at our centre were included. For those on pegvisomant therapy data were collected during previous SRL treatment only. Exclusion criteria were known cholelithiasis or cholecystectomy predating SRL therapy and absence of ultrasound surveillance. The following data were recorded: age at diagnosis, gender, baseline IGF1, baseline and follow-up USS findings, UDCA dose and duration of USS follow-up.
Results
Out of 57 eligible patients, 1 had pre-existing cholelithiasis, USS surveillance was absent in 6 patients and 9 individuals had only baseline USS data available. For the remaining 41 patients with complete dataset, mean age at diagnosis was 46 years, 60% were females and mean baseline IGF1 was 105 nmol/L. Median duration of follow up was 6 years (interquartile range 6). Cholecystectomy was performed in 4/56 patients (7.1%) for BAE; 3/4 required emergency admission for pancreatitis, cholecystitis and/or cholangitis. Moreover, 25/41 (61%) patients developed BAE (13 with gallstones and 12 with sludge) during follow-up. 22 patients were treated with UDCA with a median daily dose of 350mg (interquartile range 300-600mg). In 16/22 (73%) patients (7 with gallstone and 9 with sludge) a complete response was observed on follow-up USS.
Conclusion
BAE occured frequently in our cohort of patients with acromegaly on SRL. The use of UDCA therapy is highly efficacious at dissolving sludge and gallstones once detected on USS monitoring. Further studies are needed to establish whether low-dose UDCA prophylaxis may be useful to prevent BAE in patients on SRL therapy.

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AEP524

Effectiveness of bilataral inferior petrosal sinus sampling in diagnosis of ACTH dependent cushing syndrome

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Purpose
We aimed to determine the effectiveness of bilateral inferior petrosal sinus sampling (IPSS) in the differential diagnosis of adrenocorticotropic hormone-dependent Cushing Syndrome (ACTH-dependent CS).
Method
51 patients diagnosed with ACTH-dependent CS between 2010-2019 in the Endocrinology Clinic in ıhı Hamidiye Etfal Health Training and Research Hospital were included in the study. The diagnosis of Cushing's Disease (CH) was made when the basal central/peripheral ACTH ratio was> 2 and/or the rate after CRH stimulation was> 3 in the IPSS procedure. With the inter-sinus ratio> 1.4, lateralization was determined. The diagnosis of CD was confirmed by immunohistochemical staining of pathology specimens. Sensitivity, specificity, positive and negative predictive values were calculated.
Results
In 51 patients with ACTH-dependent CS, IPSS was performed in 31 patients whose mass was not found on MRI or whose mass size was < 6 mm. One patients whose IPSS failed due to anatomical variation and 5 patients whose pathological confirmation could not be made were excluded. The data of 22 patients with pituitary cushing syndrome and 3 patients with ectopic CS (total 25 patients) were examined. In 2 0f 3 patients, ectopic CS was diagnosed primarily with the results of 8 mg dexamethasone suppression test, CRH stimulation test and sella MRI, and postoperative immunohistochemical staining was confirmed. While the sensitivity, specificity, positive and negative predictive values of IPSS in the differential diagnosis of pituitary and ectopic ACTH-dependent CS were 75%, 100%, 100%, 14,28% before CRH stimulation, they were 87.5%, 100%, 100%, and 25% after CRH stimulation, respectively. When the results were evaluated together before and after stimulation, these rates were found as 91,6%, 100%, 100%, and 33,3%, respectively. In 17 (77.27%) of 22 patients whose IPSS showed the pituitary, correct lateralization was confirmed by the operation.
Conclusion
IPSS is an effective test in the differential diagnosis of ACTH-dependent CS.Its sensitivity increases after CRH stimulation. However, while the efficacy of this procedure is high in the central/ectopic distinction, its capacity to lateralize the lesion is limited.

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AEP525

Prognostic factors for remission in Cushing's disease after pituitary surgery 'bout 100 cases'

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Introduction
Cushing's disease described in 1973 by Harvey Cushing is the most frequent cause of endogenous hypercorticism in adults in 80-85% of cases of Cushing's syndromes, it is secondary to a pituitary microadenoma most often, its treatment is first-line neurosurgical.
Aim of the study
To evaluate the results of the short and medium term therapeutic management of Cushing's disease and to try to determine the predictive factors of remission.
Material and methods
Retrospective study: 85 patients recruited by CPMC. All of our patients underwent clinical, biological and morphological (CT and/or static MRI) pituitary and adrenal evaluation as well as petrous sinus catheterization (n = 9).
Surgical results
All our patients were operated on and 14% resumed Surgically; the transphenoidal route (TSP) has been the rule for all of our patients; the procedure performed is adenomectomy in 88% (selective 84% and enlarged 16%) and hemi-hypophysectomy in 12% of cases. 'The extirpated pituitary adenoma' is identified in 95% by histology. 8.33% of our patients underwent a positive immunohistochemical examination in all cases. Pituitary surgery in cushing's disease resulted in 69% remissions in microadenomas immediately after surgery. Reoperation may improve outcomes if initial surgery fails 8/12 (66%). However, the risk of long-term recurrence is high, 25% beyond 10 years.
Conclusion
Despite advances in diagnosis and treatment, CD is still difficult to treat. TSP surgery is the standard treatment. Our results are satisfactory: the experience of the neurosurgeon remains a fundamental asset. In the event of post-op recurrence, additional radiotherapy treatment is offered in combination with synthetic anti-cortisol drugs.

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AEP526

Radiotherapy results non-functional pituitary adenomas about 50 cases

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Introduction
Non-functional pituitary adenomas (AHNF) are large tumors expressed primarily by neuro-ophthalmological signs in the foreground and pose a problem of therapeutic management and prognosis.
Materials and methods
We report a retrospective study of 50 files of 'non-functional' pituitary adenomas collected between 1993 – 2005 with the aim of evaluating the results of surgery and conventional pituitary radiotherapy with a minimum follow-up of 2 years for each patient. [Average follow-up: 60 months, range: 24-120 months].
Results
Our series was divided into 26 men and 24 women, the average age was 47 years with extremes of 17 to 80 years. The circumstances of discovery are the typical intracranial tumor syndrome in 26 cases (52%) and visual disturbances in 19 patients (38%). -On the neuroradiological level: it was an expansive pituitary macroadenoma in all cases (100%) and in 19% of cases of giant adenomas (≥ 4cm). - On the pituitary level: there was total or partial anterior pituitary insufficiency in 31 patients (62%) and diabetes insipidus in 3 cases (6%). - On the therapeutic level: 90% of our patients have been operated, including 20% resumed surgically; conventional radiotherapy (55 grays in 28 sessions) completed the surgery in 76% of cases.

Surgery			Surgery+ Radiotherapy	
Number	Progressive recovery (%)		Number	Progressive recovery (%)
n= 45	n= 23 (51%)		n =38	n=11(29%)
	remainder +	remainder		
	n=15	n= 8		

Conclusion
The so-called 'non-functional' pituitary adenomas are large pituitary tumors with significant locoregional and endocrine repercussions with a very mysterious physiopathological mechanism. They are now recognized with greater frequency thanks to advances in immunohistochemistry. The indication for surgical treatment is not the subject of any discussion. However, the therapeutic attitude in the event of postoperative tumor residue remains controversial. Recurrences can be observed very late and therefore justify very long-term monitoring.

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AEP527

Copeptin predicts clinical outcome in schizophrenia spectrum disorder

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Background
Vasopressin, the main hormone regulating sodium-water balance, is involved in higher brain functions, e.g., cognition, emotion regulation and social functioning. In patients with an acute psychotic episode, increased vasopressin levels have been described and impaired higher brain functions are associated. Copeptin, the stable surrogate marker of vasopressin, has been shown to predict outcome in somatic diseases, i.e., stroke, myocardial infarction, and increases under psychological stress. In acute psychosis no reliable biomarker has proven to predict clinical outcome. The aim of this study was to investigate whether copeptin can be used as predictor of psychotic relapse in patients with an acute psychotic episode.
Methods
In this prospective, observational study we enrolled patients with an acute psychotic episode either within a schizophrenia spectrum disorder (SSD) or affective disorder. On hospital admission, baseline characteristics including current and prior medication, drug use and disease severity, i.e., Positive and Negative Syndrome Scale, Global Assessment of Functioning, Perceived Stress Scale, State-Trait Anxiety Inventory and Beck Depression Inventory, were assessed and fasting serum copeptin and cortisol were sampled. Psychotic relapse, defined as rehospitalization due to disease progression or reporting of psychotic relapse, was assessed one year after inclusion. The primary endpoint was copeptin at inclusion predicting time to psychotic relapse using Cox Proportional Hazard Model.
Results
We included 73 patients (74% male, mean [SD] age 35.3 [9.8] years) of whom 53 were diagnosed with SSD and 20 with affective disorder (n=17 bipolar, n=3 depression with psychotic symptoms). Serum copeptin predicted psychotic relapse with a hazard ratio (HR) of 1.1 (95%-CI 1.01-1.2, p=0.03) in patients with SSD, but not in affective disorder (HR 1.0, 95%-CI 0.8-1.1, p=0.6). Highest diagnostic accuracy for psychotic relapse was found at a copeptin cut-off of 7 pmol/l with a HR of 3.9 (95%-CI 1.3-11.8, p=0.01). Neither cortisol, prior or current antipsychotic medication, trigger of acute psychosis nor psychopathological ratings were significantly associated with psychotic relapse. Diagnosis of cannabis abuse was significantly associated with psychotic relapse in SDD (HR 3.3, 95%-CI 1.4, 8.0, p=0.008). Adjusting for cannabis abuse, copeptin remained significantly associated with psychotic relapse and identified patients with highest risk of psychotic relapse (p=0.015).
Discussion
Our study indicates that copeptin is a promising biomarker improving outcome prediction of psychotic relapse in patients with an acute psychotic episode within SDD. Our findings may be used to identify patients at risk of psychotic relapse and in need for a more intensive care.

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AEP528

Craniopharyngiomas presenting as incidentalomas – Results of KRANIOPHARYNGEOM 2007

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Purpose
Childhood-onset craniopharyngiomas (CP) are diagnosed due to clinical symptoms (symCP) or incidentally (incCP). We investigated clinical manifestations and outcome in incCPs and symCPs.
Methods
IncCP were discovered in 4 (3m/1f) and symCP in 214 (101m/113f) CP recruited 2007–2014 in KRANIOPHARYNGEOM 2007. Age, sex, height, body mass index (BMI), tumor volume, degree of resection, pre- and postsurgical hypothalamic involvement/lesions, pituitary function and outcome were compared between both subgroups.
Results
Reasons for imaging in incCP were cerebral palsy, head trauma, nasal obstruction, and tethered-cord syndrome, whereas headache (44%), visual impairment (25%), and growth retardation (17%) lead to imaging in symCP. Tumor volume at diagnosis was smaller in incCP (median 2.39 cm3; range: 0.14–4.10 cm3) when compared with symCP (15.86 cm3; 0.002–286.34 cm3). Age, gender, BMI, height, hydrocephalus, tumor location, and hypothalamic involvement at diagnosis of incCP were within the range of these parameters in symCP. Complete resections were achieved more frequently (3/4 patients) in incCP when compared with symCP (20%). Surgical hypothalamic lesions were distributed similar in incCP and symCP. Irradiation was performed only in symCP (33%). No noticeable differences were observed concerning survival rates, endocrine deficiencies, BMI, height, functional capacity and quality of life of the 4 incCP cases when compared with the symCP cohort.
Conclusions
IncCP are rare (1.8%) and characterized by lack of endocrine deficiencies, resulting in normal height and BMI, no hydrocephalus, and smaller tumor volume at diagnosis when compared with symCPs. Outcome of the observed incCP is similar with symCP.

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AEP529

Severe hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) as a primary presentation of neurosarcoidosis

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Introduction/Background
Sarcoidosis is a multi-system inflammatory disease of unknown etiology, characterized by abnormal collection of inflammatory cells termed as granulomas. This disease usually involves lungs, skin, or lymph nodes, but can less commonly affect the eyes, liver, heart and brain. Neurological involvement is rare and appears in 5-10% of the cases. Neurosarcoidosis most frequently affects the cranial nerves, the hypothalamus and the pituitary gland. Hyponatremia has been found in some patients with sarcoidosis and few case reports can be found in the literature. We hereby present the case of a 52 year-old gentleman who was diagnosed with SIADH secondary to neurosarcoidosis and presented with severe symptomatic hyponatremia.
Case report
A 52-year old gentleman presented with worsening confusion, lethargy and poor sleep. He had background history of seizures previously diagnosed as epilepsy and was on different anti-epileptic medications. There were no focal signs of neurological involvement other than intermittent confusion and difficulty in organizational skills. He was found to have severe hyponatremia with concomitant serum hypo-osmolality. Anti-epileptic medications were revised in the context of SIADH, but computed tomography (CT) of thorax, abdomen and pelvis revealed mediastinal and hilar lymphadenopathy with normal liver parenchyma. His serum angiotensin converting enzyme (ACE) levels were high, however; calcium levels were within normal range. He had mild hyperprolactinemia with slightly low thyroid stimulating hormone (TSH) and oestradiol levels. Magnetic resonance imaging (MRI) of his brain revealed features consistent with neurosarcoidosis and electroencephalogram (EEG) showed epileptiform activity likely secondary to the same disease. He underwent endobronchial ultrasound biopsy of the mediastinal lymph nodes that showed non-caseating granulomas thus confirming the diagnosis of sarcoidosis.
Treatment/Outcome
Patient was started on oral steroids, tab prednisolone 1 mg/kg body weight with fluid restriction. His sodium levels started improving with improvement in his clinical symptoms. He was advised follow-up in endocrinology and neurology clinics.
Conclusion
This case report highlights that SIADH presenting with severe hyponatremia can be an initial presentation of neurosarcoidosis. Sarcoidosis should be considered in the differential diagnoses of SIADH and hyponatremia.
Keywords: hyponatremia, granuloma, sarcoidosis, inflammation.
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AEP530

Case report of family form of multiple endocrine neoplasia syndrome type 1 with a non-classic course

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Multiple endocrine neoplasia type 1 (MEN1) is a rare hereditary condition that most often manifests with primary hyperparathyroidism followed by other syndromes, but there are other variations in the clinical presentation, which can increase the risk of medical error and worsen prognosis. A 32-year-old woman presents with complaints of low glucose levels, hunger, weakness, sleep disturbances, which are stopped by taking sweets. At the age of 16, a pituitary macroadenoma, prolactinoma resistant to the treatment was diagnosed (4 years of treatment with bromocriptine, transnasal adenomectomy, followed by 10 mg per week cabergoline didn't achieve normoprolactinemia (prolactin increased to 18,000 mIU/ml). Normoprolactinemia was achieved after repeated surgery at the age of 30). At the age of 28, primary hyperparathyroidism was diagnosed. Ultrasound of the thyroid gland revealed multiple formations of the parathyroid glands. So, a clinical diagnosis of MEN1 was made. Total resection of 4 parathyroid glands was performed with autotransplantation of the least altered gland into the muscle of the left forearm. Postoperatively, hypocalcemia with severe convulsive syndrome occurred, which required intravenous calcium gluconate, after which it was transferred to calcium tablets and active metabolites of vitamin D. Genetic verification of MEN1 syndrome was carried out (R415X gene mutation). A year later, the patient's sister was diagnosed with hyperparathyroidism, genetic study revealed the same mutation. Subsequently, the formation of the adrenal glands (hormone-inactive) and the pancreas were detected. As part of this hospitalization, a fasting test was carried out (completed after 9 hours due to the development of hypoglycemic syndrome, at the end of the test C-peptide, insulin was within normal limits, proinsulin was significantly increased (29 mmol/L (0.7-4.3). According to the results of instrumental research methods, two formations were identified in the head and tail of the pancreas (0.8 and 2.5 cm). After selective blood sampling from the veins of the portal system, an organ-saving operation was performed. With further observation C-peptide, insulin, cortisol, parathyroid hormone remain within the normal range, but proinsulin remains elevated (up to 6-7.8 pmol/l). Given the presence of formations in both adrenal glands, in the head of the pancreas, it is not excluded that they acquire hormonal activity in the future, and therefore the patient will be screened. A detailed description of cases, especially with a non-classical course, can improve the preventive and therapeutic-diagnostic approach, which will have a beneficial effect on the quality of life and prognosis for such patients.

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AEP531

Transsphenoidal surgery in acromegaly: Experience in a tertiary hospital

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Background
Acromegaly is an infrequent chronic multisystemic disease associated with a significant morbidity and mortality rate. The treatment of choice is transsphenoidal surgery (TSS) because of its low risk of mortality and few complications.
Aims
To determine the cure prevalence after TSS of growth hormone (GH) secreting pituitary adenomas. To analyze the predictive factors of non-remission after the surgery.
Materials and methods
Retrospective study of 97 patients with acromegaly diagnosis who underwent surgery (n=86) in La Paz University Hospital from 2000 to 2020. The surgery was carried by three neurosurgeons who meet the requirements of being experts in pituitary gland surgery. We performed a descriptive analysis of the patient`s baseline characteristics and surgery outcomes. A multivariate regression analysis was used to review the possible predictive factors of non-healing. Remission was defined if the age and sex-adjusted IGF-1 level were normal and either the basal GH was <1ng/ml or the nadir GH was <0.4ng/ml following oral glucose tolerance test and absence of tumor on MRI.
Results
Out of the total sample, 56.1% were female and 43.9% were male. Diagnostic suspicion was due to symptoms that were secondary to hormonal hypersecretion in 76.3%. GH-secreting pituitary adenoma was found in 94.1% (36.5% microadenomas and 57.6% macroadenomas) of the total patients. 70% of pituitary adenomas showed signs of extension (51% microadenomas and 65% macroadenomas). The surgical cure rate overall was 53.4% (76.9% microadenomas). Tumor remnants were found on MRI in 40% of the patients (23.07% microadenomas and 57.7% macroadenomas). Recurrence occurred in 2.7% of them. Surgical reintervention was performed in 13.3% and radiation therapy was required in 26.5%. Medical treatment was indicated in 94.1% of patients who were not cured and in 6.8% of patients with recurrence. Median GH levels after surgery were 1.6ng/dl (IQR 73.93ng/dl) and IGF-1 257ng/dl (IQR 1095 ng/dl). Multivariate analysis indicated that the non-healing post-surgical predictive factors were IGF-1 values above the upper limit of normal (x LSN) [OR: 9.95 (2.71-53.82)], GH x LSN [OR: 9.62 (3.04-41.65)], macroadenoma [OR: 21.57 (3.08-228.04)], GH + PRL cosecretion [OR 10.84 (1.68-103.4)] and GH + PRL + TSH [OR 33.86 (1.30-1390)].
Conclusions
1) TSS continues to be the first line treatment in acromegaly, although in large and/or invasive adenomas other therapies may be required. 2) Tumor size and initial GH and IGF-1 values are factors that most influence surgical outcomes. 3) TSS performed by an expert surgeon increased higher cure rates.

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AEP532

Gender differences in eating-related behaviour and traits of patients with craniopharyngioma

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Introduction
Craniopharyngiomas are rare and benign tumours of the suprasellar region along the craniopharyngeal duct. Their clinical manifestations result from tumour compression or therapy-induced damage of the surrounding tissue, namely visual impairment, pituitary deficiencies and increased intracranial pressure. Hypothalamic damage often leads to central obesity and fatigue. The impact of these changes on quality of life and body perception has been well described in the literature, but specific analyses of gender differences are scarce.
Methods
We assessed eating-related behaviour and traits in 26 patients with craniopharyngioma (15 female, 11 male) in a cross-sectional study using standardized questionnaires (Three-Factor-Eating-Questionnaire, TFEQ; Eating Disorder Examination Questionnaire, EDE-Q; Body Image Questionnaire FKB-20). We calculated group comparisons using the chi square test or Mann-Whitney U test with a significance threshold of 0.05.
Results
Female and male patients did not statistically differ in terms of age (mean 51.1 [range: 32-68] vs. 55.6 [26-77] years), BMI (32.1 [19.5-47.9] vs. 31.3 [23.9-41.0] kg/sqm), frequency of surgery or radiation, and pituitary deficiencies. Female patients had nominally, but not significantly higher insulin sensitivity as assessed by Matsuda ISI (f: 4.0 [0.9-17.3]; m: 2.4 [0.8-5.3]). Global score from EDE-Q was significantly higher in female patients (2.3 [0.8-3.7] vs. 0.9 [0.1-1.7]; p=0.002) as were the subscales eating concern (2.8 [0-5] vs. 0.9 [0-2]; p=0.001) and shape concern (3.2 [0.0-5.8] vs. 1.4 [0.0-2.9]; p=0.009). Women in our cohort also exhibited a significantly higher negative body assessment (AKB score in FKB-20; 32.2 [15-48] vs. 18.6 [11-28]; p=0.001) and significantly lower vital body dynamic (23.2 [15-35] vs. 31.2 [21-44]; p=0.007). Cognitive control of eating behaviour is increased in female patients (11.3 [4-20] vs. 7.1 [1-15]; p=0.042).
Conclusions
Female patients with craniopharyngioma exhibit a significantly impaired eating behaviour, body perception and cognitive concern with eating as compared to male patients. The reasons for these differences remain to be elucidated.

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AEP533

Improved response to somatostatin analogue (SSA) therapy in acromegaly following treatment pause

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Background/methods
Patients with uncontrolled acromegaly or receiving high cost medical therapy despite initial treatment, usually transsphenoidal surgery (TSS), were considered for a ^{11}C-methionine PET-CT scan (11C-Met PET-CT). This imaging technique may identify a target for TSS or radiotherapy when MRI appearances are inconclusive[1]. In preparation, four patients on long-term SSA were taken off treatment 3 months prior to the scan. Due to issues with the cyclotron, 2 scans had to be deferred (increasing the duration of the treatment pause). We reintroduced SSA therapy in all 4 patients and noticed an improvement in biochemical response.
Results

Patient	1	2	3	4
Primary therapy	Medical	TSS	TSS	TSS
Treatment prior to 11C-Met PET-CT	Octreotide LAR 20 mg 6-weekly	Octreotide LAR 10mg 4-weekly	Lanreotide ATG 120 mg 4-weekly	Lanreotide ATG 120 mg 4-weekly
IGF1×ULN$^{\varphi}$ at diagnosis (year)	1.8 (1999)	6.1 (2011)	4.6 (2012)	2.1 (1994)
Duration of SSA treatment (years)	18	1	4	23
IGF1×ULN$^{\varphi}$ at treatment pause	1.07	1.14	0.78	1.41
Duration of treatment pause (months)	8	6	4	8
IGF1×ULN$^{\varphi}$ prior to treatment restart	1.5	1.13	1.0	1.33
Duration of treatment post SSA restart (years)	3	2	3	3
Latest IGF1×ULN$^{\varphi}$	0.87	0.98	1.06*	0.8

11C-Met PET-CT outcome	Awaiting Surgery	Deferred	No surgical target	Deferred
Current treatment	Octreotide LAR 20 mg 6-weekly	Octreotide LAR 10 mg 6-weekly	Lanreotide ATG 120 mg 12 weekly*	Lanreotide ATG 120 mg 4-weekly

¥ Upper limit of normal; * Dose frequency increased from 12 weekly to 10 weekly (patient living abroad and had requested reduced dosing frequency)

Discussion

Tachyphylaxis is defined as a diminishing response to successive doses of a medication, rendering it less effective. SSA therapy is not anticipated to demonstrate tachyphylaxis in acromegaly[2], although there has been one report of partial tachyphylaxis[3]. Our four patients appear to have experienced a resensitisation to SSA therapy following a short treatment pause as evidenced by improved biochemical control; despite two of them having a reduced dosing frequency. The possibility of a treatment pause improving the sensitivity and biochemical control following reintroduction of SSA therapy has been reported in polycystic liver disease[4].

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AEP534

Does concomitant prolactin measurement increase the accuracy of inferior petrosal sinus sampling?

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Purpose

Inferior petrosal sinus sampling (IPSS) is the gold standard test for the differentiation of pituitary Cushing disease from the ectopic ACTH syndrome (EAS). The measurement of prolactin during IPSS can be helpful to improve the accuracy of the procedure. We aimed to evaluate the effect of measuring prolactin levels as a predictor for the accuracy of IPSS procedure and evaluate its' impact on the lateralization of adenoma.

Material and methods

In this retrospective cohort study, we reviewed 51 patients who had undergone IPSS for the investigation of ACTH-dependent hypercortisolism at Marmara University E&R Hospital between 2012 and 2019. Plasma ACTH (adrenocorticotropic hormone) and prolactin levels were measured both centrally and peripherally during IPSS procedure in all patients. The prolactin adjusted ACTH inferior petrosal sinus/peripheral (IPS/P) ratio was calculated to assess the accuracy of the sampling procedure.

Results

Forty-nine patients had proven CD, one was EAS. Forty-seven patients had above two ACTH IPS/P ratio at baseline, and all the proven CD patients' post-corticotropin releasing hormone (CRH) ACTH IPS/P ratio was above three. Prolactin IPS/ P ratio was above 1.8 in all patients. While prolactin adjusted ACTH IPS/P ratios were >1.3 in all patients with proven Cushing's disease, it was 0.7 in the patient with EAS. Both baseline ACTH and prolactin levels were positively correlated with post-CRH ACTH and prolactin levels (r:0.735, p<0.001; r:0.910, p<0.001, respectively). While post- CRH, ACTH levels were significantly increased from baseline to 3rd,5th,10th minutes in the P and IPS samples (p<0.001), prolactin levels were not showed a statistically significant increase after stimulation with CRH both in the P and IPS samples (p:0.116, p:0.712). Positive lateralization was observed in 55.1% of patients with ACTH gradient, but when prolactin adjusted ACTH IPS/IPS ratio used in addition to the ACTH gradient, the ratio was increased to 67.3%.

Conclusion

Prolactin IPS/P ratios are useful to define successful catheterization, and prolactin adjusted ACTH IPS/P ratio can be helpful to improve the accuracy of results during IPSS procedure.

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AEP535

The alpha-subunit of glucoprotein hormones and anatomopathological aspects of pituitary adenomas

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Introduction

The pituitary glycoprotein hormones, luteinizing hormone (LH), follicule-stimulating hormone (FSH), thyroid-stimulating hormone (TSH) and human chorionic gonadotropin (hCG) are comprised of two separate noncovalently bound subunits:alpha and beta units. The alpha subunit is identical in all of the hormones,while the ńsubunit is unique for each hormone and confers the specific immunologic and functional activity.Hypersecretion of the glycoprotein alpha subunit has previously been reported in patients with pituitary,with or without concomitant hypersecretion of pituitary hormones. The objective of our work is to describe the variation of alpha subunits according to the anatomopathological aspects of patients with pituitary adenoma.

Material and methods

A retrospective study that focused on the cases of pituitary adenomas,collected at the Endocrinology-Diabetology and Nutrition Department of Mohammed VI University Hospital in Oujda, over a period of 6 years and a half.The data were collected from medical records and the analysis was done by SPSS version 21 software. Sub-unit rate was considered normal between 0.04 and 0.7mUI/ml.

Results

Thirty two percent out of 74 cases of patients with pituitary macro adenoma benefited from pre-operative measurement of alpha sub-units.A low level was found in 12.5% of the patients,whose anatomopathological type was respectively: one case of prolactinoma, one case of non-secreting pituitary adenoma and one patient with a multisecreting pituitary adenoma.Their average age was 31.6 years with a mean subunit rate of 0.03 Mui/ml. This rate was also elevated in 16.7% of cases,varying from 1.5 to more than 10times the normal range, in a patient with gonadotropic adenoma with concomitant elevation of serum FSH and LH gonadotrophins, in a case with non-functional adenoma, a patient with somatotropic adenoma and a patient with somatotropic adenoma. A normal rate was found in the majority of patients, i.e.70.8% of patients mostly women (53%of women) with a mean rate of 0.28mIUi/ml.These cases include:6 patients with prolactinoma, 5cases with non-functional adenoma, 3cases with corticotropic adenoma, 2cases with mixed adenoma secreting both prolactin, LH and GH and one case with somatotropic adenoma.

Conclusion

We conclude that a-subunit hypersecretion may be more common than previously recognized among patients with pituitary tumors. Its high rate may indicate the anatomopathological type of pituitary adenoma,but remains unspecific.The biological and clinical significance of a subunit cosecretion in patients with pituitary tumors is not known at this time.Whether such cosecretion is of importance in the pathogenesis of these tumors or whether it alters the clinical course or response to therapy deserves further study.

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AEP536

Pituitary apoplexy- a single-center, retrospective study of clinical outcomes

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Introduction

Pituitary apoplexy is a rare entity characterized by abrupt hemorrhage and/or ischaemia of the constituents of sella turcica. It usually occurs in a previously unsuspected pituitary tumor. It may have an acute or subclinical presentation and it may represent a neuroendocrinological emergency.

Aim

This study aims to analyze predisposing or precipitating factors, clinical status, imaging and hormonal features, therapeutic management and its outcome for patients presenting with pituitary apoplexy.

Methods
We performed a retrospective analysis which included 36 patients diagnosed with pituitary apoplexy (we included both acute and subclinical presentations), evaluated during 2019 in Department of Pituitary and Neuroendocrine Pathology at the 'C.I. Parhon' The National Institute of Endocrinology Bucharest, Romania.
Results
36 patients with pituitary apoplexy were included (19 men, 17 women; mean-age at diagnosis 49.2 years, range 14-72 years). Half of the patients presented a classical pituitary apoplexy episode, whilst the other half had oligosymptomatic pituitary haemorrhage described on CT or MRI scan. Only 9 (25%) cases were previously known to have a pituitary adenoma (non-secreting adenoma in most cases). 8 patients (25%) presented at least one precipitating factor, hypertension being the most common. The top 3 symptoms of apoplexy in our patients are headache (44.4%), visual abnormalities (44.4%) and digestive manifestations (22.2%). 23 patients (63.8%) underwent neurosurgical intervention, 11 of them having typical clinical presentation. 75% of the patients had remnant intrasellar mass after the apoplectic event. At diagnosis, corticotropic deficiency was noted to be the most common deficit in patients with classical pituitary apoplexy (4/7 patients) while gonadotropic deficiency had the greatest prevalence in subclinical cases (6/ 9 patients). 25 patients (69.4%) remained with longterm hormone replacement therapy. Out of 16 cases with visual disturbances, 11 patients were operated and 5 managed conservatively. 9 of the operated patients and all cases with conservative treatment had improvement in vision. 4 cases (11%) developed postoperative diabetes insipidus.
Conclusions
Pituitary apoplexy should be managed with a multidisciplinary approach. Although there is an important visual recovery in these patients, the outcome of pituitary function is less favourable.

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AEP537

The perspective of patients with pituitary disease on work according to the expanded ICF model: A qualitative study

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Purpose
As the majority of patients with pituitary disease are of working age, their health situation may negatively impact their functioning at work. However, work participation can also be influenced by contextual (environmental and personal) factors. The aim of this qualitative study was to investigate the perspective of patients with pituitary disease on their functioning at work and on contextual factors contributing to work-related problems, using the expanded International Classification of Functioning, Disability and Health (ICF).
Methods
Semi-structured interviews, focusing on contextual factors influencing work ability and experience, were conducted with eight patients with different types of pituitary adenomas (Cushing's disease, prolactinoma, acromegaly, non-functioning adenoma). Following the steps of an experiential thematic analysis, forty categories were identified, which were organized into eleven themes according to the expanded ICF.
Results
Patients reported various problems in work-related activities (e.g., problems with reading and making more mistakes) and work participation (e.g., working fewer hours or losing their job). Influencing environmental factors included type of employment, perceived job security, financial security, relationships with colleagues/managers, collaboration with others, physical vs. mental work, managing position, flexibility at work, corporate culture, and physical work environment (work-related), and traveling distance to work, financial savings, and (non)professional support (other environmental factors). Influencing personal factors included professional ambition, sense of duty, motivation, job satisfaction, and feeling of fulfilment (work-related), and personality, acceptance, coping styles, and lifestyle (general personal factors).
Conclusion
The expanded ICF model used in this study can bridge the gap between the approach of occupational health professionals and healthcare professionals involved in care for people with a pituitary disease. Patients with pituitary disease report limitations in activities and restrictions in participation at work, which are influenced by several environmental and personal factors. Healthcare professionals and occupational health professionals should be aware of these influencing factors and should address those that are modifiable in order to provide holistic, multidisciplinary patient-centered care. This can improve patients' well-being and functioning at work with the ultimate goal to improve HRQoL.

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AEP538

Silent somatotroph giant pituitary adenoma with the first manifestation at the age of 15 with a 16-year follow up- case report

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Background
Silent somatotroph pituitary tumours are very rare, representing only 2-4% of all pituitary tumours in surgical series. Little is known about the course of the disease and efficacy of possible treatment modalities.
Presentation of the case
A male, born in 1990, was first admitted to the hospital at the age of 15, due to sudden ptosis of the right eye and headaches, present for 1 year before the diagnosis. Magnetic resonance imaging (MRI) of the head revealed a solid, homogeneous tumour in the Turkish saddle, 47x37x37 mm in diameter, described as slightly hyperintense in T2- images and FLAIR sequences, slightly hypointense in T1- images and homogeneously enhancing after contrast administration. The tumour expanded into the sphenoid sinuses, medial part of the left cavernous sinus and filled completely the right cavernous sinus, surrounding the whole circumference of the right internal carotid artery. It compressed the right temporal lobe, hypothalamus and the optic chiasm. The patient underwent a transsphenoidal partial resection of the pituitary tumour, with histopathological confirmation of pituitary neuroendocrine tumor (PitNET) with features of nuclear atypia. Immunohistochemistry was positive for growth hormone (GH), +/- for prolactin, negative for the remaining pituitary hormones, MIB1 10%. In electron microscope images, silent somatotroph, sparsely granulated PitNET was confirmed. Neither before surgery nor during 16-year observation did the patient present any clinical symptoms of acromegaly. Upon diagnosis, full endocrinological evaluation was not performed, however, Insulin-like Growth Factor-1 (IGF-1) concentrations were within the normal range, with elevated GH levels and no suppression in the oral glucose tolerance test. Medical treatment with long-acting somatostatin analogue was introduced. Since the surgery, the patient underwent both endocrinological and neurosurgical assessment regularly. Over time MRI images were stable: in the last MRI performed in 2019 a partially empty sella was described, with the invasion of right cavernous sinus by a 20x32x25 mm lesion surrounding the right internal carotid artery. Endocrinological follow-up revealed secondary hypothyroidism and proper function of the gonadal, adrenal and somatotroph axis, with normal concentrations of prolactin and no clinical nor biochemical symptoms of diabetes insipidus. No visual field deficits were discovered during ophthalmological examination.
Conclusion
Although antiproliferative effect of somatostatin analogues has been reported, very little data concerting silent somatotroph pituitary tumours and the treatment options is currently available. Further multicentre studies are needed to investigate the course of those very rare pituitary tumours and create the standards of treatment.

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AEP539

Assessing quality of life and cardio-vascular risk in patients with acromegaly: A single tertiary center case series

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Background
Acromegaly is a rare disease, caused by an autonomous excessive secretion of growth hormone (GH). Apart from skeletal alterations, the GH excess leads to metabolic and visceral disease. Thus, one of the most frequent associated complications is the cardio-vascular one represented by hypertension, cardiomyopathy and ischemic heart disease. The presence of multiple complications in patients with acromegaly leads not only to increased morbidity and mortality but also decreased quality of life.
Methods
The study gathers 42 patients with acromegaly (16/26 m/f) divided into two subgroups on the basis of treatment (SA – somatostatin analogue as monotherapy/in dual therapy with dopamine agonist; PEG- GH receptor blocker- Pegvisomant- in monotherapy or dual therapy with SA). Assessment of the hormonal and metabolic status was performed in all subjects. Regarding cardio-vascular function, we calculated the SCORE risk using the European High Risk Chart and the Framingham Risk score for coronary heart disease, while also measuring several important parameters through 2D echocardiography. Quality of life was assessed using ACRO-QoL, a disease-specific questionnaire and SF-36, a generic questionnaire.
Results
There were no significant differences between the PEG and SA groups regarding total ACRO-QoL scores (76.64 ± 15.38 vs. 78.82 ± 17.65) and SF-36 (85.78 ± 37.43 vs. 87.89 ± 31.77). Instead we have found a significant lower personal relations score in the PEG group compared to SA (26.85 ± 6.024 vs. 27.96 ± 5.84, p=0.026). Concerning the cardio-vascular function, there was a significantly lower SCORE risk (1.72 vs. 1.91, p=0,034) and Framingham score (6.63 vs. 7.73, p=0,013) in the PEG group compared to the SA group and the PEG group had also lower blood pressures at the moment of examination using less antihypertensive drugs (1.75 ± 0.88 vs. 3 ± 1.14, p=0.038). Also, there were no significant differences regarding 2D echocardiography parameters in the two groups.
Conclusion
The results confirm that GH receptor blocker (Pegvisomant) has a better cardio-vascular outcome for the patients despite having similar quality of life scores compared to the SA group, the only difference being lower personal relations score assessed through ACRO-QoL questionnaire.

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AEP540

A micromegaly case: Difficult to determine whether a metabolic state or an acromegaly subset

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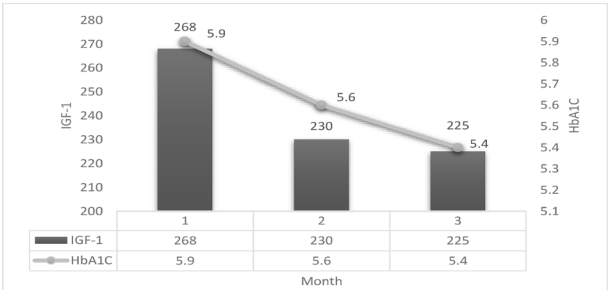
Introduction:
Acromegaly is caused by excess levels of growth hormone (GH) and insulin-like growth factor 1 (IGF1), which usually result from a pituitary adenoma. At the presence of classical symptoms, the diagnosis is confirmed by increased serum IGF1 concentrations and high serum levels of GH that are not suppressed in an an oral glucose tolerance test (OGTT). A nadir GH cut-off of 0.4 µg/lwith ultrasensitive assays is considered as diagnostic. However, some patients with lower nadir GH despite elevated IGF-1 levels, also named as micromegalic, were reported.
Case
We present a case of 35 years-old woman, who got involved a clinical trial in outpatient clinic of Marmara University Medical School Endocrinology and Metabolism Deparment. An elevated IGF-1 level was detected by coincidence. The patient did not have acromegaly-related complaints. Her weight was 74 kg, height was 178 cm. Waist circumference was 92 cm. Her body mass index was 23.3 kg/m^2 and his waist to height ratio was 0.51 kg/cm. In biochemical evaluation, GH level was 3.36 µg/l, IGF-1 level was 268 (63.4-223) µg/l. After an oral glucose load, GH level supressed to 0.08 µg/l. During OGTT insulin levels were recorded as 10.65, 52.53, 31.41 mU/L; glucose levels were recorded 92, 95, 85 mg/dl at 0,60, 120 minutes; respectively. Hemoglobin A1c (HbA1c) level was 5.9%. The pituitary magnetic resonance imaging (MRI) showed a suspected 2 mm adenoma on the right side of the pitutary gland. According to the laboratory results regarding glucose intolerance, calori restriction and exercise were advised to the patient. IGF-1 and HbA1c levels decreased after life style intervention.



Conclusion
The pathologic mechanism of the discordance betwwen GH and IGF-1 in acromegaly is still unknown. Metabolic processes might be the underlying reason that was shown in a recent study which eucaloric very-low-carbohydrate ketogenic diet was useful in maintaining IGF-1 control. ń̀n our case, it is difficult to determine whether excess IGF-1 levels were a consequence of the glucose intolerance or GH-secreting pituitary adenoma.
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AEP541

Successful recovery after COVID-19 infection in a patient with diabetes insipidus and pituitary insufficiency due to a pituitary stalk tumor

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Background
Fluid balance in patients with diabetes insipidus and COVID-19 is very fragile. The prevalence of hyponatraemia in patients with pneumonia due to COVID-19 seems to be low, but in patients admitted to intensive care units (ICU) is high (up to 20.5%). In contrast, hypernatraemia may also develop in COVID-19 patients in ICU (up to 3.7% of cases), due to insensible water losses from pyrexia, increased respiration rate and use of diuretics. Both hypo and hypernatremia were associated with increased mortality and sepsis.
Case report
A 35 years old, non-smoker women with diabetes insipidus and pituitary insufficiency due to a pituitary stalk tumor (12/8/12 mm diameter) developed COVID-19 in august 2020. She also had obesity (BMI= 38.7 kg/m2), vitamin D insufficiency (25 OH vitamin D= 22.7 ng/mL) and dyslipidemia. Blood pressure, renal function were normal and she had no diabetes mellitus. Endocrine assessment 6 months prior to COVID-19 infection showed gonadotroph insufficiency (FSH=4.1 mUI/ml, LH=1.37 mUI/ml, estradiol<10 pg/ml), central hypothyroidism on levothyroxine treatment (TSH= 1.6 mUI/l, FT4= 9.2 pmol/l) and low normal basal 8 a.m. cortisol levels (4.77 µg/dl) with stimulation to low dose (1 µg, iv) short Synacthen test up to 19.6 µg/dl (ie 540 nmol/l) at 30 minutes and 16.2 µg/dl (ie 446.4 nmoll) at 60 minutes. 8 a.m. ACTH level was normal (16.4 pg/ml). Serum prolactin level was suppressed (0.4 ng/ml) on small dose dopamine agonist therapy (Cabergoline 0.5 mg/week). At COVID-19 diagnosis she was on Desmopressin 240 µg/day, Levothyroxine 50 µg/day, Cabergoline 0.5 mg/week, Cholecalciferol 500 IU/day and Rosuvastatin 5 mg/day. She presented a mild disease with fever, cough, but not pneumonia and did not required hospitalization'. Plasma sodium monitoring was not possible, but the patient did not experienced abnormal variations in fluid balance and body weight was stable. Due to suboptimal adrenal reserve, she was advised (by virtual counselling) taking oral glucocorticoids and to progressively decrease the dose after full recovery. She also received supportive treatment. She fully recovered and 2 months after infection she displayed normal serum natremia

(Na=145 mmol/l), high-normal serum osmolality, similar pituitary function and high titer of anti SARS Cov-2 IgG (95.1 IU/ml, normal range < 12 IU/ml).
Conclusion
Patient education, virtual patient counselling, careful monitoring of fluids intake and excretion, daily body weight monitoring and glucocorticoid dose adjustments are mandatory in patients with diabetes insipidus and pituitary insufficiency during Covid-19 infection.

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AEP542

Descriptive analysis of patients with Multiple Endocrine Neoplasia type 1. Experience at a tertiary hospital

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Background
Multiple Endocrine Neoplasia type 1 (MEN 1) is a genetic syndrome caused by inactivating mutations of the menin gene, which predisposes to the development of endocrine tumors. The causative mutations, clinical manifestations, and age of tumor development are highly variable. The objective of this study is to describe the characteristics of patients with MEN1 in our hospital.
Material and methods
We performed an observational, descriptive, unicentric study of patients diagnosed with MEN1 followed in the Department of Endocrinology of La Paz University Hospital in the last 10 years. Results of categorical variables were expressed in absolute or relative frequencies and those of continuous variables in mean and standard deviation.
Results
Eleven patients (7 women/4 men) with an average age of 39.4±16.0 years old were diagnosed with MEN1. Eight patients (72.7%) were the index case, and the other three were diagnosed during genetic screening. 63.6% of the patients had other affected relatives. Patients of the same family, who expressed the same mutation, differed in the clinical presentation. The most common manifestation was primary hyperparathyroidism (PH), which appeared in all the patients. The age at diagnosis of PH was 38.3±15.1 years and was the first manifestation in two patients. After surgery (subtotal parathyroidectomy or total parathyroidectomy with forearm auto-implantation), 63.6% of patients were cured, 18.2% developed transient hypoparathyroidism, and 27.3% permanent hypoparathyroidism. 81.8% of patients had pancreatic neuroendocrine tumors (pNET) (45.5% non-functioning pNET, 9.1% concomitant insulinoma and gastrinoma, 9.1% insulinoma, and 18.2% gastrinoma). Five patients had multifocal pNETs. pNETs were localized except for two patients, one patient with gastrinoma had lymph node metastases, and another with non-functioning pNET had liver and splenic metastases. The average age at diagnosis of pNET was 39.3±15.3 years, and it was the first manifestation in one patient. After surgery, 77.7% of patients with pNET developed insulin-dependent diabetes mellitus. 72.7% of patients had a pituitary adenoma (27.3% non-functioning adenoma, 36.4% prolactinoma, and 9.1% mixed prolactin-and-GH secreting adenoma). The average age at diagnosis of pituitary adenoma was 31.5±11.8, being the first clinical presentation in three patients. Other manifestations were an adrenal adenoma in three patients, lipomas in two patients, and thymoma in one patient.
Conclusions
It is a small but representative cohort of patients with MEN1. Our results are similar to those described in the literature. Thymoma is an atypical presentation rarely reported in MEN1 and was present in one patient of our cohort.

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AEP543

Pituitary apoplexy secondary to anticoagulation for pulmonary thromboembolism

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Introduction
Pituitary apoplexy (PA) consists of acute infarction/hemorrhage of the gland, involving mostly a previously unrecognized adenoma. One of its most documented precipitating factors is anticoagulation in the context of acute coronary syndrome treatment. To our knowledge only one report described a PA secondary to anticoagulation for pulmonary thromboembolism.
Case report
A 75-year-old men with known hypertension was hospitalized for bilateral pulmonary thromboembolism. At D2 of enoxaparin, complained of a sudden, strong, frontal headache. Pituitary-MRI confirmed a heterogeneous, T1-hyperintensive lesion of 28x22x26mm compatible with apoplexy. Analytical study showed hypogonadotrophic hypogonadism, high ACTH, hypercortisoluria, hypokalemia. The patient noticed tiredness, weight gain, and erectile dysfunction for 6 months, but there were no Cushing stigmata. It was decided a conservative management. At first month revaluation potassium and ACTH normalized. After three months pituitary imaging showed involution of the lesion and there were no other deficits. One year later developed hypercortisolism.
Conclusion
Considering the high prevalence of undiagnosed pituitary adenomas, physicians must be alert for risk factors for PA such as anticoagulation, used in multiple pathologies. Case reports in the context of pulmonary embolism are rare. Our case highlights the need to be aware of this emergent problem in order to prevent further complications.

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AEP544

30-year postoperative course of invasive prolactinoma in a male patient

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Most of prolactin secreting tumors excellently respond to low doses of dopamine agonists (DAs). However, management of giant, invasive prolactinomas, partially or completely resistant to DAs is a challenge. Male patient was referred to endocrinologist in 2008, at the age of 63 years, presented with headaches, pressure sensation behind the left eye, decreased vision and fatigue for the last 2 months. In 1986 (at the age of 40 years) blurred vision had appeared for the first time and pituitary macroadenoma (prolactinoma) with endo-supra-infra-laterocellar growth was revealed. Decreased libido had started earlier. In 1986 partial adenomectomy with subsequent gamma radiation therapy were performed. For 6 years after this treatment he received bromocriptine (BRC), L-thyroxine and testosterone with no signs of tumour remnant growth. In 1993 he had discontinued BRC, had no complaints and was lost to follow-up until 2008. At examination in 2008 gynoid type of obesity (BMI 39 kg/m2) and pronounced hyperprolactinemia with prolactin (PRL) level of 66928 mU/l (ULN 360) were revealed. Macroprolactinemia was excluded. Pituitary MRI showed adenoma 38ґ41ґ40mm with intrasellar and left paracellar growth, invasion to sphenoid sinus, infratemporal space and cavernous sinus, surrounding left carotid artery. Considering location and extension of pituitary mass repeat surgery was not recommended, and cabergoline (CAB) was started from 0,5 mg/week with stepwise dose increase. Under CAB treatment at increasing dose up to 3 mg/week PRL reduction from 66928 (ULN 360) to 1554 (ULN 407) mU/l was achieved by 2009. Pituitary MRI in 2010 showed a reduction of adenoma size to 29x27x25mm with signs of invasion. Unfortunately, further increase of CAB doses up to 5-7 mg/week along with correction of hypopituitarism was not effective. PRL level had increased up to 122000-172200 mU/l (ULN 407). Stereotactic radiation therapy in 2012, 2014 had also failed to stop further growth of macroadenoma (up to 86x43x55mm) with orbital invasion, compression of the left optic nerve and progressive visual deterioration. Patient had died in 2016. This case emphasizes the necessity of the permanent follow-up with continuous, usually lifelong administration of DAs in patients with macroprolactinomas after non-radical pituitary surgery. Initiation of CAB demonstrated dramatic (about 49 times) reduction of PRL level and positive MRI changes even in a patient with invasive giant prolactinoma. On condition of uninterrupted DAs treatment it would probably be possible to control hyperproplactinemia, improve patient's quality of life, to prevent further growth of residual tumour, development of CAB resistance and visual impairment.

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AEP545

Postoperative central diabetes insipidus after transsphenoidal adenomectomy in patients with Cushing's disease

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Purpose
Postoperative central diabetes insipidus (PCDI) is one of the complications of transsfenoidal adenomectomy (TSA) in patients with Cushing's disease. Identification of predictors of PCDI development and clinical course could optimize the management of such patients.
Aim
To study the prevalence of PCDI in patients with Cushing's disease after transsphenoidal adenomectomy and to find the risk factors of its development.
Methods
Medical histories of 116 patients with Cushing's disease were retrospectively analyzed. All patients underwent TSA in Almazov Centre during the period from January 2016 to December 2018. 111 patients were operated on initially, and five were re-operated. Clinical, preoperative MRI images and histology data were studied.
Results
Among 116 patients PCDI developed in 25 (22%) cases (23 women (92%)). Eighteen patients (72%) had transient form of the disease, and seven (28%)-permanent. In two cases (8%) triphasic DI was confirmed. Adenoma size and localization did not differ in patients with and without PCDI. In 9 patients without PCDI and 8 patients with PCDI the presence of neurohypophysis tissue was confirmed by histological examination of the removed sample. Among 111 initially operated patients PCDI developed in 23 (20,7%), among five re-operated patients – in two (40%). Need for desmopressin therapy for 6 months or more indicated the permanent form of the disease. The average dose of desmopressin in patients with transient form of the disease was 120 mcg (min 30 mcg; max 240mcg). The average dose of desmopressin in patients with permanent PCDI was 210 mcg (min 60 mcg; max 360mcg).
Conclusion
The prevalence of central diabetes insipidus after TSA among patients with CD is high and amounts to 22%. In most cases the form of the disease is transient. Repeated surgery is the risk factor of PCDI development. The need for high doses of desmopressin increases the likelihood that diabetes insipidus will be permanent. The need for desmopressin therapy for 6 months or more indicates a permanent form of the disease.

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AEP546

A double-blind, randomized, placebo-controlled trial of SPI-62 safety and efficacy for the treatment of Cushing's syndrome

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11ṕhydroxysteroid dehydrogenase type 1 (HSD-1) controls the intracellular cortisol pool that has access to cytosolic glucocorticoid and mineralocorticoid receptors. HSD-1 activity is elevated in patients with Cushing's syndrome (CS).1 Patients with CS and constitutionally low HSD-1 activity showed no hypercortisolism-related symptoms despite very high 24-hour urine free cortisol.2,3 A recent pilot trial of a HSD-1 inhibitor in patients with classical or mild CS showed positive trends on glycemic control and body habitus.4 SPI-62 is a potent, selective HSD-1 inhibitor. In four prior clinical trials once-daily SPI-62 dosing, without titration, was associated with few adverse events and substantially reduced intracellular cortisol.5-7 We have shown that in a double-blind, randomized, placebo-controlled, 6-week pilot trial in subjects with diabetes, SPI-62 was associated with clinically meaningful decreases on HbA1c, glucose, cholesterol, and triglycerides. Adult patients with ACTH-dependent CS will be randomized to receive SPI-62 followed by placebo, or placebo followed by SPI-62, in an upcoming international, multicenter clinical trial. Patients with urinary biomarker of HSD-1 activity (allotetrahydrocortisol + tetrahydrocortisol)/tetrahydrocortisone $\geq$ 1 will be eligible. Patients with recent radiation therapy or surgery, or planned surgery, for CS, and patients with pseudo-CS, cyclic CS, or exogenous CS will be excluded. Medical therapy for CS will be subject to washout before randomization, while medications intended to treat specific symptoms and comorbidities (except glucocorticoid or mineralocorticoid receptor antagonists) will be continued on stable regimens. Efficacy will be assessed based on glycemic control, body habitus, blood pressure, blood lipids, bone biomarkers, mood, cognition, and quality of life. Safety will be reported for all subjects who receive at least one dose of study drug and will include hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axis monitoring. This will be the first randomized placebo-controlled trial of a HSD-1 inhibitor in the treatment of CS.

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AEP547

Long-term survival in a patient with corticotroph pituitary carcinoma and brain metastases

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Background
Pituitary carcinoma (PC) is a very rare clinical entity, which is defined as a pituitary tumor that has metastasized to sites distant from the pituitary. It may present as hormone-secreting, invasive and recurrent macroadenoma causing a mass effect.
Case presentation
We present a 58-years old male patient with corticotroph pituitary carcinoma and brain metastases who underwent 9 neurosurgical interventions, radiotherapy and chemotherapy with temozolomide. In 1995 a non-functioning pituitary macroadenoma impinging the optic chiasm and causing visual filed defects was visualized on MRI. First debulking transcranial surgery was performed in 1995 and led to improvement in visual field but was complicated by anterior pituitary deficiency and diabetes insipidus. In 2006 a significant regrowth of a tumour was noted. The patient was again operated in 2006 and then due to aggressive tumor growth he required further debulking surgeries in 2007, 2008, 2009, 2010 and 2011. In 2012 ACTH-dependent Cushing syndrome was diagnosed and the patient was administered ketoconazole but long-term therapy was impossible because of the toxic liver injury. In 2013 stereotactic fractionated radiotherapy (5400 cGy/g) was applied and allowed for tumour size reduction and remission of hypercortisolemia. Despite clinical improvement, in 2014 routine pituitary MRI showed 3 brain metastases. Further imaging studies,i.e. 18-FDG PET/CT and somatostatin receptor scintigraphy were performed revealing increased radiotracer uptake only by a residual pituitary tumor mass. Transcranial biopsy from a lesion in the parietal lobe confirmed metastasis of corticotroph pituitary carcinoma. Pathology report from the next transcranial pituitary surgery in 2015 confirmed a highly proliferative Crooke cell corticotroph adenoma (ACTH (+) p53 >30%, Ki-67>5%, MGMT<5%). Subsequently, radiosurgery (gamma-knife) of 3 metastatic lesions was applied and temozolomide in a dose of 400mg/day for 5 days, 14 cycles in total, was initiated achieving stabilization of the disease. In 2017 MRI showed progression of the tumor requiring next transsphenoidal surgery and new brain metastases. Gamma-knife radiotherapy was performed again in 2019 to brain metastases and consecutive pituitary neurosurgery in 2020. Due to deteriorating symptoms of hypercortisolemia and positive response to short-acting pasireotide test, pasireotide LAR has been initiated in 2020.
Conclusions
The management of PC is challenging, requiring a multimodal approach using repeated neurosurgeries, radiotherapy and chemotherapy. Despite the usually described in the literature poor prognosis in PC, this multimodal management may lead to long-term survival, even 7 years as in presented case.

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AEP548

Clinical features and pituitary function in primary empty sella syndrome

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Introduction
Empty sella syndrome (ESS) is a rare condition in which the sella turcica is partially or completely filled with cerebrospinal fluid. ESS can be classified as primary or secondary, depending on the identification of underlying etiologies. Whether empty sella has any functional implications in causing pituitary hormonal disturbances needs to be understood. The aim of our study was to assess the incidence of pituitary hormonal disturbances in patients with ESS and to determine any association between empty sella and these hormonal abnormalities.
Methods
We report a retrospective study of 46 cases of ESS collected in the endocrinology department over the period from 1991 to 2020. The clinical and biochemical profile of ESS patients was analyzed.
Results
Our study included 46 cases with a male: female ratio of 1:3.5 suggesting female predominance. The mean age of our patients was 50.4 years (21-81 years). The frequency of primary ESS among ESS was 70% in our series. Headache was the most frequent reason for consultation, 66.67%. Obesity was noted in 20% and multiparity in 62%. On the endocrine examination, anterior pituitary insufficiency was found in 58% of cases and hyperprolactinemia in 14% of cases. Finally, 0.5% of our patients showed central diabetes insipidus. Hormone deficiency substitution was preconized. The evolution was marked by the persistence of signs of anterior pituitary insufficiency in 13% of cases and headaches with visual disorders in 48.2% of cases. The comparative study concluded that failure of lactation in the postpartum period was found to be significantly correlated with hormonal dysfunction (p=0.046). The presence of headache is significantly associated with the absence of hormonal impairment in patients with primary ESS (p= 0.01).
Discussion-conclusion
The primary empty sella syndrome is of increasing interest due to frequent radiological exploration of the sellar region using mainly MRI. It is important to consider this syndrome in front of an obese, multiparous woman with headaches, and to carry out an exhaustive hormonal and radiological exploration in order to detect hormonal deficiencies.

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AEP549

Primary lymphocytic hypophysitis diagnosed during pregnancy: Case report

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Primary lymphocytic hypophysitis is an autoimmune endocrinopathy affecting mainly women during pregnancy and psot-partum. We report the observation of a 28 year old patient, G5P2C2 with a progressive pregnancy at 32 SA, with a history of hypertension without any particular familial history. The patient had an ophthalmologic examination as part of the exploration of the repercussions of hypertension, which objectified an abnormal excavation of the left eye at the fundus examination supplemented by a visual field that found complete narrowing of the left eye and temporal hemianopsia of the right eye. A pituitary MRI without injection found an intra-selar mass with supra-selar extension evoking a pituitary adenoma. Clinical examination was without particularity, apart from headaches, On the hormonal level, a slight hyperprolactinemia of about 179 ng/ml was found. In this context, the diagnosis of pituitary disease is highly likely, and the patient was put on corticosteroid therapy at a dose of 3 bolus of 120 mg of methylprednisone with a relay of prednisone at a dose of 40 mg/day. After 3 days of CTC, the control visual field returned to normal, with a disappearance of a few drops of methylprednisone. Four months postpartum, magnetic resonance imaging showed complete resolution of the pituitary mass. In total: the diagnosis of Primary lymphocytic hypophysitis must be made in an evocative context such as pregnancy and postpartum, as early as possible, to avoid an unnecessary aggressive treatment and the evolution of the pathology with a risk of hormonal repercussions, essentially corticotropic.

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AEP550

Improvements in quality of life after treatment in three acromegalic patients

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Acromegaly is a rare disease. In more than 99% of cases this is due to a benign pituitary growth-hormone secreting adenoma. This leads to changes in appearance, enlargement of the internal organs and, after a long period of time, to multiple comorbidities.
Objectives
To determine which factors might have contributed to the lower quality of life in three acromegalic patients.
Materials and methods
The patients completed a Romanian translation of Acromegaly Quality of Life Questionnaire (AcroQol) in two separate occasion, while they were re-evaluated in our clinic. All the other data were collected retrospectively, form their medical files. All three patients are female. Patient 1, aged 68 years old, was diagnosed and treated for a pituitary macroadenoma in 2013 by neurosurgery. Patient 2, aged 59 years old, was diagnosed in 2001 and was treated twice by neurosurgery (2003 and 2004) and in 2004 with Gamma Knife. Patient 3, aged 70 years old, was diagnosed with a mixt pituitary microadenoma, secreting GH and PRL, in 2001 and was treated with a dopamine agonist until 2013, when she underwent neurosurgery. All three patients are currently under treatment with a somatostatin analogue and have varying degrees of hypopituitarism for which they receive substitution therapy. Patient 2 and 3 have controlled disease and Patient 1 has partially controlled disease. Patient 1 and 3 are obese and have more than 3 comorbidities associated with acromegaly, including psychiatric disorders. AcroQoL is a disease-specific, self-administered questionnaire to asses quality of life in people diagnosed with acromegaly. It contains 22 items, divided into two scales, one evaluating physical and the other, psychological aspects (also divided in two sub-dimensions-physical appearance and personal relationships). The score varies between 0 (worst HRQol) and 100 (best HRQol).
Results and discussions
Patient 1 had a total score of 27.27 in 2017 and 48.86 in 2020. Patient 2 had a total score of 38.36 in 2017 and 56 in 2019. Patient 3 had a total score of 38.36 in 2017 and 45.45 in 2020. All three patients had the lowest score in the appearance sub-domain at the first presentation. Patient 1 had the lowest score in personal relationship sub-domain at the second re-evaluation. At the last evaluation Patient 3 had the lowest global score, while at the first presentation Patient 1 had the lowest score. In conclusions, for all these three patients the control of acromegaly improved quality of life.

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AEP551

MODY 3 and acromegaly: An improbable association treated with bromocriptine

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Introduction
Maturity Onset Diabetes of the Young (MODY) is an autosomal dominant disease, diagnosed mainly in young individuals with a strong family history of diabetes, that results from mutations impairing pancreatic β cell function. The MODY 3 subtype, caused by a HNF1α mutation, with consequent deficit in insulin secretion, is the most frequent and responds more effectively to sulfonylureas, compared to metformin. Acromegaly is a rare condition characterized by hypersecretion of growth hormone, usually by a pituitary adenoma, that leads to multiple comorbidities, including insulin resistance. There is no association described in the literature between MODY 3 and acromegaly.
Case report
A 33-year-old man, with obesity, obstructive sleep apnea and colon polyposis, with family history of MODY 3, came to an endocrinology appointment after

being diagnosed with diabetes 3 years before. He was on insulin therapy since diagnosis, with negative pancreatic β cell immunity. At the first visit we noticed an acromegalic facies, a BMI of 31.8 kg/m^2, with a suggestive history of acromegaly for about 10 years. In this context, a pituitary study was requested that revealed hGH 5.04 ng/ml (N 0.06–5.00), IGF-1 773 ng/ml (N 71.2–234), ACTH 64.0 pg/ml (N 9–52), cortisol 14.2 µg/dl (N 6.2–19.4) and prolactin 404.0 ng/ml (N 4.04–15.2). At that time, he was on insulin glargine 10 units, gliclazide 60 mg/day and metformin 2000 mg/day, with a HbA1C of 7.4%. MRI revealed a pituitary macroadenoma with deviation of the pituitary stalk. Therefore, the diagnosis of acromegaly was assumed and the patient was started on bromocriptine 10 mg/day. Insulin was suspended and gliclazide increased to 90 mg/day. In the following months, he noticed a great improvement in glycemic control, leading to self-suspension of gliclazide. Six months after, metformin had been reduced to 1000 mg/day, with a HbA1c of 6.1% and a marked decrease in IGF-1 values (279 ng/ml), with normalization of prolactin levels. One year after diagnosis the patient is still kept on bromocriptine 10 mg/day and metformin 1000 mg/day, with HbA1c of 5.7%, and with a positive genetic study for MODY 3. Considering the favorable evolution, surgical treatment was postponed.

Conclusion

It is a rare case of association of MODY 3 and acromegaly. Bromocriptine therapy allowed a clear improvement of tumor secretion and glycemic control, highlighting the role of insulin resistance in the presented case.

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AEP552

A complex case of refractory hypercalcaemia, end-stage diabetic nephropathy with pituitary mass and hypopituitarism– is there a unifying diagnosis?

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A 54-year-old female presented with one week of weakness, fatigue, headache, worsening constipation, and general malaise. Background history included long-standing type 1 diabetes (glutamic acid decarboxylase positive), on continuous subcutaneous insulin infusion, proliferative diabetic retinopathy, end-stage diabetic nephropathy on haemodialysis and subclinical hypothyroidism. Tertiary hyperparathyroidism was diagnosed (adjusted calcium 2.82 mmol/l, phosphate 1.42 mmol/l, parathyroid hormone 62.6 pmol/l (RR 1.6–6.9)). Calcium level had been controlled prior to admission on Cinacalcet 90 mg and alfacalcidol 0.5micrograms daily. The patient deteriorated, becoming progressively drowsy with frequent hypoglycaemia, despite insulin downtitration. Calcium levels further increased. Etelcalcetide, pamidronate and denosumab were all implemented as treatment. However, worsening hypercalcaemia (corrected Calcium 3.78 mmol/l, ionised calcium 1.91 mmol/l) warranted transfer to the Intensive Care Unit for continuous veno-venous haemodialysis. Computed tomography of brain, thorax, abdomen and pelvis identified no cause for hypercalcaemia. Following positive parathyroid imaging, a three-gland parathyroidectomy with implantation of the 4th gland was undertaken on day 34 of admission for refractory hypercalcaemia. Histology was consistent with parathyroid hyperplasia. Postoperatively, episodes of fluctuating cognition, ongoing headaches, nausea, hypotension, and hypoglycaemia prompted Magnetic Resonance Imaging (MRI) of the brain (Gadolinium contrast contraindicated due to end-stage kidney disease). This revealed an enlarged pituitary gland extending into the suprasellar space, with thickening of the pituitary stalk, new from MRI two years prior. Visual field testing did not reveal hemianopia. Hypopituitarism was subsequently diagnosed: cortisol 32 nmol/l, adrenocorticotropic hormone 17 ng/l, TSH 0.02 miu/l, free T4 10.7 pmol/l on L-thyroxine 50 micrograms, estradiol <92 pmol/l, follicle stimulating hormone 1.8 IU/l, luteinizing hormone <0.5 IU/l. Intravenous hydrocortisone resulted in symptom resolution within days. Positron emission tomography showed no abnormal tracer uptake in the pituitary gland or elsewhere. IgG4 level was normal at 0.344 g/l. Cerebrospinal fluid and serum angiotensin converting enzyme levels were raised at 3.6 U/l (0.5–2) and 79 U/l (8–65) respectively. Quantiferon study was indeterminate. Following multidisciplinary conference discussion, surgery was felt not to be indicated. Pituitary biopsy was not undertaken. MRI eight months later showed pituitary gland normalisation. Adrenal insufficiency (AI) remains. This case highlights the importance of maintaining a high index of suspicion for unusual diagnoses when met with puzzling clinical scenarios. While limited by lack of contrast-enhanced MRI and absence of tissue diagnosis, we believe that the pituitary mass, hypopituitarism and hypercalcaemia were related to the same disease process, likely a hypophysitis, given its resolution on follow-up imaging. AI symptoms are non-specific, and AI remains an important diagnostic consideration.

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AEP553

A rare case of panhypopituitarism and diabetes insipidus secondary to sarcoidosis

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Introduction

Sarcoidosis is a multisystem disorder, characterised by the presence of non-caseating granulomas. 5–13% of cases involve the nervous system. Neurosarcoidosis carries a poor prognosis and can lead to an infiltrative process in the hypothalamo-hypophyseal region, resulting in panhypopituitarism and central diabetes insipidus (DI). These are rare but serious complications of neurosarcoidosis.

Case

A 26-year-old female with no past medical history was found unresponsive at home. While being transported to hospital in an ambulance she suffered a cardiac arrest. She was treated with two minutes of CPR and one shock for ventricular fibrillation. On arrival to the emergency department she was intubated, ventilated and admitted to ICU. Initial biochemical evaluation revealed deranged electrolytes: potassium 2.4 mmol/l, sodium 124 mmol/l and magnesium 0.68 mmol/l. ECG was abnormal with a prolonged QTc of 535ms. A collateral history revealed amenorrhoea, weight-loss and fatigue over the preceding 6 months. Pituitary hormonal evaluation prior to treatment was consistent with panhypopituitarism: thyroid-stimulating hormone: 0.29 miu/l, free-thyroxine: 9.8 pmol/l, ACTH: <2 n g/l, IGF1: 34 mg/l, oestrodiol: <92 pmol/l, FSH: <0.5 iu/l, with an inappropriately normal cortisol (331 nmol/l) for the concurrent illness. Following admission she developed polyuria of 10 litres/24-hours and repeat biochemistry testing revealed a fast rise in sodium to 141 mmol/l. DI was diagnosed based on evidence of significant polyuria, rapidly rising sodium and clinical improvement with a combination of frequent subcutaneous and oral desmopressin with IV hydrocortisone. Initial CT imaging revealed diffuse infiltrations in the liver and spleen. Liver biopsy confirmed non-necrotising granulomatous inflammation. Lumbar puncture showed elevated protein of 716 mg/dl. MRI-brain demonstrated thickening of the meninges, particularly enhancement of the pachymeninges around the skull base and pituitary infundibulum, in keeping with neurosarcoidosis. MRI-cardiac revealed increased intensity in the myocardium, consistent with sarcoidosis. CT-PET confirmed active sarcoidosis in the liver and spleen. Following a diagnosis of multisystem-sarcoidosis with panhypopituitarism and central-DI, treatment was initiated with intravenous corticosteroids, hormonal supplementation (desmopressin, levothyroxine) and immunosuppression (methotrexate, infliximab). An ICD was inserted for the prevention of sudden cardiac death. Over the following weeks she demonstrated a positive response to treatment with improved energy levels, normalization of electrolyte and hormone levels and resolution of polyuria.

Conclusion

Panhypopituitarism and central DI secondary to neurosarcoidosis is a rare clinical manifestation that should be considered in patients presenting with symptoms of neuroendocrine dysfunction. Immediate treatment with desmopressin, corticosteroids, thyroxine and immunosuppressants can prevent rapid decline and loss-of-life.

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AEP554

Assessment of a developmental neurotoxicity test using Ki-67 in ReNcell CX cells

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Ki-67 can be solely detected within the cell nucleus, whereas in mitosis, most of the Ki-67 proteins are located on the chromosome surface. Ki-67 is present during all phases of the cell cycle (G1, S, G2, and M), but BrdU

is only present in the S phase. This study examined whether it is possible to establish a developmental neurotoxicity test in human neural progenitor cells using Ki-67 instead of BrdU (5-bromo-2'-deoxyuridine). In the present study, Ki-67-expressed ReNcell CX cells, a human neural progenitor cell line, were evaluated as a marker of proliferation in neurotoxicity, compared to propidium iodide (PI) and BrdU. ReNcell CX cells were treated with developmental neurotoxic chemicals (aphidicolin, hydroxyurea, cytosine arabinoside, 5-fluorouracil, and ochratoxin A) or non-neurotoxic chemicals (sodium gluconate, sodium bicarbonate, penicillin G, and saccharin). The PI-positive cell numbers were increased in neurotoxic chemicals (10^{-4} and 10^{-5} M), and non-neurotoxic chemicals (1 and 10^{-2} M) compared to the control, whereas the number of BrdU-positive cells decreased when exposed to the neurotoxic chemicals (10^{-4} and 10^{-6} M) and non-neurotoxic chemicals (1 and 10^{-2} M). Furthermore, the number of Ki-67-positive cells decreased when exposed to high doses of neurotoxic chemicals (10^{-4} and 10^{-6} M) compared to non-toxic chemicals (1 and 10^{-2} M). On the other hand, the number of Ki-67-positive cells decreased when exposed to non-neurotoxic chemicals at high doses (1 and 10^{-2} M). Furthermore, there was no difference in the results of BrdU and Ki-67, suggesting that Ki-67 could be used as a proliferation marker instead of BrdU in ReNcell CX cells

Keyword: Ki-67, ReNcell CX, PI, BrdU.

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AEP555

Abberant expression pattern of circadian clock genes in Type 1 gastric neuroendocrine neoplasms compared to ECL hyperplasia

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Purpose

There is a continuity of changes ranging from enterochromaffinlike (ECL) cell hyperplasia to type 1 gastric neuroendocrine neoplasms (GNEN1) with important clinical implications. Although the effect of the circadian clock system on tumorigenesis has been addressed, the role of the peripheral clock system in the transition from ECL-cell hyperplasia to GNEN1 remains to be explored.

Methods

Six patients diagnosed with GNEN1 and 10 patients with ECL-cell hyperplasia were included. Blood samples were collected at 0800 h, 1500 h and 2000 h for peripheral blood mononuclear cells (PBMCs) isolation. The mRNA expression of Clock-related genes (CLOCK, BMAL1, CRY-1, PER-2 ROR-α and REV-ERBbeta) were evaluated by real-time quantitative PCR from PBMCs.

Results

In patients with GNEN1, BMAL genes where lower expressed at night than early in the morning *(P* = 0.02), whereas patients with ECL-cell hyperplasia expressed lower transcript levels of PER2 and REV-ERB beta at these time points *(P* = 0.03, *P* = 0.05, respectively). In addition, patients with GNEN1 expressed lower transcript levels of CLOCK, PER2 and REV-ERB beta in the early evening than in the morning *(P* = 0.04; *P* = 0.03; *P* = 0.05, respectively). When comparing the two groups (GNEN1 vs ECL-cell hyperplasia) at the three different time points, we confirmed a marginal increase in CLOCK, PER2 and REV-ERB beta expression early in the morning *(P* = 0.06, 0.02 and 0.07, respectively); a marginal increase in REV-ERB beta expression in the early evening *(P* = 0.09) and a marginal increase in BMAL at night *(P* = 0.09) in patients with GNEN1.

Conclucions

Our findings point towards an uregulated expression of Clock-related genes in patients with GNEN1 as compared to EC-cellL hyperplasia, suggesting a possible involvement in GNEN1 tumorigenesis.

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AEP556

Value of cross- sectional area of the median nerve in acromegalic patients

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Introduction

Median nerve neuropathy is commonly associated with acromegaly.

Objective

This study aims to investigate ultrasound examination of median nerve in acromegalic patients and assess the relationship with activity and duration of disease.

Patients and methods

We prospectively examined the cross sectional area (CSA) of median nerve with high-resolution ultrasound in 107 acromegalic patients (70 females and 37 males) and in 77 healthy controls (51 females and 26 males) matched for age, gender. The t-student tests and Pearson correlation were used for data analysis.

Results

The cross sectional area of median nerve was increased in acromegalic patients compared with controls (11.9 ± 0.5 mm^2 vs 7.8 ± 0.3 mm^2, $P < 0.001$). The average level of IGF-1 in acromegaly patients was ø 249,9ng/ml and for GH was ø 2,63 ng/ml. Positive correlation between was found the levels of IGF-1 and CSA in whole study group ($R = 0.400$, $P < 0.001$) and female population ($R = 0.466$, $P < 0.001$). In male population our results did not reach statistical significace ($P = 0.07$). Relationship between CSA and duration of acromegaly in both genders was not confirmed.

Conclusion

In our study we confirmed the enlargement of the median nerve in acromegaly patients. This enlargement is proportional to the degree of IGF-1 levels and is not dependent on the duration of the disease and age of patients.

Keywords: acromegaly, carpal tunnel syndrome, cross sectional area, median nerve.

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AEP557

Response to treatment with temozolomide in cases with invasive pituitary macroadenomas: A single-center experience

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Introductıon

Recent studies suggest temozolomide as an effective treatment modality in invasive pituitary adenomas that did not respond to conventional treatments. In this case series, we present three cases of invasive pituitary adenomas that did not respond to conventional medical treatments and radiotherapy and were subsequently treated with temozolomide.

Cases

The first patient had an invasive prolactinoma that did not respond to the maximum doses of cabergoline, the patient underwent trans-frontal surgery and conventional radiotherapy. On immunohistochemical staining, methylguanine DNA methyltransferase (MGMT) was negative. The treatment with temozolomide 150 mg/m^2 for five days every 28 days was started. Three and 20 months later, a significant decrease in prolactin level and a 50 and 95% decrease in tumor size were observed, respectively, and remained unchanged after five years of treatment. The second patient with acromegaly that could not be controlled by 2 transsphenoidal surgeries, conventional radiotherapy, and 40 mg octreotide LAR. Treatment with 150 mg/m^2 of temozolomide for five days every 28 days was started. However, despite a small decrease in serum IGF-1 and GH levels, a reduction in tumor size did not ensue. The third patient had a non-functioning pituitary adenoma and underwent 2 transsphenoidal and one transcranial surgery and subsequent gamma knife radiosurgery, she developed 3. and 6. cranial nerve palsies, so temozolomide treatment was started at a dose of 150 mg/m^2 for five days every 28 days. However, temozolomide treatment was

discontinued due to the absence of response after 3 months. Nevertheless, MGMT immunostaining was not performed in both cases.

Dıscussıon

Studies suggest temozolomide treatment as an effective treatment modality in invasive pituitary adenomas non-responsive to currently available conventional treatments. However, most of the information regarding the effect of temozolomide in invasive non-functional adenomas and GH secreting adenomas are sparse. Low tumoral expression of MGMT was suggested as a sign of favorable response to temozolomide. Although most GH-secreting adenomas are reported to express low levels of MGMT, our patients with acromegaly did not respond to temozolomide treatment. On the other hand, the patient with non-functioning pituitary adenoma did not respond to temozolomide as well. Therefore, temozolomide treatment may not be effective in cases with acromegaly and non-functioning invasive pituitary adenomas.

Patient	Age/ Gender	Diagnosis	Tumor size (mm)	Temozolomide treatment duration (months)	Response
1	38/M	prolaktinoma	58 × 47	18	complete
2	44/F	acromegaly	85 × 45	6	none
3	50/F	null-cell adenoma	50 × 28	3	none

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AEP558

Hypopituitarism secondary to a pituitary metastasis as a first manifestation of an invasive nasopharyngeal carcinoma

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Introduction

Nasopharyngeal carcinoma is characterized by distinct geographical distribution and is particularly prevalent in East and Southeast Asia. Environmental factors, genetic structure, and Epstein Barr virus infection are involved in the etiology of the disease. While nasal and otological symptoms are the most common (80%), intracranial extension is prevalent among 8% of cases and pituitary localization is rarely described in the literature. We report the rare case of a patient in whom the diagnosis of nasopharyngeal carcinoma was mislead by its pituitary extension.

Observation

A 50-year-old woman was referred to our department for pituitary macroadenoma. Her past medical history was unremarkable. She presented with headache, visual disorders, weakness, nausea, vomiting, and increased episodes of hypoglycemia. No polyuria was reported. Pituitary MRI showed a large mass extending from the sella turcica to the sphenoid sinus, optic chiasm, and nasopharynx. The first diagnosis was an extending pituitary macroadenoma. On physical examination, she had a body weight of 51 kg, a body mass index of 21.7 kg/m^2, a blood pressure of 100/60 mmHg, a regular pulse of 80 beats/mn. Biological investigations revealed corticotrope deficiency, secondary hypothyroidism, hypogonadotropic hypogonadism, and hyperprolactinemia (31 ng/ml). The patient was put on hormone replacement therapy. After corticosteroid treatment initiation, a diabetes insipidus was revealed. The second MRI showed a nasopharynx infiltration. Endoscopic biopsy confirmed the diagnosis of undifferentiated nasopharyngeal carcinoma (NPC) with intracranial extension. The patient was referred to oncology department for chemo and radiotherapy.

Conclusion

Although pituitary metastasis is a rare condition, it should be a part of the differential diagnosis of pituitary macroadenoma with hypopituitarism. The management of this case necessitates a multidisciplinary approach.

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AEP559

A rare case of panhypopituitarism secondary to neurosarcoidosis initially treated as sepsis of unknown origin

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Sarcoidosis is a very rare inflammatory disease and UK prevalence was 8% between 2008 to 2012 of which only 15 % developed neurosarcoidosis. Our patient is a 83 year old gentleman who presented with symptoms of lethargy,low blood pressure and confusion over 2 weeks . He had multiple comorbidities including heart failure , chronic kidney disease ,permanent pacemaker , hypertension. His bloods showed normocytic anaemia and raised inflammatory markers , with eosinophilia and he was started on broad spectrum antibiotic but his condition continued to deteriorate . There was no evidence of infection. He had mild postural hypotension probably due to his comorbidities. His free thyroxine was low with inappropriately low normal TSH. He was commenced on thyroxine and his conscious levels dropped. Therefore cortisol level were checked, which were low therefore followed by full pituitary profile , and short synacthen test . Pituitary profile revealed low FSH , LH , IGF-1, testosterone in keeping with panhypopituitarism.Results of short synacthen test were inadequate suggesting a central cause. He also had CT scan of brain which was unremarkable. He later had CT pituitary as MRI was not compatible due to pacemaker but no significant abnormality was found . His autoimmune screen for vasculitis showed weakly positive p-ANCA. He was reviewed by neurology team and lumbar puncture was done which did not show any CNS infection but raised CSF-protein and CSF-ACE level . He also had high normal serum ACE level , raised calcium and peripheral eosinophilia . He was started on intravenous hydrocortisone 100 mg QDS and patient's conscious level and general condition improved remarkably. His hydrocortisone was changed to oral prednisolone 30 mg daily and confusion settled and mobility improved slowly over the next 2 weeks. The steroids were slowly weaned down to maintenance dose of 5 mg. The low dose levothyroxine was continued and he remains well on 5 mg prednisolone and 75 microgram of levothyroxine . Pan-hypopituitarism secondary to neurosarcoidosis is a rare manifestation and was considered in this patient but he was not suitable for tissue diagnosis due to comorbidities. We were unable to get MRI to see infiltration but clinical improvement with steroids and investigations-higher end of normal serum ACE levels ,raised CSF-ACE levels, eosinophilia and raised calcium are all in keeping with clinical diagnosis of neurosarcoidosis . Neurosarcoidosis can also present without pulmonary involvement and prompt diagnosis and treatment is life saving.

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AEP560

Treatment patterns, healthcare utilization and related costs of acromegaly in a real-world setting in finland

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Introduction

Acromegaly is a chronic disease associated with multiple comorbidities and increased incidence of cancer and mortality. The diagnosis often takes several years after the onset of symptoms. The costs of acromegaly in Finland are not known. This study aimed to characterize the treatment patterns, healthcare resource utilization, and direct costs of acromegaly in Finland.

Methods

All adult (≥18 years of age) patients with first acromegaly (ICD-10: E22) diagnosis during 2010–2016 were identified from the electronic health records (EHR) of Helsinki and Tampere University Hospitals. The EHR data were complemented with data from the national Finnish patient registers. The study period was 2010–2019, which covered a two-year baseline period prior to, and a three-year follow-up period after the diagnosis of acromegaly.

Results

The cohort consisted of 63 newly diagnosed patients with acromegaly (37 male/26 female) with a mean age of 47.6 years. Altogether, 75% (30/40) of the patients with baseline information on tumor size, had a macroadenoma, and the median growth hormone (GH) and insulin-like growth factor-1 (IGF-1) values at diagnosis were 248% and 263% of the upper limit of normal (ULN), respectively. The most common comorbidities were hypertension (37%), sleep apnea (24%) and arthropathy (19%). The participants had on an average nine follow-up healthcare visits annually (range 1–21), approximately 2.8 months apart. Transsphenoidal surgery was the most common first-line treatment (75%). First-line pharmacotherapies were somatostatin analogues

(12% as monotherapy, 3% in combination with surgery), and dopamine agonists (7% as monotherapy, 2% with surgery). IGF-1, GH, and prolactin levels decreased gradually after the treatment initiation. Of the patients with a minimum 12 months of follow-up, 48% (24/50) reached a GH level <2,5 µg/l after 6 months of treatment initiation. The mean total annual cost was 10,500ń of which 69% (7,200ń) were related to healthcare resource utilization and 31% (3,300ń) to pharmacotherapy. The healthcare resource utilization cost was highest during the first year after the diagnosis (12,500ń), while annual pharmacotherapy costs increased gradually after the diagnosis.
Conclusions
The baseline patient demographics are in line with previous data from France and Sweden. In Finland, a vast majority of patients undergo surgery as first-line treatment. Approximately two-thirds of the total costs were related to healthcare resource utilization and one-third to pharmacotherapy.

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AEP561

A growth retardation revealing a pituitary stalk interruption syndrome: A case report

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Introduction
Pituitary stalk interruption syndrome is an entity radiologically defined by the association of an absent or thin pituitary stalk, an ectopic posterior lobe and a hypoplasia or aplasia anterior lobe. It can manifest as a several of hormonal deficiencies. The circumstances of discovery are multiple. This case illustrates a pituitary stalk interruption syndrome revealed by a growth retardation.
Case presentation
An 11-year-old child consulted for a growth retardation. The diagnosis of complete growth hormone deficiency was retained. He was put on somatropin until the age of 18. The patient did not present a polyuria polydipsia syndrom. The examination found a height of 1 m 63 between –3 and –2 standard deviations, with a target height of 1 m 71. The external sexual organs were infantile masculine type, the penis was 6 cm, and testicles were lower size 2cm with a Tanner stage G1P2A1. His bone age was 13 years and 6 months with a chronological age of 19 years. Hormonal exploration showed a normal thyroid hormone assesment, intermediary cortisol level 240 mmol/l. He benefited from an insulin hypoglycemia test showing a cortisol peak at 394 nmol/l confirming corticosteroid insufficiency. Exploration of the gonadotropic axis showed low testosteronemia at 0.09 ng/ml (N: 0.5–5), normal FSH and LH levels at 2.32 and 0.72 miu/l respectively confirming a gonadotropic insufficiency. The patient was treated with hydrocortisone at a dose of 10 mg daily. Induction of puberty was initiated by testosterone enanthate at a dose of 62.5 mg in one monthly injection and then gradually increasing the dose to 250 mg per month. The evolution was marked by a clear improvement with a Tanner stage G2P3A3.
Conclusion
Pituitary stalk interruption syndrome is one of the etiologies of hypopituitarism. It is a congenital and progressive pathology. The earlier the diagnosis is made, the better the prognosis, especially in terms of growth, which has a significant psychological impact. Hence the importance of early diagnosis of this entity as well as regular monitoring of the pituitary gland assessment in order to treat any deficiency in time.

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AEP562

Cognitive impairment, obesity, and hypopituitarism - several entities or one syndrome?

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Introduction
Prader-Willi syndrome (PWS) is a multisystemic genetic disorder caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region. Despite PWS present manifestations from birth, affected individuals can remain undiagnosed until adulthood.
Clinical case
Woman, 40 years old, with cognitive impairment, referred to endocrinology due to morbid obesity (BMI 44.5 Kg/m^2). Despite being followed in a Nutrition consultation, she was unable to comply with the food plan, due to insatiable appetite and food voracity that was difficult to control. She had a previous diagnosis of hypothyroidism and was under levothyroxine (LT4) 100 µg id. She reported menarche after the age of 20 and oligomenorrhea. She also had occasional episodes of asthenia, lethargy, and hypothermia, with no defined etiology, especially when she had respiratory infections, in winter. A previous brain CT revealed an empty sella. On physical examination, she had short stature (1.51 m), characteristic facies (almond-shaped eyes, thin upper lip, lip inversion), small hands and centripetal obesity Analytically, she had TSH 1.24 (N 0.358–3.74) µUI/ml, free-T4 1.42 (N 0.76–1.46) ng/dl, under LT4, negative anti-TPO and anti-Tg antibodies, ACTH 23.0 pg/ml, morning cortisol 5.69 µg/dl, PRL 17.05 (N 2.8–26.0) ng/ml, IGF-1 52 (N 76–271) ng/ml), estradiol 215 pmol/l, LH 2.55 mUI/ml, FSH 3.02 mUI/ml and HbA1c 5.3%. Pituitary MRI showed a small pituitary gland. The diagnosis of hypopituitarism was established, and she started prednisolone 5 mg/day (in addition to LT4). After the introduction of the glucocorticoid, the patient did not have episodes of lethargy and hypothermia again and her general condition improved significantly. A genetic study was carried out by suspicion of PWS, which was confirmed. Along with a progressive weight gain, she developed type 2 Diabetes *mellitus*, being treated with Liraglutide 1.2 mg/day and metformin 850 mg BID, with good metabolic control.
Conclusion
SPW involves the hypothalamic-pituitary axis and is responsible for multiple endocrinopathies. The different syndrome components can appear progressively throughout life, delaying the diagnosis. In the presence of an obese patient, with food voracity since childhood and cognitive impairment, it is important to suspect of PWS and exclude the presence of hypopituitarism, to establish an appropriate therapeutic plan.

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AEP563

Invasive Thyrotropin-secreting pituitary adenoma: A case report

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Introduction
Thyrotropin-secreting pituitary adenoma is a rare cause of hyperthyroidism which must be differentiated from other etiologies of inappropriate TSH secretion.
Observation:
We report the case of a 49 years old male patient with no particular pathological history, addressed for thyrotoxicosis (weight loss, irritability, thermophobia, dyspnea and palpitation) with no goiter or ophtalmopathy. Echocardiography showed dilated cardiomyopathy and pulmonary arterial hypertension. Hormonal testing revealed elevated TSH levels 27 and 69 mUI/l, associated with elevated FT4 level 29 pmol/l. Pituitary MRI showed intra and suprasellar expansive process, invading the base of the skull, measuring 46.7 × 67.9 × 50.5 mm with moderate hydrocephalus. Neurological examination revealed frontal syndrome and damage to the left nerve III. Exploration of the other pituitary axes concluded to central adrenal insufficiency and central hypogonadism with elevated GH levels; IGF1 and prolactin levels were not elevated. Surgical resection of adenoma was rejected by neurosurgeons due to its large size and operative risk. The evolution under hydrocortisone, treatment of heart failure including beta blocker, bromocriptin and somatostatin analogs was initially favorable with amelioration of hyperthyroidism symptoms and regression of behavioral disorder. However, control MRI revealed an increase in the volume of the adenoma 76 × 66 × 67 mm with significant loco regional invasion. Patient's evolution was marked by death secondary to cerebral herniation.
Conclusion
Invasive Thyrotropin-secreting pituitary adenomas are a therapeutic management problem. If pituitary surgery is contraindicated or declined, medical treatment reduces the symptoms of hyperthyroidism but tumor evolution is unpredictable.

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AEP564

Successful pregnancy in a female with a large prolactinoma after pituitary tumor apoplexy

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Introduction
Pituitary apoplexy is a rare condition which may cause death of the patient in severe cases and many times leads to hypopituitarism. It results from haemorrhagic infarction of a pre-existing pituitary adenoma or within a physiologically enlarged gland .
Case report
Our patient is a 31-year-old female, with a history of macroprolactinoma for approximately 7 years . Who presented to our hospital with a history of severe headache, vomiting and visual disorders, she was pregnant in 24 weeks of amenorrhea. The magnetic resonance imaging (MRI) was compatible with apoplexy adenoma. The hormonal exploration finds a corticotropic and thyrotropic insufficiency and the prolactin level was 1048 ng/ml. After treatment with corticosteroid therapy, she underwent transsphenoidal excision of the pituitary adenoma .The condition of the patient improved within a few days. The patient had no further complaints during the pregnancy and at 38 weeks gestation delivered a healthy baby. And 3 months later, she became pregnant. An MRI without contrast was performed in 12 weeks of amenorrhea, which showed empty Sella syndrome. The decision was to discontinue cabergoline, and follow the patient regularly until delivery. A repeated MRI with contrast was performed after delivery which showed empty Sella syndrome.
Conclusion
This case shows an unusual course of a large prolactinoma following pituitary tumor apoplexy with resolution of the pituitary tumor. She had a successful pregnancy, and after delivery there was no regrowth of the pituitary adenoma.
Keywords : prolactinoma, apoplexy, pregnancy, empty sella syndrome.
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AEP565

Recurrent hypoglycemia as an initial presentation of Isolated ACTH deficiency

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Introduction:
Adrenocorticotropic hormone (ACTH) deficiency can occur either due to decreased or absent production of the hormone by the pituitary gland. A decline in the production of ACTH can result in adrenal insufficiency. The exact etiology of ACTH deficiency is unknown. A defect in the hypothalamus or pituitary gland may be the cause. This can also be congenital involving mutations of the TBX19 gene (also referred to as TPIT) on the long arm of chromosome one (1q23-q24) and the corticotropin releasing hormone (CRH) gene on the long arm of chromosome eight (8q13). The inheritance pattern is thought to be autosomal recessive.
Case report
The case report discusses the presentation of 66-year old lady with generalized weakness, blurred vision and diaphoresis. She presented twice to the emergency department with almost same symptoms or complaints. At first presentation, her hypoglycemic event was treated and considered as secondary to her poor oral intake. She was admitted on her second presentation and continued to have recurrent hypoglycemia during her hospital stay requiring emergency management. Her serum cortisol and ACTH levels were significantly low, but other pituitary hormone levels were within normal range. Short synacthen test showed adequate adrenal response, however; long synacthen test was inconclusive. Computed tomography (CT) of the adrenal glands was normal.
Treatment/Outcome
She recovered symptomatically with hormone replacement therapy with cortisol initially through intravenous route and later orally. She was advised follow-up with out-patient magnetic resonance imaging of pituitary gland and possible genetic testing.
Conclusion:
Isolated ACTH deficiency presents with general symptoms that sometimes delay the diagnosis or it is missed entirely. Early consideration of this entity is anticipated to facilitate making an early diagnosis.
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AEP566

Functioning gonadotroph adenoma accompanied by erythrocytosis in an elderly man

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Introduction
Clinically functioning gonadotroph adenomas (FGA) are rare, especially in men. We present a case of a LH/FSH-secreting functioning gonadotroph macroadenoma in an elderly patient, which manifested with visual impairment and was accompanied by secondary erythrocytosis.
Clinical case
A 62-y.o. male was admitted to our hospital with a 9-month history of visual impairment and a 5-year history of plethora of the face, neck and upper half of the trunk. Before admission, brain MRI was performed and revealed a pituitary macroadenoma. At admission, MRI confirmed a 40 × 41 × 33 mm pituitary macroadenoma with supra-infra-retro-para (D, S) extension (Knosp IV). Hormonal evaluation revealed secondary hypothyroidism (TSH 0.795 IU/l (0.25–3.5), fT4 6.95 pmol/l (9–19)), normal IGF-1 104.6 ng/ml (16–245) and late-night salivary cortisol 5.11 nmol/l (0.5–9.65). There were high FSH 22.5 IU/l (1.6–9.7) and high-normal LH 10.3 IU/l (2.5–11) and testosterone 28 nmol/l (11–28.2), which allowed us to suspect a FGA. Moreover, there were elevated hemoglobin 196 g/l (132–172), hematocrit 56.7% (40–51) and red-cell count 6.660.000 per mm^3 (4.300.000–5.800.000), which was consistent with secondary erythrocytosis due to testosterone excess. On ophthalmological examination bitemporal hemianopsia was found. The patient underwent transnasal transsphenoidal surgery. Before surgery, three procedures of blood exfusion were performed to minimize perioperative risks. Immediately after surgery, there was a rapid decline in FSH 4.19 IU/l, LH 0.513 IU/l and testosterone 0.62 nmol/l. However, secondary hypothyroidism persisted (TSH 0.088, fT4 5.78) and secondary adrenal insufficiency manifested (morning serum cortisol 175.6 nmol/l (171–536)), which required replacement with levothyroxine and hydrocortisone. Transient hyponatremia was also noted. The levels of hemoglobin (152 g/l), hematocrit (44.9%) and red-cell count (5.150.000 per mm^3) returned to normal. Immunohistochemical examination of the tumor showed positive FSH expression in 30% of cells and positive LH expression in 80% of cells. Ki-67 index was 3%.
Conclusion
This is a rare case of FGA with predominant LH expression leading to hyperandrogenism and secondary erythrocytosis in an elderly patient. As in the majority of the described cases this case manifested with visual impairment, though signs of erythrocytosis had manifested long before. Though drug-associated secondary erythrocytosis due to testosterone overdose is well studied, the possibility of endogenous testosterone overproduction in patients with erythrocytosis should also be considered.
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AEP567

Lymphocytic auto immune hypophysitis : A case report

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Introduction
Lymphocytic hypophysitis is an autoimmune inflammatory pathology of the pituitary gland responsible for partial or global hypopituitarism. In this context, we report a clinical case illustrating this entity.

Clinical case
A 31-year-old woman with a family history of hypothyroidism and a personal history of vitiligo was seen in the 8th month of pregnancy for headaches that have progressed rapidly in 4 weeks. She reported visual blurring, without asthenia nor polyuropolydipsic syndrome. Ophthalmologic examination showed normal fundus and bitemporal amputation of the visual field. The hormonal balance showed a thyrotropic insufficiency with a low TSH at 0.25 mui/l and a low ft4 at 10.2 pmol/l, an intact corticotropic axis, and normal baseline GH and IGF1 levels. The pituitary MRI showed symmetrical pituitary hypertrophy heterogeneous and hypersignal in T2 ponderation, and isosignal in T1, compressing the optic chiasma, the posterior pituitary lobe was in place with spontaneous hypersignal in T1 ponderation. Therapeutically, the patient received oral corticosteroid therapy at a dose of 0.5 mg/kg/day over a period of one month in the peri-partum followed by gradual decline over one month. The evolution was marked by the regression of the headaches. A cesarean delivery was decided because of the risk of intracranial hypertension. Pituitary imaging was practiced two months after childbirth, showing a marked decrease in pituitary volume at the expense of the suprasellar region with relief of compression on the optic chiasma. The patient underwent a hormonal reassessment thus eliminating iatrogenic corticotropic insufficiency after stopping corticosteroid therapy. She was treated with L-thyroxine replacement therapy in front of a deficient thyreotropic axis. Four months later the patient developed weight loss with orthostatic hypotension. Pituitary assessment showed corticotropic insufficiency and control imaging showed a decrease in pituitary size with an upper edge concave upwards. She was then put on hydrocortisone at a dose of 15 mg per day with a good clinical outcome.
Conclusion
Lymphocytic hypophysitis is a rare entity whose best known mechanism is an immune disorder. The presence of a history of autoimmune diseases, the female sex and the pregnant state are strongly suggestive of this etiology. The median and symmetrical nature of the pituitary hypertrophy on imaging is also ecovative of this diagnosis. This is an evolving pathology, so the deficit of the pituitary axes may appear later, hence the benefit of a regular clinical and biological monitoring of the pituitary axis.

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AEP568

Managing pituitary disease during COVID-19 pandemic: A case report

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Introduction
The COVID-19 pandemic has significantly affected health systems all over the world, putting on a hold medical care and delaying surgical interventions. Patients with pituitary tumors, especially those who associate hormonal hypersecretion or defficiency and mass effects represent a management challenge even in a non-pandemic time.
Case description
A 41 years old, non-smoker, overweight, male patient was admitted in our clinic for bitemporal hemianopsia, diplopia, diziness and erectile dysfunction, symptoms that had started six months prior. The patient did not associate other comorbidities. The magnetic resonance examination of the pituitary showed a large mass of 30.9/40.5/29.4 mm, with sellar and parasellar extension, invasion of the left cavernous sinus and compression the optic chiasm. Preoperatively, the hormonal profile revealed hypogonadotroph hypogonadism and no other hormonal deficiencies. We reccommended neurosurgical resection of the tumor, but during the hospitalization in our clinic he was diagnosed with SARS-CoV-2 infection which delayed the surgical intervention. The patient showed minimal COVID-19 symptoms, no lung damage and was referred to a COVID-19 support center, where he received symptomatic treatment and remained until the RT-PCR assay for SARS-CoV-2 was negative. Transsphenoidal surgery was performed, with favorable post-operative evolution and no complications. The histopathological exam established the diagnosis of pituitary non-functioning macroadenoma. Our patient underwent transsphenoidal intervention 9 days after he was discharged from de COVID-19 supportive center and was negative for SARS-CoV-2 (17 days after diagnosis). The post-operative pituitary MRI showed a tumor remnant of 19/33/25 mm. The hormonal evaluation showed persistence of gonadotroph pituitary insufficiency, with no other hormonal abmormalities and with visual field improvement. We started substitutive therapy with testosterone undecanoate, 1000 mg i.m. every 3 months, with good clinical response.
Conclusion
So far, there is no consensus on the management of the pituitary patients which associate COVID-19, only recommendations for several emergencies, including pituitary apoplexy and adrenal crisis. Endonasal pituitary surgery for SARS-CoV-2 positive patients is considered a high risk intervention and it must be postponed, except for major emergencies. The evolution of our patient was positive, without significant impact on disease progression of the delayed intervention.

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AEP569

Craniopharyngioma presenting with amenorrhea and a polyuric polydipsic syndrome

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Introduction
Craniopharyngioma is a rare type of benign brain neoplasm , arising from the pituitary stalk or gland and found most commonly in children . The clinical presentation is variable and may include endocrine or ophtalmogical disorders, intracranial hypertension syndrome and other neurological symptoms.
Observation
We report the case of a 16 year-old girl with a normal staturo-ponderal development and no medical history , who consulted for a nine months secondary amenorrhea associated to a polyuric polydipsic syndrome (volume of urines > 5L/day and urine density 1005), with no other symptoms . The biology showed an hypotonic urine and an hypogonadotropic hypogonadism ; low gonadotropin levels (FSH at 3.7 mU/ml , LH at 1.51 mU/ml) associated to oestradiol deficiency at 12.51 pg/ml . We completed the evaluation of the hypophyseal function and found a corticotropic and a thyrotropic insufficiency . In front of this hypopituitarism , a pituitary MRI was performed , revealing an heterogeneous tumor in the sella and supra sellar space , measuring 18 × 16 × 12 mm in diameter , with disappearance of the posterior pituitary signal .Taking in consideration the young age of the patient, the diagnosis of a pituitary macroadenoma is unlikely , and the cerebral CT-scan showed multiple calcifications in the periphery of the pituitary mass in favor of the diagnosis of craniopharyngioma . The clinical presentation of the tumor was in this case the association of secondary amenorrhea to a diabetes insipidus. The procedure to follow was to put the patient under hydrocortisone, levothyroxine and desmopressin treatement and preparing her for an endonasal transsphenoidal resection of the pituitary tumor .
Conclusion
Even though it is a benign tumor , craniopharyngioma is a serious pathology with severe repercussions if not early diagnosed and treated , and post surgical surveillance is a must, to detect any recurrence which is frequent .

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Reproductive and Developmental Endocrinology

AEP570

Flow medicated dilation is associated with matrix metalloproteinase-2 in healthy postmenopausal women

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Introduction
Menopausal transition has been associated with an increase in cardiovascular risk, which is possibly linked with the hormonal imbalance following ovarian senescence. Both insulin levels and circulating androgens (FAI) have been associated with endothelial dysfunction, through studies evaluating flow mediated dilation (FMD). We aimed to investigate whether the link between

these hormones and FMD might be explained by markers of oxidative stress, like metalloproteinases −2 and −9 or the heat shock protein 60 (HSP60).
Methods
This study included a total of 159 apparently healthy postmenopausal women, retrieved from a University Menopause Clinic. Exclusion criteria included intake of anti-hypertensive or dyslipidemic medications or menopause hormone therapy during the last 6 months, as well as previously diagnosed peripheral vascular disease or cardiovascular disease. We performed a fasting venous blood sample for biochemical, hormonal assessment and evaluation of markers of oxidative stress and the heat shock protein. Sonographical assessment took place immediately thereafter in one session, including brachial artery tonometry and assessment of flow mediated dilation (FMD).
Results
Correlation analysis showed that mean FMD values were associated with FAI (r = −0.238, P-value = 0.010) as well as with insulin levels (r = –0.196, p-value=0.032). There was a borderline correlation between MMP2 values and FMD (r = 0.159, P-value 0.061), while MMP2 values correlated with log-transformed HSP60 (r = −0.237, P-value=0.011). Multivariable analysis showed that FMD values were associated with FAI and MMP2 levels (Model R^2 14.2%, FAI b-coefficient = −0.354, P-value = 0.016; MMP2, b-coefficient = 0.286, P-value=0.029), but the effect of insulin was lost, in a model that also included age and menopausal age, SBP, body mass index. The results of the multivariable model remained significant after additional adjustment for log-transformed values of HSP60.
Conclusion
In this sample of postmenopausal women, values of FMD were independently associated with levels of free androgens and MMP2. The action of insulin on vascular endothelium seems to be mediated by MMP2. Further studies are needed to explore these findings.

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AEP571

Relationship between vitamin D and thyroid status in women of reproductive age with subclinical hypothyroidism and TPO-Ab +

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Background
Today thyroid diseases occupy the first place among all endocrine pathologies and remain one of the most difficult problems. The prevalence of subclinical hypothyroidism, according to various data, is 4–15%. The category of women of reproductive age deserves special attention, as thyroid dysfunction affects a woman's fertility and pregnancy. Vitamin D deficiency in the population remains a global problem. The purpose of the study is to determine the level of 25-hydroxy vitamin D3 [25 (OH) D3] in women with subclinical hypothyroidism and investigate the relationship between hypothyroidism and vitamin D deficiency.
Materials and methods
We examined 90 women with subclinical hypothyroidism, TPO-Ab + and 25 healthy women, the average age of women with subclinical hypothyroidism was 25.8 ± 1.6 years, of women in the control group was 24.4 ± 1.4 years. The levels of TSH, FT4, FT3, TPO-Ab and 25 (OH) D3 was determined. 25 (OH) D3 was measured by radioimmunoassay, the level of TSH, FT4, FT3 was measured by the immunochemical method.
Results
The level of 25 (OH) D3 was 18.24 ± 1.24 ng/ml (at a rate of 30–50 ng/ml) in women with subclinical hypothyroidism and 29.28 ± 1.02 ng/ml in women of the control group. In all women with subclinical hypothyroidism, vitamin D levels were defined as insufficient or deficient (vitamin D deficiency is detected at less than 20 ng/ml, vitamin D insufficiency is detected at 20–29.9 ng/ml), their TSH level was 5 , 7 ± 0.84, FT4- 14.6 ± 1.12, FT3–3.9 ± 0.82, TPO-Ab - 384 ± 2,46 (P <0.001). It was investigated that the level of 25 (OH) D3 was inversely correlated with TSH levels and TPO-Ab in women with subclinical hypothyroidism.
Conclusions
We investigated that low levels of 25 (OH) D3 were present in all women with subclinical hypothyroidism. An inverse correlation occurred between a decrease in the level of 25 (OH) D3 and an increase in the level of thyroid-stimulating hormone (r = –0.39, P <0.05), between a decrease in the level of 25 (OH) D3 and an increase in the level TPO-Ab (r = –0.37, P <0.05) In order to improve the compensation of hypothyroidism in women of reproductive age, it is recommended to add vitamin D supplements to the main treatment.

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AEP572

Relationship between KLK3 and the immune system of young women living in two areas with different environmental impact during a menstrual cycle. Preliminary data. (ECOFOODFERTILITY Project)

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Introduction
Kallikreins are a subgroup of serine proteases which in women are produced by Skene's glands. It evaluated the variation of concentrations in KLK3 and immunoglobulins IgA, IgM, IgG and IgE in the menstrual cycle (follicular (FP), ovulatory (OP) and luteal (LF) in young women living in two areas with different environmental impact.
Materials and methods
82 women aged between 22 and 34, normo-menstruating, no smokers, no habitual drinkers, no professionally exposed, no intake of contraceptive pills for at least 2 years, living for at least 5 years in the selected areas, have been enrolled. 49 residing in high environmental impact area (group A) and 33 in low environmental impact area (group B).The technique used to measure in serum KLK3 is an ultra-sensitive enzyme immunoassay.
Results
88.3% of the group A shows a significant positive peak in the OP (P <0.0001: FP = 3.92 + 1.6, OP = 25.63 + 5.4 and LP = 5.1 + 2.1) and 94.3% of group B shows a significant negative peak in the OP (P <0.0001: FP = 4.43 + 2.1, OP = 1.42 +0.9 and LP = 8.95 + 2.9).It emerges: In group A, no relationship is examined. Group B;

- for IgA there is a significant negative peak in OP (P <0.005: FP = 332 + 31.7,
- OP = 320 + 38.3 and L P = 353 + 50.1).
- for IgM there is a significant positive peak in OP (P <0.001: FP = 171 + 8.9, FO = 180 + 12.1 and LP = 186 + 10.8).
- for IgG there is a not significant variation between the various phases (p = NS: FP = 1435 + 136.1 OP = 1435 + 240.5 and LP = 1438 + 176.4).
- for IgE there is a significant negative peak in OP (P <0.0001: FP = 25.86 + 3.9, OP = 21.45 + 4.5 and LP = 25.72 + 4.7). The group B shows variation in the concentrations of immunoglobulins which in the case of IgA and IgE is strictly correlated with the peaks concentrations of KLK3.

Conclusions
For group B, a correct immune regulatory function of KLK3 seems to be maintained given the correlation between KLK3 with IgA and IgE, while this does not happen for group A, where external environmental factors such as pollutants known to be present in the selected area could play an interference effect of molecular communication pathways.

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AEP573

Spontaneous thelarche and menarche in children with turner syndrome

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Introduction
Turner syndrome (TS) is usually accompanied by hyperhonadotroic hypogonadism and primary amenorrhea due to gonadal disgenesis. One-third of girls with TS have spontaneous thelarhe (ST). Regular menstrual cycles occur in at most 6% of this patients.
Objectives
To analyze the characteristics of pubertal development in children with different karyotype variants of TS.
Methods
This is a retrospective study, analyzing clinical data from medical records of 135 patients with TS from 13 to 18 years, who were regularly followed-up in the Republican Center of Endocrinology (Minsk). Karyotype was identified in blood lymphocyte culture in all patients. Depending on the karyotype, 4 groups of patients were identified the first group with X-monosomy (n =72), the second group with mosaic variant 45,X/46,XX (45,X/47,XXX/46,XX; 45,X/47XXX) (n =18), the third group with isochromosome iXq (n =16) and the fourth group with other karyotypes (n =29). Retrospective

assessment of the age of thelarche and menarche was performed. The results were processed using SPSS.22.
Results
TS was diagnosed in patients with characteristic phenotypic signs according to the results of karyotyping at the age of 9.8 [3.8–12.8] years. A total of 17.8% (n = 24) of TS girls experienced ST. The average age of ST was 12.5 ± 1.61 years. Estrogen replacement was initiated in 78.5% (n = 106) of girls. Spontaneous pubertal development was more frequently observed in TS with mosaicism (50%) than in TS with X-monosomy (2.8%), isochromosome iXq (18.75%) and other karyotypes (34.5%) (χ^2 =29.4; P < 0.001). Spontaneous menarche was observed in 61.1% (n = 11) of TS girls over 15 years old with ST (9.1% of all patients). The average age of spontaneous menarche was 14 ± 0.97 years. 38.9% (n = 7) of TS girls with ST showed no progression of pubertal signs for 6 months and secondary amenorrhea, which required prescribing sex hormone replacement therapy. In patients with a mosaic variant of the karyotype 45,X/46,XX spontaneous completed pubertal was observed more frequently (50%, χ^2=28.8; P < 0.001). A regular menstrual cycle was also observed in a girl with a 45,X karyotype, suggesting the presence of mosaicism in the ovaries in monosomia X in peripheral blood leukocytes.
Conclusions
Our data showed much higher rates of ST and spontaneous menarche in girls with mosaic variant 45,X/46,XX (45,X/47,XXX/46,XX; 45,ŕ47ŕŕ) of TS compared to other karyotype variants. Karyotype should be taken into account when deciding on expected puberty and possibly reproductive potential.

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AEP574

Decline in AMH concentrations following radioactive iodine treatment in women with differentiated thyroid cancer: A systematic review and meta-analysis

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Purpose
Radioactive iodine (RAI) is frequently used as adjuvant therapy in patients with differentiated thyroid cancer (DTC). However, its effect on ovarian reserve has not been fully elucidated, with studies yielding inconsistent results. The aim of this study was to systematically review and meta-analyze the best available evidence regarding the effect of RAI on ovarian reserve in premenopausal women with DTC.
Methods
A comprehensive literature search was conducted in PubMed, Cochrane and Scopus, until December 6th, 2020. Data were expressed as weighted mean difference (WMD) with a 95% confidence interval (CI). The I^2 index was used to assess heterogeneity.
Results
Four prospective studies were included in the qualitative and quantitative analysis. Anti-Müllerian hormone (AMH) concentrations decreased at three (WMD –1.66 ng/ml, 95% CI –2.42 to –0.91, P < 0.0001; I^2 0%), six (WMD –1.58, 95% CI –2.63 to –0.52, P = 0.003; I^2 54.7%) and 12 months (WMD –1.62 ng/ml, 95% CI –2.02 to –1.22, P < 0.0001; I^2 15.5%) following a single RAI dose compared with baseline (three studies; n = 104). With respect to follicle-stimulating hormone (FSH) concentrations, no difference was observed at six (WMD +3.29 IU/l, 95% CI –1.12 to 7.70, P = 0.14; I^2 96.8%) and 12 months (WMD +0.13 IU/l, 95% CI –1.06 to 1.32, P = 0.83; I^2 55.2%) post-RAI compared with baseline (two studies; n = 83). No data were available for antral follicle count.
Conclusions
AMH concentrations decrease at three months and remain low at six and 12 months following RAI treatment in women with DTC. No difference in FSH concentrations post-RAI was observed.

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AEP575

Erectile dysfunction as a marker of newly diagnosed endocrine and metabolic disorders

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Aim
The aim of this study was to evaluate: a) the prevalence of a previously unknown endocrine / metabolic dysfunction, namely hypogonadism, thyroid dysfunction, hyperprolactinemia, and diabetes or prediabetes, in a population of patients affected by Erectile Dysfunction (ED); b) the differences in ED severity according to the presence/absence of specific endocrine / metabolic dysfunctions.
Material and Methods
A total of 1332 subjects, referred to the Andrology Unit (Sant'Andrea University Hospital of Rome) for a condition of ED, were studied. Exclusion criteria were: i) age <18 or >75 years; ii) already diagnosed of endocrine/metabolic disorders, as listed above. The study included: andrological clinical examinations and hormonal profile. The diagnosis of ED was made using the International Erectile Function Index-5 questionnaire (ED: total score ≤21). ED severity was considered according to presence/absence of spontaneous erections, maintenance/achievement deficiency.
Results
Overall, the mean ± SD age was 54.3±13.7 years. A rate of 88.3% of the patients had a stable relationship; 80.0% of the patients referred difficulty in the maintenance of the erection, while 19.9% in the achievement. The spontaneous erections were absent in 24.0% of patients, sporadic in 50.7% and present in the remaining 25.2%. In the 10.3% of the patients there was at least another one sexual or ejaculatory dysfunction (premature/delayed/retrograde ejaculation, anorgasmia, low sexual desire). A total of 19.4% of the patients were already in treatment for glycaemic disorders or endocrine dysfunctions. Among the remaining 1077 patients, the prevalence of subjects with unknown endocrine/metabolic disorders was 30%. Particularly, 190/1077 (17.6%) were diagnosed as affected by hypogonadism (total testosterone < 2.64 mg/dl) 56/1077 (5.2%) diabetes (DM; HbA1c: ≥ 6.5%) or prediabetes (HbA1c 6–6.5%), 40/1077 (3.7%) thyroid dysfunction (TSH<0.3 ulU/ml or TSH>10 ulU/ml), 37/1077 (3.4%) hyperprolactinemia (PRL >25 ng/ml). Among the subgroups, patients with hyperprolactinemia were younger compared to the total group (44.6±12.9 years; P < 0.05), and patients with new diagnosis of DM showed more severe form of ED compared to the total group (difficulty in the achievement of erection: 46/56 (82.2%, P < 0.05; absence of spontaneous erection 23/56 (41.1%), P < 0.05).
Conclusions
In this study, a new diagnosis of an endocrine and/or metabolic dysfunction was carried out in more than a quarter of cases. Since most endocrinologic causes of ED are treatable, every effort should be made to exclude potential hormonal aetiologies underlying ED at an early stage. Finally, ED should also be considered as an early marker of DM as well as endocrine dysfunctions.

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AEP576

A rare case of ovotesticular DSD by 46XX /46XY genetic chimerism

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Introduction
We present the very rare case of a patient with ovotesticular disturbance of sexual development (DSD) by 46 XX/46 XY genetic chimerism.
Case report
A 47-year-old patient with male appearance consulted for gynecomastia developed in the last 3 – 4 years. Clinical examination showed genital organs ambiguity with a small scrotum, no palpable testis, a clitoris instead of penis. Painful bilateral gynecomastia of 5–6 cm in diameter was present. From the patient's pathological antecedents we retain a surgical correction for hypospadias in 2001 and an inguinal hernia surgically cured in 2017. Hormonal dosages showed secretion of both *testosterone* (low level for male

values) and *estradiol* (elevated level for male values), a slight elevation of FSH and LH and normal Prolactin. No other hormonal disturbances were noted. An IRM investigation of the pelvis showed the presence of *an uterus* of 28/22 mm and *one ovary* of 20/28 mm, with follicular structure, the *absence of prostate and seminal vesicles*, in the right scrotum a small structure of 20/14 mm suggesting a testis, a small structure of 26/27mm suggesting a *clitoris*. All this features lead to the diagnosis of ovotesticular disturbance of sexual development, previously known as true hermaphroditism. The karyotype analysis showed the concomitant presence of 50% cells with 46XX karyotype and 50% cells with 46XY karyotype, indicating a genetic chimerism. The hormonal treatment consisted in Testosterone 23 mg/day in transdermal application and Raloxifen 60 mg/day for gynecomastia. The patient will be treated by removal of both uterus, ovary and testis followed by rseplacement therapy with testosterone, as the attributed and assumed sex is male.

Conclusion

Genetic chimerism is defined by *the simultaneous existence of two or more genetically distinct cell lines in a single individual*. 46XX/46XY is an example of tetragametic chimerism. It is a very rare condition resulting from several possible mechanisms, the most probable being the *intrauterine fusion of two different gametes*, one 46 XX and one 46 XY. leading to ovotesticular DSD.

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AEP577

A novel heterozygous mutation in CYP19A1 Gene c.456_462del p.(Ser153Profs*24) in a girl with aromatase deficiency

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Background

Aromatase deficiency is an extremely rare autosomal recessive condition due to mutations on *CYP19A1* gene. Despite the size and complexity of this gene, only about 40 cases with aromatase deficiency have been reported.

Case report

The patient was born at term from non-consanguineous parents. Maternal signs of virilization were verified during third trimester (deep voice, acne on arms and face enlargement). Ambiguous genitalia were recognized at birth. The patient was referred to the Pediatric Endocrinology Department (PED) and presented complete fusion of the labia majora, clitoromegaly, and a posterior urethra. Mother reported improvement in virilization signs few days after birth. Laboratory work-up at 2 days of life showed 17-hydroxy progesterone (17-OHP) of 18 (0.07–0.77) ng/ml, total testosterone (TT) of 0.7 (20–64) ng/dl, whereas ionogram, adrenocorticotropic hormone, dehydroepiandrosterone sulfate, aldosterone and renin were normal; at 15 days, 17OHP was 12.4 (0.13–10.6) ng/ml, TT <20.0 (20–64) ng/dl and androstenedione 2.8 (0.18–0.80) ng/ml. The karyotype was 46,XX and pelvic ultrasound revealed a normal uterus, vagina and bladder. At 11 months of age, she was submitted to vulvoplasty and the parents decided to suspend the follow-up at the PED. At 12 years and 4 months, she presented to the emergency department (ED) with severe pain in the left iliac fossa, absence of stool passage for 2 days and vomiting, presenting Tanner stage III pubic hair and Tanner stage I breasts. Laboratory findings showed 17-OHP 1.86 (0.11–0.98) ng/ml, TT 0.4 (0.07–0.28) ng/ml, LH 31 (0.02–4.7) mUI/ml, FSH 33 (1.0–10.8) mUI/ml and estradiol 16 (10–24) pg/ml. Pelvic MRI revealed a complex genital malformation, ovarian cystics and suspected hydrocolpos. Treatment with LHRH agonist was implemented. She underwent left oophorosalpingectomy and histology documented left anexal necrosis with multicystic left ovary torsion, without hydrocolpos, and treatment with LHRH agonist was suspended. At 13 years and 2 months, she was admitted to the ED with right ovary torsion and underwent urgent laparoscopic surgery. LHRH agonist was restarted. Genetic analysis of the patient revealed two probably pathogenic variants in heterozygote in the *CYP19A1* gene: a previously described mutation (c.1263+5G>A p.?) and a novel mutation [c.456_462del p.(Ser153Profs*24). Puberty was induced with transdermal estrogens.

Conclusion

We identified a novel mutation in the *CYP19A1* gene in a patient who presented with ambiguous genitalia and maternal virilization during pregnancy. Our case had large polycystic ovaries and two episodes of ovarian torsion. In addition, it shows the difficulties during the follow-up and the complexity of the disease. We speculate that these mutations can potentially result in partial aromatase activity with remaining estrogen biosynthesis.

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AEP578

Turner Syndrome–An unusual presentation of normal stature and incomplete puberty

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Introduction

Turner syndrome(TS) is characterized by complete/partial monosomy or by a structural defect in one of X chromosomes. Despite clinical hallmarks of short stature(SS) and gonadal dysgenesis(GD), phenotype is variable and related to underlying chromosomal pattern. Loss of the distal segment of the short arm of x-chromosome(Xp-), including haploinsufficiency of short stature homeobox-containing (SHOX) gene, is thought to be the main factor for growth failure. Regarding GD, results from accelerated follicular atresia. Spontaneous puberty occurs in only 15–30%, but only half of those complete puberty with menarche. We report an uncommon presentation of a teenage TS female with normal stature, whose only apparent Turner feature was secondary amenorrhea(SA).

Case report

A 17-year-old girl was referred to our endocrine clinic for SA. Spontaneous menarche occurred at 13 years-old. Subsequent menstruation was regular during first 3 months, and became irregular, in the following 2.5 years. Thereafter, she became amenorrheic during 1.5 years. She was born at term, after an uneventful pregnancy. Her birth length and weight were 50.5 cm (0.48 SDS) and 3300 g (-0.2 SDS). She has mild intellectual disability. Height growth was on P50–75 until 12, with an increase to P90 since then. Her target height is 162.5 cm (-0.11 SDS). Physical examination, recorded 170 cm of height (1.09 SDS; P85), weighed 66 kg (SDS 0.95) and had low set ears. Her breast development and pubic hair were Tanner's stage III and IV, respectively. Endocrine evaluation revealed FSH levels of 106 UI/l and LH levels of 51.9 UI/l, and undetectable estradiol. The remaining pituitary hormones were within normal ranges, as haematological and biochemical tests. Anti-mullerian hormone was <0.01 µg/l. Pelvic ultrasound revealed an uterus of normal dimensions and ovaries were undetectable. Echocardiogram, audiogram and renal ultrasound were normal. Karyotype analysis showed a 46,X,psu idic(X)(q21.32) TS, representing partial monosomy of Xq and partial trisomy of Xp(long arm of x-chromosome). Low-dose oral contraceptive pill was initiated. Currently, at 20 years-old, she presents a complete pubertal development with a final height of 172 cm (1.34 SDS).

Conclusions

In this case, the SHOX gene overdose in Xp- may have mitigated the SS phenotype which is typical of TS. Additionally, TS karyotype may be a predictor of spontaneous puberty, being less frequent in the classic 45,X karyotype. TS should be considered in patients with SA despite no typical somatic stigmata. There is paucity of literature reporting TS with normal/tall height and spontaneous puberty.

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AEP579

Congenital GH deficiency in children: What are the differences between isolated and combined/total and partial somatotropic GH deficiency?

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Introduction
Growth hormone (GH) deficiency is a rare but not exceptional cause of statural delay in children. The results of GH stimulation tests and the exploration of other pituitary axes allow us to conclude on the nature of the deficiency: total or partial and its possible association with other pituitary deficits.
Methods
This is a retrospective descriptive study including 75 patients followed for congenital GH deficiency.
Results
The comparison of the demographic, auxological and biological characteristics between total and partial somatotropic deficits showed that the average age of discovery was 8.51 ± 4.21 years for the total deficit vs 9.62 ± 4.09 years for the partial deficit with no significant difference *(P* = 0.344). Male gender was predominant for both types of deficits (61% for total deficit vs 67% for partial deficit; *P* = 0.639). The initial SD height was –2.77 ± 1.5 SD for total deficit vs –2.19 ± 1.2 SD for partial deficit. BMI (SD) was 1.27 ± 0.5 for total deficit vs 1.75 ± 0.5 for partial deficit *(P* = 0.251). IGF1 (SD) was 3.36 ± 0.33 vs 2.81 ± 0.5 *(P* = 0.474). The hypothalamic-pituitary MRI was pathological for most patients with total somatotropic deficit (60%) and normal for most patients with partial deficit (67%) with a significant difference *(P* = 0.038). For the comparison between isolated and combined deficits, we found a significant difference only for IGF1(SD) (which was –3 ± 1.5 SD for isolated deficit and -3.44 ± 0.5 SD for combined deficit *(P* = 0.002).
Discussion and conclusion
The total deficit was mainly associated with pathological MRI in our series, which was consistent with the series in the literature. For the other series, patients with combined pituitary deficit compared to subjects with isolated deficit were significantly smaller in height, with a larger delta (target height-height) and lower weight.

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AEP580

Adverse effects of gender affirming hormonal therapy in transgender persons: assessing reports in the French pharmacovigilance database

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Background
Only limited data are available regarding adverse effects of gender affirming hormonal treatment (HT) mainly due to the lack of population-based studies with adequate controls, thus making spontaneous reporting systems a valuable tool to detect potential side reactions.
Objective
In this nationwide retrospective study, we aimed to analyse adverse drug reactions (ADRs) in relation to gender affirming HT reported in the French pharmacovigilance database by patients and by health care professionals and to categorize the type of ADRs.
Research design and methods
We requested for all the individual case safety reports related to gender affirming HT recorded in the French pharmacovigilance database (FPVD) before the 27th of May 2020. An endocrinologist and a pharmacologist reviewed all cases. We excluded cases that have already been published or for which gender affirming HT was not the suspected drug.
Results
A total of 38 reports of ADRs were identified. We excluded 5 cases where gender affirming HT was not the suspected drug and 5 cases that have already been published. Among the remaining cases, 6 concerned transgender men (age range 21–40 years) and 22 transgender women (age range 22–68 years). In transgender men all reported ADRs were cardiovascular events with pulmonary embolism in 50% of cases. Treatment with testosterone enanthate was involved in all subjects. Therapy was discontinued in 3 cases and total recovery was observed in 2 of them. In transgender women, antiandrogens, mainly cyproterone acetate (CPA), were involved in 68% of reported cases. Estrogens were implicated in 77% of cases, mostly in association with progestins or CPA. Cases of meningioma were the main ADRs observed, followed by cardiovascular ADRs such as ischaemic stroke or acute coronary syndrome. Two cases were related to self-induced drug intoxication. Gender affirming HT was completely discontinued in 14 transgender women and a total recovery was noted in 8 of them.
Conclusion
Our data show a previously unreported and non-negligible proportion of cases indicating cardiovascular ADRs in young transgender men treated with testosterone enanthate. In transgender women, meningioma was the most frequently reported ADRs followed by cardiovascular events. A continued vigilance and further research are necessary to identify risk factors that might lead to individualisation of treatment strategies. There is a necessity to increase the awareness and implement preventive and education measures.

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AEP581

Analysis of insulin like peptide 5 (INSL5) levels and their association between hormonal and metabolic parameters in polycystic ovary syndrome patients

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Objectives
Polycystic ovary syndrome (PCOS) is the most common reproductive disorder that onsets peripubertally and increases morbidity by affecting quality of life. Insulin like peptide 5 (INSL5) is a relaxine/insulin family member gut-peptide hormone that is expressed by various tissues including the hypothalamus, pituitary and ovary. In the present study, we aimed to characterize serum INSL5 levels in PCOS women and determine association of circulating serum insulin like peptide 5 (INSL5) with serum AMH level, metabolic and hormonal parameters.
Materials and Methods
The present study included 45 women diagnosed with polycystic ovary syndrome between the ages of 18–35, who had not received medical treatment in the last six months, and 35 healthy women of the same age range as control group in Bolu Abant Izzet Baysal University School of Medicine, Department of Endocrinology and Metabolism. Anthropometric, hormonal, metabolic parameters and INSL-5 levels were determined in all patients. Pelvic ultrasonography was performed to examine ovarian size and follicle numbers.
Results
In the present study, INSL5 was 12.5 (3.8–59.5) ng/ml in the PCOS group and 15.5 (5.3–37.4) ng/ml in the control group. There was no statistically significant difference in terms of INSL5 between the groups *(P* = 0.103). INSL5 was negatively correlated with body mass index (BMI), free androgen index (FAI), insulin, HOMA-IR, triglyceride, total cholesterol, LDL, fat mass and positively correlated with sex hormone binding globulin (SHBG) in PCOS group. In multivariate linear regression analysis, FAI was significantly associated with serum INSL5 levels ($\beta = -1.1$, $P = 0.015$).
Conclusion
There was no statistically significant difference in INSL5 levels between PCOS patients and healthy subjects, suggesting that the peptide does not have a diagnostic value in PCOS. Negative correlation between INSL5 and FAI, insulin, HOMA-IR and atherogenic lipid profile supports the studies suggesting that this peptide might be related to glucose and lipid metabolism. In multivariate regression analysis, independent relationship of INSL5 with FAI indicates that further studies are required to evaluate the relationship between INSL5 and PCOS.
Key Words: PCOS, INSL5.

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AEP582

Hyperandrogenism and portosystemic shunt - report of two cases

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Introduction
Severe hyperandrogenism is a warning sign in young women. Differential diagnosis includes neoplastic, non-neoplastic and iatrogenic causes. The association of hyperandrogenism and congenital or acquired portosystemic shunt (PSS) has been rarely described, with its pathophysiology being unclear.
Case 1
A 22 year-old woman with diagnosis of autoimmune hepatitis, portal hypertension and PSS since 15 years old, presented with a 4 years history of oligomenorrhea and hirsutism [Ferriman-Gallwey (FG) score 12]. Examination revealed BMI 30.7 Kg/m^2 and virilization signs. Total testosterone (TT) was 3.60 ng/ml (0.1–0.56) and androstenedione 12.4 ng/ml (0.5–4.7). 17OHP, S-DHEA and SHBG were normal. Serum glucose 83 mg/dl, insulin 20 uUI/ml (1.9–23), HOMA-IR 0.7. CT scan excluded adrenal lesions. Ultrasound showed "ovaries with 56 and 58 mm and multiple peripheral follicles". In view of the severe hyperandrogenism of probable ovarian etiology, catheterization of the ovarian veins was performed, excluding ovarian lateralization or central/peripheral gradient of androgen levels. The patient completed 17 months of goserrelin acetate with slight improvement in hyperandrogenism (TT 1.88 ng/ml, androstenedione 8.58 ng/ml). Due to poor therapeutic adherence and necessary contraception, an ethonogestrel implant was applied.
Case 2
A 18 year old woman, with portal hypertension due to portal vein agenesis diagnosed at 4 years old, presented with menstrual irregularities and hirsutism (FG score 10) since menarche at 14. She had a BMI 28.9 Kg/m^2 and no signs of virilization. TT was 2.12 ng/ml and androstenedione 5.27 ng/ml. 17OHP, S-DHEA and SHBG were normal. Serum glucose was 71 mg/dl and insulin 12.57 uUi/ml, HOMA-IR 2.2. On ultrasound, "right ovary (30.4 × 26.4 mm) with functional cyst and multifollicular left ovary (31.4 x16 mm)" stood out. Abdominal-pelvic MRI confirmed portal vein agenesis and excluded ovarian and adrenal lesions. In view of the mild clinical symptoms and the need for contraception, a levonorgestrel IUD was inserted.
Conclusion
PSS can cause hyperinsulinemia by direct passage of secreted insulin to the systemic circulation and consequent insulin resistance by downregulation mechanisms. This is a possible explanation for the hyperandrogenism associated with PSS, similarly to what happens in polycystic ovary syndrome. Decreased hepatic clearance of androgens, in particular testosterone, may be an additional factor. Treatment depends on age, degree of virilization and pregnancy goal which justified the different approach in these patients.

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AEP583

Low intelligent quotient (IQ) in patients with Klinefelter Syndrome are associated with impaired quality of life: A systematic review with meta-analysis

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Objective
This was a systematic review with meta-analysis aiming to identify if patients with Klinefelter syndrome (KS) had a reduced full scale intelligent quotient (IQ) when compared to controls. Reduced IQ is shown to have a negative multifaceted effect on individuals' Quality of Life (QoL), having been shown as a *predictor of future success, increased criminal behaviour, post-traumatic stress disorder (PTSD), lower academic achievements and increased prosocial deficits*. Assessment of patients' IQ can support clinicians in delivering patient care intervention which can address individualised QoL deficits and patients' unmet needs. This is particularly relevant and crucial in achieving holistic nursing care to intervention.
Design
Meta-analysis was completed in Review manager 5.4, using continuous data and running an inverse variance random-effects model, using Std. mean difference for the effect measure, a forest plot was created. This analysed the results on full scale IQ from all studies that used both controls, KS participants and a validated measuring tool to record IQ. Seven studies in total were appropriate to be combined for meta-analysis. The seven studies included were extracted from the initial systematic review analysing factors that can influence QoL in patients with KS.
Data sources
Medline, Cochrane, Embase, Psychinfo, CINAHL, BASE and grey search from the reference lists of key publications.
Eligibility criteria
RCT's, Cohort studies, cross sectional studies and Epidemiology studies involving patients with KS and reporting on QoL parameters. Both adult and paediatric participants were included.
Results
The results from the meta-analysis suggest association with a lower full-scale IQ and a KS diagnosis. There is strong significant difference between patients with KS and Controls, significant P and Z values mean the probability of achieving the results by chance are lowered and the null hypothesis can be rejected. The statistical differences identified suggest a negative association between full scale IQ and KS when compared to controls, suggesting lower full-scale IQ can be associated with KS.
Conclusions
Significant Z & *P* values (Z=8.10, *P* <0.00001) indicate that men with KS have a significantly lower IQ than healthy controls which has a negative impact on patients' QoL. Currently there are no validated scales to measure QoL parameters, including IQ, for patients with KS. Future research is needed to develop a KS-specific scale for use in clinical practice to identify patients' deficits in QoL parameters and plan appropriate care management plans to improve patients' QoL.
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AEP584

Primary ovarian failure: descriptive study of 50 cases

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Introduction
Primary ovarian failure currently represents an increasingly frequent cause for consultation in endocrinology, from 4 to 18 % of the causes of primary amenorrhea and 10 to 28 % of the causes of secondary amenorrhea.
Objectives
In this context, we report a retrospective study of 50 patients followed between 2000 and 2020 for early menopause, in order to assess the etiologies and risk factors favouring this pathology as well as its subsequent impact.
Results
The average age of our patients was 31 years with extremes ranging from 10 years to 40 years. A family history of early menopause was noted in only 6% of women. The reason for consultation was secondary amenorrhea in 52% of cases followed by primary amenorrhea in 32%. In our study we found that the majority of women are nulliparous, in 68% of cases. The diagnosis was confirmed by an average FSH level of 87.25 mIU/l, LH at 28.45 mIU/l, the average E2 value was 2.4 pg/ml and the average prolactin value was 29.02ng/ml The study showed that the main aetiology was premature autoimmune ovarian failure in 58% of cases, a congenital cause in 24% of cases, and chemotherapy and radiotherapy are involved in 6% of cases. All the women in our survey presented complications following their menopause, of which 70% presented short-term complications, mainly sleep disorders, hot flashes and urinary genital disorders, 20% of the women presented metabolic complications at medium term and long term and 48% of women presented mainly cardiovascular complications.
Conclusion
Hormone replacement therapy is necessary to avoid the increased risk of all these complications, especially osteoporosis and cardiovascular complications. If you want to become pregnant, in vitro fertilization with oocyte donation is currently the most effective technique

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AEP585

Long-term psychosocial effects of gender affirming hormone therapy on transgender men

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Background/Aims
Gender affirming hormone therapy (GAHT) has been reported to have positive psychosocial effects on transgender people. In present study, we aimed to investigate longitudinally the short-term and long-term impacts on social adaptation, body image, features of alexithymia and aggression changes in transgender men after GAHT administration.
Methods
The single center, longitudinally follow-up study included transgender men who had admitted to the Endocrinology and Metabolism outpatient clinic of Istanbul University-Cerrahpasa, Cerrahpasa Medical School. Thirty-nine transgender men were asked to complete the Social Adaptation Self-Evaluation Scale (SASS), the Toronto Alexithymia Scale (TAS-20), the Body Image Scale (BIS), and the Buss-Perry Aggression Questionnaire (BAQ) both before GAHT, and after 12 months of GAHT administration. GAHT involves the administration of intramuscular injections of either 250 mg of testosterone esters depot every 3 weeks, or 1000 mg of testosterone undecanoate every 12 weeks.
Results
In the first year of hormone therapy, there was no significant change in terms of social adaptation according to SASS (44.8 ± 6.4 vs 43.7 ± 6.3, P = 0.261). Although the body images scores of transgender men measured by BIS were in the borderline of statistical significance, they increased after GAHT compared to baseline (139 ± 27.9 vs 148.1 ± 26.5, P = 0.058). When transgender men were evaluated in terms of alexithymia, while it became more difficult for individuals to identifying feelings (P = 0.039) after GAHT, there is no difference emerged in terms of difficulty describing feelings (P = 0.797) and externally-oriented thinking (P = 0.522). On the other hand, there was no change in aggressive behavior after GAHT according to the BAQ total and subscales (physical aggression, verbal aggression, hostility and anger) (P > 0.05 for all).
Conclusions
Our findings indicate that GAHT causes transgender men to perceive their body images more positively, and has no effect on their social adaptation and aggressive behavior. On the other hand, GAHT may ended up with more alexithymic scores in transgender men population.
Keywords: social adaptation, body image, alexithymia, aggressive behaviors, gender affirming hormone therapy.

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AEP586

Changes in androgen profile in transgender women with or without gonadectomy

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Objectives
The European Network for Investigation of Gender Incongruence (ENIGI) is a multicenter prospective cohort study. All participants receive a standardized gender affirming treatment (GAHT) protocol including regular follow-up. The current study compared changes in androgens upon starting GAHT and during follow-up in transgender women (TW) with or without gonadectomy by investigating serum total testosterone (TT), calculated free testosterone (cFT), DHEA, DHEAS, androstenedione and SHBG.
Methods
This research was part of the ENIGI study. Sex steroids were assessed at baseline and 12 and 24 months of follow-up using immuno-assay (SHBG, DHEAS) and LC-MS/MS (TT, DHEA, androstenedione). FT was calculated. GAHT was initiated at baseline: estrogens (oral or transdermal) and anti-androgens (cyproterone acetate 25–50 mg/day). After orchiectomy the anti-androgen therapy was stopped and the estrogens were continued unchanged. Data from 113 TW with ≥2 years of follow-up at Ghent, Belgium were analyzed prospectively. Subgroup analyses were performed in TW who underwent orchiectomy (group A, n = 59) vs TW who did not (group B, n = 54), at baseline, pre-operatively vs at month 12, and post-operatively vs at month 24.
Results
In group A, serum TT levels decreased from 572.69 ± 11.76 ng/dl to 18.71 ± 11.91 ng/dl (baseline vs pre-gonadectomy, P < 0.001) and cFT decreased from 11.34 ± 0.35 ng/dl to 0.26 ± 0.35 ng/dl (baseline vs pre-gonadectomy, P < 0.001). No further effect of gonadectomy on serum TT and cFT levels was assessed, although a trend towards decrease was observed. SHBG increased post-gonadectomy (P < 0.001). Androstenedione, DHEA, DHEAS decreased from baseline to pre-gonadectomy (P < 0,001), but remained stable afterwards. Similarly in group B, serum TT, cFT, androstenedione, DHEA and DHEAS decreased between baseline vs 12 months (P < 0.001), while SHBG increased (P < 0.001); all variables remained stable afterwards. Comparing groups after 24 months, no differences in serum TT levels were found. However, SHBG was higher in group A vs group B (73.2 ± 39.6 nmol/l vs 57.2 ± 37.2 nmol/l respectively, P = 0.004), whereas cFT (0,18 ± 0.12 ng/dl vs 0,26 ± 0.26 ng/dl, P = 0,016), androstenedione (71.0 ± 32.4 ng/dl vs 85.3 ± 37.2 ng/dl, P = 0.042) and DHEA (4.99 ± 3.61 µg/l vs 7.34 ± 4.62 µg/l, P = 0.002) were lower.
Conclusion
Serum TT and cFT levels remained unchanged post-orchiectomy compared to before, if low TT was confirmed when on GAHT (including anti-androgens) reflecting patient compliance. At 24 months, TW who underwent orchiectomy had lower cFT, androstenedione and DHEA and higher SHBG, compared to those with a continued stable dose of anti-androgens.
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AEP587

Endocrine features in Noonan syndrome

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Introduction
Noonan syndrome can result from different mutations, the most frequent being in PTPN11. The diagnosis is often made by the clinical picture of short stature, facial dysmorphisms and heart defects. From an endocrine point of view, growth retardation, hypogonadism and a higher frequency of thyroid autoimmunity are highlighted.
Objectives
To analyse endocrine features in patients with Noonan syndrome (SN).
Material and Methods
Review of the clinical files of patients with NS followed in an external endocrinology appointment since 1997.
Results
Data from 4 male patients with NS were analysed. D1: Clinical diagnosis in the 1st year of life and molecular confirmation at age 9 (PTPN11 mutation). Height-weight evolution below P5. Pubertal induction at age 14, with normal gonadal function after testosterone suspension. Currently 26 years old, 1.44m - below the target family height (TFH) of 1.69m - BMI 18.5 kg/m^2 and dyslipidaemia. D2: Early clinical diagnosis due to dysmorphisms and cardiac anomalies with posterior molecular confirmation (PTPN11 mutation). He presented normal growth rate, hypogonadism with puberty induced at 13 years and 5 months of age and subclinical hypothyroidism with negative autoimmunity. Currently the patient is 35 years old, has 1.74m (within the TFH - 1.75m), BMI 19.9 kg/m^2 and maintains testosterone therapy. D3: Clinical diagnosis in the postnatal period due to poor height-weight evolution and phenotype, molecular confirmation at age 14 (mutation in SOS1 - Noonan-Querubinism variant). Growth within P5, spontaneous puberty and no hypogonadism. Currently the patient is 23 years-old, 1.65m (TFH 1.79m), BMI 20.6 kg/m^2, without other endocrine anomalies. D4: Molecular diagnosis at age 14 (PTPN11 mutation). Growth curve at P25–50 and pubertal induction at age 16. Currently 22 years old, 1.73m (within the TFH - 1.70m), BMI of 20.0kg/m^2, maintains testosterone therapy. All the patients presented heart disease, bone malformations and delayed psycho-motor development. Ophthalmological and dental abnormalities were reported in 3 and haematological anomalies in 1 patient.
Conclusions
In this sample, the endocrine features were heterogeneous: 2 patients reached a stature below the TFH, 1 had short final stature; in all but one, there was a need for pubertal induction; 2 were diagnosed with hypogonadism. Follow-up in appointments allowed for growth monitoring, pubertal induction at the appropriate time, and continued testosterone therapy when indicated.
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AEP588

Establishment of an assay for the effects of neurodevelopmental toxicity using Sox1-GFP cells

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Developmental toxicity tests have been made by embryonic stem cell tests at the European Centre for the Validation of Alternative Methods or by embryonic body test in our laboratory. However, no neuronal-specific developmental toxicity test has been made yet. Therefore, this study was carried out using a 46C cell line, mouse embryonic stem cells with an endogenous Sox1-GFP reporter, to exploit the developmental neurotoxicity test. The expression of Sox1, a marker for neural progenitor, can be detected by green fluorescence and the fluorescence density is a critical factor to achieve neuronal differentiation. 46C cells were treated for 24 hours with 5-fluorouracil, hydroxyurea, chlorpyrifos, clioquinol, diazinon, nicotine and lead acetate as developmental neurotoxicants, or saccharin, sodium bicarbonate, sodium gluconate, and penicillin G as non-neurotoxicants. CCK-8 assays were performed to determine IC_{50} values after 48 hours of chemical treatment. The fluorescence intensity of GFP was measured after 4 days of treatment with cells using an automated digital microscope. Through CCK-8 assay, IC_{50} values of developmental neurotoxicant chemicals were obtained, whereas non-neurotoxicant chemicals showed low effects. In addition, the fluorescence intensity of GFP was not decreased with non-neurotoxicants. However, neurotoxicants decreased the fluorescence intensity of GFP at higher concentrations. This decrease of fluorescence intensity indicates that the neuronal differentiation of 46C cells is inhibited by the chemicals. Taken together, this study produced a model of the developmental neurotoxicity tests used embryonic stem cells that may use to evaluate the toxicity of new chemicals or new candidate drugs.

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AEP589

Growth retardation in hypothyroidism and growth hormone deficieny : A case report

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Introduction
Growth retardation is a multifactorial process involving genetic, nutritional and hormonal factors. It has a significant psychological impact. The etiologies are multiple. This case illustrates a growth retardation related to more than one etiology.
Case presentation
A 22 year-old patient consulted in orthopedics for a right lameness. Diagnosis of primary hip osteochondritis had been suspected on standard X-ray and confirmed by magnetic resonnance imaging. He consulted in endocrinology for a small height relative to target height. Clinical examination showed a height at 1 m 56 (−3.3 standard deviations), a body mass index at 31.27 kg/m^2 and a Tanner stage G5P5A5. The bone age was less than chronological age with a difference of 6 years. Biology assessment showed a TSH at 100, low ft4 at 0.1 ng/ml, GH at 2.05 ng/ml and peak GH at 0.31 ng/ml (<5 ng/ml) in L-dopa test. The diagnosis of peripheral and complete growth hormone deficiency were confirmed. The rest of the pituitary assessment showed a cortisol at 358 nmol/l, hyperprolactinemia at 37 ng/ml secondary to hypothyroidism, testosteroemia at 7.95 nmol/l LH at 2.6 mUI/l concluding to a functional gonadotropic insufficiency related to hyperprolactinemia. The patient had a thyroid ultrasound showing a thyroiditis and an pituitary MRI showing a pituitary gland of normal size and morphology, a pituitary stalk and a posterior lobe in place with a normal signal. The patient has been treated with substitution by L thyroxin. He could not benefit from recombinant growth hormon since he had already a lean growth cartilage on the x-ray. The evolution was marked by the normalization of the thyroid serum level. He was referred to orthopedics for the management of his joint pathology.
Conclusion
Growth retardation is a frequent reason for consultation. Its psycological repercussions are significant. It may be secondary to one or more causes, especially when it is a severe delay. Hence the interest of looking for an associated growth hormone deficiency early to guarantee the child a gain in height via treatment with recombinant growth hormone.

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AEP590

Turner syndrome with isochromosome Xq (about two observations)

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Introduction
Turner syndrome is a chromosomal abnormality linked to the total or partial absence of the X chromosome. Its prevalence is 1/2500 female newborns. It constantly associates a stature delay and ovarian failure, with an increased risk of various malformations. The objectives of this study are to show the importance of the cytogenetic study in the management of patients with delayed height and / or primary amenorrhea, and to search for a possible correlation between cytogenetic abnormalities and the clinical expression of Turner syndrome.
Patients and methods
We report the medical observations of two patients followed at the medical genetics department of the Ibn Rochd University Hospital in Casablanca for Turner syndrome, with a mosaic karyotype, carrying a structural anomaly and a monosomy of the X chromosome.
Results and discussion
Stature delay and primary amenorrhea were the indications for the achievement of the constitutional karyotype. There are other circumstances in which Turner syndrome is discovered : prenatal on ultrasound signs, at birth in cases of lymphedema, or in adulthood in case of infertility. In addition to the delay in height, the clinical examination may find in 2/3 of cases a non-specific facial dysmorphia, as well as other associated anomalies, mainly coarctation of the aorta, which can be associated with arterial hypertension. or left heart failure in the perinatal period. The typical karyotype is characterized by a homogeneous X monosomy (45, X), but this cytogenetic type accounts for only 42 to 48% of the chromosomal abnormalities described in Turner syndrome. The homogeneous structural abnormalities of the X chromosome are found in 20 to 25% of cases, and the mosaic karyotype is responsible for 25% of cases, and it consists of a normal cell population and a cell population carrying a monosomy of the chromosome X. The originality of these two observations is that the cytogenetic study revealed a mosaic Turner syndrome, consisting of in the two reported cases of two abnormal cell populations, one carrying an anomaly in number and the another an anomaly in the structure of the X.
Keywords: Turner syndrome, mosaic, isochromosome, stature delay, primary amenorrhea.

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AEP591

Hypogonadotropic hypogonadism revealing a classic form of 21 hydroxylase deficiency in a 39 year old man

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Classical forms of 21 hydroxylase defisciency are generally observed during bith life and present as loss of salt or rapid puberty in young boy. We report a rare case of classical 21 hydroxylase defisciency presented as low gonadotrophines contrasted with normal level of testosterone. This was related to a 39 years old patient consulted for male infertility. Clinical exam was normal, including a normal level of blood tension. Liquid chromatography–tandem mass spectrometry revealed a high serum progesterone level, high 17-hydroxyprogesterone (17OHP) (262 ng/ml), and high levels of 17OHP metabolites, suggesting a classic form of 21OHD. Genetic exam has found heterozygoty with triple mutation of CYP21A2 gene including two forms of classical 21 hydroxylase defisciency. CT scann revealed a bilateral non nodular adrenal hyperplasia. Our case report illustrates the fact that a classic form of 21OHD can be diagnosed in late adulthood, manifested by hypogonadotropic hypogonadism and azoospermia , associated with elevated 17OHP.

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AEP592

Spuriously high testosterone concentrations testosterone gel users: A marker for detection

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Context
Contamination of collected blood samples by application of testosterone gel near the venipuncture site can cause spuriously elevated serum testosterone concentrations. Often this will be detected only in case of extreme discrepancies between lab result and clinical effects. Because in vitro testosterone cannot be metabolized as the testosterone *in vivo* we hypothesized that measuring estradiol, as a metabolite of testosterone after aromatizing, could give a biochemical clue for contamination.
Objective
To assess the prevalence of high serum testosterone-to-estradiol ratio in users of testosterone gel compared to users of long-acting testosterone injections (testosterone undecanoate, TU).
Design and Methods
In this study of the retrospective Amsterdam Cohort of Gender Dysphoria (ACOG) study, 474 trans men with testosterone (in nmol/l) and estradiol (in pmol/l) concentrations measured at least one year after oophorectomy, were included between 2004 and 2018. The proportion of trans men with a testosterone-to-estradiol ratio above the 97.5% percentile of the median of the TU injection users was measured in both groups. Both testosterone and estradiol were measured by or recalculated to LC-MS/MS. Logistic regression was used for statistical analysis.
Results
168 trans men (42 ± 13 years) using testosterone gel and 306 trans men (35 ± 12 years) using TU injections were included. The groups had a similar average BMI of 26 kg/m^2. The mean testosterone-to-estradiol ratio of the TU injection users was 0.29 nmol/l per pmol/l, the limit of the 97th percentile was 0.59. Of the testosterone gel users, 8.3% (95% CI 4.6–13.6%) had a testosterone-to-estradiol ratio above 0.59, vs 2.7% (95% CI 0.6–7.6%) in the TU injection users. The odds ratio (OR) for this difference was 3.3 (95% CI 0.9–11.8). Using a cut-off point of 0.60 (99th percentile) we found 13 samples (7.7%, 95% CI 4.2–12.9%) with a higher testosterone-to-estradiol ratio in the testosterone gel group and one (0.9% 95% CI 0.0–4.9%) in the TU group (OR 9.3, 95% CI 1.2–72.2).
Conclusion
Trans men using testosterone gel sometimes show a considerably increased testosterone-to-estradiol ratio compared to those using TU injections, probably caused by contamination at the phlebotomy site. However, the prevalence of such a high ratio is still quite low. We conclude that the testosterone-to-estradiol ratio can be used in clinical practice as a biochemical clue for contamination. Further studies might reveal whether measurements of other testosterone metabolites might improve the detection of spurious elevations.

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AEP593

49, XXXXY syndrome associated with diabetes mellitus with insulin resistance, delayed neurocognitive behaviour, abnormal stature, and osseous deformity- a rare case

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Back ground
49, XXXXY syndrome is a rare defect of sex chromosomes frequently considered as a variant of Klinefelter syndrome. It is often associated with more severe dysmorphic features, hypogonadism, mental retardation, musculoskeletal abnormality, and rarely with diabetes mellitus due to insulin resistance.
The goal: To describe clinical, biochemical, hormonal, radiological and developmental status of the patient with 49, XXXXY karyotype.
Report of the patient
22 years old male referred because of tall stature, sexual perversion with underdeveloped genitalia and poor scholastic performance. The patient was born by caesarean section, weight 2500 g, no history of hypoglycaemia or jaundice. He had delayed mile stone of development. He had normal height as per his fellow peer till the age of 15 yrs followed by rapid increase in height after that.
Physical examination
Revealed acanthosis nigricans with skin tag. Height 180 cm, Weight–80 Kg, BMI 24.7 height/m^2 with Arm Span of 183 cm, B/l, Testis of 2 ml size and Stretched Penile Length–6 cm, tanner stage 1, mid parental height - 164.75 cm, Upper Segment–80 cm, Lower Segment–100 cm with US: LS ratio 0.8. There was broad forehead and nasal bridge, hypertelorism, epicanthic folds, low set ears, pes cavus , deformity of left elbow joint , genu valgum ,clinodactyly, small 4th,5th toes.Psycho-cognitive development was retarded. Binet Kamat test of intelligence showed IQ of 45 (moderate mental retardation), behavioural problems with articulation difficulties. A chromosome study revealed the 49, XXXXY karyotype.
On radiographic examination
X-rays -hand and wrist- Delayed bone age with incomplete closure of growth plate. MRI of cranio-vertebral junction showed increased Atlanta-dental interval, suggestive of Atlanta-axial instability.
Biochemical tests
Metabolically, he had insulin Resistance, with fasting insulin 65.29 m U/l & FBS–112 mg/dl with HOMA-IR score of 18.1. His FBS 126 mg^5, PPBS 145 mg% with A1c 8.1%. Serum testosterone was 14.8ng/dl, LH 17.86 mIU/ml, FSH 19.79 indicating hypergonadotropic hypogonadism.
Medical advice
He was stared metformin 500 mg twice daily with life style modification in the form of diet and exercise. Testosterone injection 100 mg im was started. A clinical psychologist consultation was taken for behavioural therapy and parental counselling.
Conclusion
Patient with 49, XXXXY karyotype needs proper hormonal, psychiatric, appropriate skeletal, and cardiological evaluation. Early detection of deficit allows starting early intervention, parallel to behavioural and cognitive therapy, to support adequate management of this syndromic subject.

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AEP594

C173R and R273W mutations but not P108L in growth hormone secretagogue receptor 1a (GHSR1a) gene may cause short stature in Pakistani children

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The combined physiological effects of somatotropic and gonadal axes have been demonstrated to cause acceleration in linear growth at puberty. In synergy, growth hormone (GH) and gonadal steroids (testosterone [T] and estradiol [E2]) stimulate longitudinal bone growth through direct stimulation of chondrocytes and osteoblasts. Amongst others, the secretion of GH is stimulated by ghrelin through its receptor called GH secretagogue receptor 1a (GHSR1a). Ghrelin is a peptide secreted by gastrointestinal mucosa of the digestive system. Ghrelin/GHSR1a system plays important roles in multiple physiological processes, especially in GH secretion and appetite regulation. The GHSR1a locus is one of the top sites suggested to contribute to the genetic variation of height. Therefore, the present study was designed to determine the association between GHSR1a variants and short stature in Pakistani population. Three SNPs, C173R, R273W and P108L in GHSR1a gene, were examined. Blood samples were obtained from 35 short stature patients (21 boys and 14 girls) exhibiting short stature and decreased appetite and 30 normal healthy controls. DNA was extracted, primers of exons of GHSR1a splice sites were designed and PCR-RFLP method was employed. The PCR product of GHSR1a digested by enzyme PstI for C173R mutation gave bands of two different genotypes, normal TT (381 and 155 bp) in 14 short stature boys and 7 short stature girls and heterozygous

TC (536, 381 and 155 bp) in 7 short stature boys and 7 short stature girls. All the controls gave normal TT genotype for C173R SNP. Furthermore, the PCR product of GHSR1a digested by enzyme PvuII for R273W mutation gave bands of two different genotypes, normal AA (144 and 32 bp) in 12 short stature boys and 9 short stature girls and heterozygous AT (176, 144 and 32 bp) in 9 short stature boys and 5 short stature girls. All the controls gave normal AA genotype for R273W SNP. On the other hand, the PCR product of GHSR1a digested by enzyme HeaIII for P108L mutation gave bands of CC (155 and 24 bp). The frequency of this genotype was 100% in controls and short stature children indicating absence of P108L mutation in both groups. In conclusion, C173R and R273W SNPs of GHSR1a gene might be associated with short stature in Pakistani population.

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AEP595

Long-term reproductive and behavioral effects of low dose bisphenol A introduction to rats during late gestation on F1 offspring

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One of the most common environmental endocrine disruptor is bisphenol A (BPA), which mimics estrogen effects. Even at low expositional dose, BPA is capable of transferring across the human placenta in active unconjugated form. The purpose of this work was to investigate the long-term effects of low dose BPA introduction to rats during the critical period of sexual differentiation of the brain on the reproductive system and the behavior of F1 offspring. Wistar dams were exposed from 15 to 21 gestational day to BPA (by gavage, 25 μg/kg bw/day), or a reference estrogen (s/c, 10 μg estradiol diacetate (E2D)/kg bw/day), or were intact. The morphology of the reproductive organs and the male and female types sexual behavior were studied in adult offspring of both sexes. In males, BPA did not change the weight of testes, accessory sex glands, morphology of testicles and ventral prostate (VP), the number of sperm in the epididymis and the blood plasma levels of testosterone (T) and estradiol (E2) compared with intact males. However, almost complete inhibition of the copulatory components of male sexual behavior was observed. BPA-exposed males primed with E2 and progesterone showed pronounced lordosis behavior in the presence of a sexually active male. Prenatal E2D caused significant loss of the VP weight and degenerative changes in the epithelium of the VP. Males of the E2D group showed enhanced sexual motivation and copulatory behaviors on the background of significantly increased level of T. Besides, these males demonstrated active female and homosexual sexual behavior in the presence of sexually active male. None of the drugs affected the structure and duration of estrous cycle. The blood plasma E2 levels in the females of both groups were reduced. BPA caused degeneration of the follicular epithelium in part of the secondary and tertiary ovarian follicles with no changes in the number of follicles. Either prenatal BPA or E2D affected female type sexual behavior of female offspring. Female ♂ BPA and E2D groups exhibited male sexual behavior (5 from 5 and 4 from 5 animals respectively). We concluded that prenatal exposure to BPA at a dose below the currently acceptable human daily intake violates sexual differentiation of developing brain.

Keywords: bisphenol A, rat, prenatal effect, sexual differentiation, brain, behavior, testosterone, estradiol, male, female

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AEP596

Novel Mutations in Human Luteinizing Hormone Beta Subunit Related to Polycystic Ovary Syndrome among Sudanese Women

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Introduction
Polycystic ovary syndrome (PCOS) is a common disorder that is not fully understood. Multiple hormonal and metabolic factors impact on disease pathophysiology resulting in various phenotypic characteristics among the PCOS population. Luteinizing hormone beta subunit (LHβ) (protein ID P01229) is mapped on (chr19p13.3) and consists of three exons. It is specific beta (β) subunit giving to LH from the anterior pituitary its specific function. LH has a central role in stimulation ovarian steroidogenesis, in particular androgen production, and the promotion of ovulation.
Objectives
To determine the biochemical changes and the genetic mutations associated with PCOS among Sudanese families.
Methods
A prospective laboratory based cross-sectional study to examine genetic mutations in LHβ that associated with PCOS in families (cases; n= (35) families, (90) females and controls; *n* = (11) families, (30) females in Khartoum State, Sudan. Quantitative Enzyme Linked Immuno-Sorbent Assay (ELISA), enzymatic methods and polymerase chain reaction (PCR) used to analyze both the biochemical parameters and polymorphism detection followed by Sanger sequencing for genotyping in addition to bioinformatics software for protein structure and function.
Results
Investigation of the biochemical parameters of PCOS cases revealed significant increase with (*P*-value <0.001) in LH, testosterone, total cholesterol (mmol/l) and LDL (mmol/l) as compared to control. While fasting glucose (mmol/l), insulin (ng/dl); triglycerides (mmol/l) and HDL (mmol/l) were statistically significant (*P*-value <0.02); (*P*-value <0.012); (*P* < 0.001); (*P*-value < 0.03) respectively. There were no differences in FSH (ng/dl): (*P* = 0.984) and prolactin (ng/dl): (*P*-value = 0.068) when compared to control group. Sanger sequencing revealed five SNPs (rs5030775, A18T (AA); rs746167425, R22K (AA); rs1800447, W28R (CC); rs35270001, H30R (A/G); and rs34349826, I35T (CC)) located on (exon 2) of LHβ gene that were statistically correlated with serum LH, testosterone and insulin levels among PCOS families.
Conclusion
Based on these findings, it can be concluded that there is a genetic inheritance mode of PCOS within the Sudanese families, and a direct relationship between PCOS and infertility problems, dyslipidemia, and insulin resistance among PCOS population.

Keywords: PCOS, Luteinizing hormone, SNPs, infertility.

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AEP597

Triple-X syndrome as a cause of primary ovarian insufficiency

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Introduction
Primary ovarian insufficiency (POI) occurs in 1% of women between puberty and 40 years old. Despite being idiopathic in 74–90% of the cases, there are other etiologies, such as genetic causes (in up to 16% of cases). Triple-X syndrome (TXS) is a common (estimated incidence of 1/1000 women) but frequently undiagnosed chromosomal abnormality. Most women are phenotypically normal, despite this fact, POI can still develop. We present a case of a woman with POI caused by a mosaicism 46XX/47XXX.
Case report
Female, 40 years old, with past medical history of idiopathic pulmonary thromboembolism, treated with apixaban. Gynecological history: 1G/1P, dystocic delivery, menarche at 11 years-old and menstrual cycles with duration of 28 days. Family history: maternal grandmother with early menopause and a paternal aunt with cognitive deficit. She presented with secondary amenorrhea, along with vasomotor symptoms, asthenia, insomnia, and headache. She had no history of previous menstrual irregularities, hirsutism, acne, alopecia, vaginal dryness, reduction of libido, visual impairment, or nipple secretion. In the physical examination, she had a body mass index of 31.6 kg/m^2, no signs of vitiligo, acanthosis nigricans, ecchymoses, moon face, buffalo hump, striae, or galactorrhoea. She also had no hypotonia, clinodactyly, scoliosis or known genitourinary anomalies. Her blood work showed: estradiol 172 pg/ml, FSH 47.9 mUI/ml, LH 53.7 mUI/ml, total testosterone 0.6 ng/ml, sDHEA 241 μg/dl, androstenedione 2.67 ng/ml, 17-OH-Progesterone 1.8 ng/ml, prolactin 12.0 ng/ml, free urinary cortisol 171.6 μg/day, TSH 2.05 μUI/ml and negative 21-hydroxylase antibodies. Bone densitometry had no evidence of osteoporosis. Karyotyping revealed a mosaicism 47, XXX[8]/46, XX[46]. She was diagnosed with POI secondary to TXS and was supplemented with calcium and vitamin D. She was not treated with oestrogen given the history of pulmonary thromboembolism, absence of osteoporosis and tolerance to the vasomotor symptoms.
Discussion
Although most POI cases are idiopathic, it is important to consider and investigate other etiologies, even in the absence of phenotypic traits.

This patient did not show any phenotypic trait suggesting chromosomal aneuploidies and the reason for this might be due to the fact that only some cells presented this abnormality. Nevertheless, women with 47, XXX karyotype can be phenotypically normal. To the best of our knowledge, these women are not at risk of having children who carry a chromosomal abnormality.

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AEP598

Successful twin delivery in a patient with partial 46,XY gonadal dysgenesis

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Introduction
Partial gonadal dysgenesis (PGD) is one of the rare 46,XY disorders of sex development (DSD), associated with variable degrees of impaired testicular development and function. Phenotypic appearance is related to the level of functional testicular hormones. Usually PGD is diagnosed in infancy because of significant genital anomaly at birth, however, spontaneous puberty is seen in up to 57% of all 46,XY PGD cases. Bilateral gonadectomy is performed in order to avoid malignancy and insufficient function of gonads, which leads to infertility. We are presenting a patient with diagnosed PGD in puberty and successful twin delivery after in vitro fertilization (IVF).
A case.
A 16-year-old female was referred to the pediatric endocrinologist due to primary amenorrhea. The patient's height was 180 cm (SDS: +2.12), weight 62 kg, BMI 19.1 kg/m^2 (SDS: –0.63), puberty development B_4P_4 Tanner stage. The ultrasound examination of minor pelvis revealed the uterus matched to a 12–13-year-old and ovaries of normal volume without follicles. The patient's FSH was 130 U/l, LH 35.6 U/l (NR 4.5–11 and 1.7–13.3 respectively), estradiol 72 pmol/l (NR 55–368), testosterone 2.1 nmol/l (NR 0.38–2.74) and prolactin 120 mU/l (NR 57–418). Human Chorionic Gonadotropin (*hCG*) stimulation test was negative. According to karyotype of peripheral lymphocytes, 46,XY DSD was diagnosed with suspected complete gonadal dysgenesis followed by laparoscopic bilateral gonadectomy. A histological analysis revealed Sertoli-like cells, a small amount of Leydig cells in the stroma with fine, round nuclei and eosinophilic cytoplasm, and no primary follicles were found. A diagnosis of PGD was confirmed. The hormone replacement therapy (HRT) was prescribed. At the age of 24 the patient underwent IVF using her cousin's donor oocytes and became pregnant with twins. The pregnancy was supported with exogenously administered hormones for the first trimester. The course of pregnancy was complicated: severe hypertension and pre-eclampsia developed (severe hypoalbuminemia with the need of albumin transfusions, pericardial effusion), one of the twins appeared in breech position. The fetuses underwent lung maturation with dexamethasone. During C-section at 29 gestational weeks, male twins weighing 1351 g and 1448 g and the APGAR score of 8 were delivered. The postnatal period was fluent.
Conclusion
The clinical case represents a rare, very phenotypically expressed and late diagnosed partial gonadal dysgenesis. As in most DSD cases, the patient's pregnancy after IVF was associated with complications, however, a successful delivery of twins was achieved.

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AEP599

Polycystic ovary syndrome, subclinical inflammation, DPP4 and the impact of a progestin test

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Introduction
Women with PCOS frequently exhibit impaired insulin sensitivity. Low-grade chronic inflammation has been associated with insulin resistance and type 2 diabetes. DPP4, also known as CD26 (T-cell activation antigen CD26) is a prolin-specific serin-exopeptidase. With its binding partner ADA (Adenosine Deaminase complexing Protein) it cleaves numerous chemokines, mitogens, neuropeptides and peptide hormones and thereby influences metabolism, immune and endocrine system as well as cell adhesion and tumor growth. Previous publications found 6–7% higher activity of DPP4 in PCOS vs non-PCOS patients, and an influence of androgens on DPP4 transcription. Since progesterone is considered to possess anti-inflammatory effects, whereas estradiol promotes inflammation, we examined progestin effects on DPP4 and other markers of inflammation and insulin resistance.
Methods
315 patients with PCOS or ovulatory dysfunction with hyperandrogenemia in the gynecological endocrinology unit at the Technical University of Munich (TUM) were invited to participate in a prospective observational study on the effects of a standardised progestin test on hormone levels and markers associated with inflammation in serum. Women with menstrual cycle lengths ≥50 days, severe obesity (BMI >36 kg/m^2) and other endocrine or metabolic disorders were excluded from the study. Participants aged 18–45 years, without steroid treatment for at least 4 months prior to entry are monitored for five visits in three consecutive cycles. At baseline, medical history, waist-to-hip ratio, ovarian morphology and serum samples are taken in the early follicular phase of the cycle, before the participants take 10 mg dydrogesterone for 14 days (progestin test). Serum samples are drawn at four predefined time points (day 10–12 of the gestagen test, day 3–7 and 19–26 of the second cycle, day 3–7 of the third cycle). The analytes in the serum samples include CRP, progesterone, estradiol, LH, FSH, prolactin, testosterone, DHEAS and SHBG as well as proteins associated with hormones and inflammation, i.e., adropin, progesterone-induced blocking factor (PIBF) and dipeptidyl peptidase 4 (DPP4).
Results
Out of the 315 patients, only 60 met the criteria for entering the study. Early results show a significant PIBF increase with higher progesterone levels both with endogenous and exogenous progestin, while limited effects on adropin or DPP4 were found so far. DPP4 levels showed strong inter-individual variations, DPP4 concentrations and activity showed a linear correlation. 65% of the CRP values were lower than ≤ 0.1 mg/dl.
Discussion
We found no increase of DPP4 concentrations or activity attributable to progestins.

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AEP600

Assisted Reproductive Technology (ART) Success Rate Among Obese And Non-Obese Women, With Infertility Associated With Polycystic Ovary Syndrome (PCOS)

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Introduction
Previous studies in women with idiopathic infertility have shown that obesity does not independently contribute to the decrease in the success of assisted reproductive technology (ART) techniques. However, few studies evaluated the success rate of ART between obese and non-obese women in infertility associated with PCOS.
Objective
To compare the number of oocytes, mature oocytes, number of embryos and the rate of live births (LB), between obese and non-obese women with PCOS after an *In Vitro* Fertilization (IVF)/Intracytoplasmic Injection (ICSI) cycle.
Material and methodology
Retrospective study of all cycles of IVF/ICSI performed at our institution between 2012 and 2018. All women with PCOS-associated infertility were included. Only cycles with a live birth delivery after 24 weeks, or cycles with no surplus embryos left were considered. The participants were stratified by Body Mass Index (BMI) and the group of Obese/Overweight women (BMI ńł25 kg/m^2) was compared with the group with Normal/low Weight (BMI ń 24.9 kg/m^2).
Results
We analyzed 49 cycles. The median infertility duration was 48 months (min-max:10–144). Median age was 33 years (min-max: 21–39) and median BMI was 26.7 kg/m^2 (min-max:17–37). Median Anti-Mullerian Hormone (AMH) was 7.5 ng/ml (min-max: 2.2–18) and median antral follicle count was 30

(min-max: 4–50). In 47% (n = 23) of couples a LB was obtained. After stratification by weight, 61.2% of women were Obese/Overweight (n = 30) and 38.8% (n = 19) were Normal/low Weight. There were no differences between the two groups regarding median age (Obese/Overweight vs Normal/low Weight: 33.5 years, min-max: 21–39 vs 32, min-max: 26–39; P = 0.741), infertility duration (48 months, min-max: 24–144 vs 53, min-max: 10–120; P = 0.071, AMH (7.5, min-max: 2.9–18 vs 6.9, min-max: 2.2–15.7; P = 0.87), or antral follicle count 30, min-max: 13–50 vs 30, min-max: 4–50; P = 0.326). Regarding the results of ART techniques, Obese/Overweight women had a non-significantly higher percentage of newborns, compared to women with Normal/low Weight (50% vs 42%, P = 0.06). We also found no differences between the median number of oocyte (Obese/Overweight Vs Normal/low Weight: 15, min-max: 1–39 vs 13 min-max 1–48; P = 0.35), mature oocyte (12, min-max: 0–35 vs 11, min-max:1–45; P = 0.85) and obtained embryos (8, min-max: 0–24 vs 6, min-max:0–32; P = 0.62).

Conclusion

In PCOS, overweight/obesity does not seem to be a limiting factor of the success rate of ART. Other parameters are probably more important, such as age.

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AEP601

Hearing abnormalities in Turner patients

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Introduction

Turner Syndrome is a relatively rare genetic disorder related to the total or partial absence of an X chromosome. Its clinical presentation is very heterogeneous. It can be associated with several organic abnormalities, including hearing disorders. The objective of our work is to study the prevalence of otologic abnormalities in our Turner patients.

Material and method

This is a retrospective descriptive study involving 17 patients followed for Turner syndrome in the Endocrinology-Diabetology and Nutrition Department of the Mohammed VI University Hospital Center of Oujda, Morocco. All patients were evaluated by otologic examination and audiometry.

Results

The mean age of diagnosis was 16.4 ± 12.4 years [3–41 years]. Thirty-five percent of patients were diagnosed in adulthood. The reason for consultation was dominated by short stature in 47% of cases. Twenty three percent of patients had recurring ear infections. One patient had an atelectasic otitis with a focal tympanosclerosis benefiting of a trans-tympanic ventilator. The examination found low ear implantation in 76.4% of the cases with detached ears in 29.4%. Conductive hearing loss was reported in 23.5% of cases, and mixed hearing loss in 11.7%. These otologic abnormalities were present in 55.5% of cases in patients with X monosomy, in 44.4% of cases in patients with mosaic of which 22.2% had an Xi isochromosome.

Discussion-conclusion

Otologic abnormalities are common in Turnerian patients, especially those with X monosomy. Sometimes patients may be clinically asymptomatic; therefore, screening at diagnosis and regular long term monitoring are recommended to detect middle ear disease and avoid its consequences.

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AEP602

Syndromic premature ovarian insufficiency: report of 2 cases with blepharophimosis-ptosis-epicanthus inversus syndrome type 1

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Introduction

Premature ovarian insufficiency (POI) is defined by menstrual disturbance (oligomenorrhea or amenorrhea) before 40 years and confirmed by two FSH levels in the menopausal range, obtained at least a month apart. Some POI cases are syndromic such as Turner's syndrome or Blepharophimosis–Ptosis–Epicanthus inversus Syndrome type 1 (BPES). BPES type 1 (MIM: 110100) is a rare autosomal dominant syndrome caused by mutations in *FOXL2, a* gene involved in folliculogenesis.

Objective

Here we report two cases with confirmed BPES type 1 collected at the outpatient clinic of the genetic department at Charles Nicolle Hospital in Tunis.

Cases presentation

The patients were referred to genetic consultation for oligomenorrhea and facial dysmorphism. The first case was familial including two affected sisters aged 32 and 38. The second case, a 31 year-old woman, was sporadic. All patients had normal intelligence. Clinical examination of the three patients showed eye abnormalities with blepharophimosis, ptosis and epicanthus inversus, normal secondary sex characteristics, and normal growth. The hormonal tests showed high FSH levels. Their karyotypes were normal: 46, XX. Based on clinical findings, the diagnosis of BPES type 1 was strongly suspected. Direct sequencing of *FOXL2* gene showed the presence of a previously reported mutation NM_023067.3:c.655C>T; p. (Gln219*), confirming the diagnosis of BPES.

Conclusion

In case of POI, a careful clinical examination is recommended to look for syndromic causes such as BPES syndrome type1 easily recognizable on the ocular abnormalities, so that appropriate management and adequate genetic counseling could be done.

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AEP603

Swyer Syndrome, 46,XY complete gonadal dysgenesis in a patient with spontaneous menarche

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46,XY complete gonadal dysgenesis, also known as Swyer Syndrome, is characterized by the presence of normal female external genitalia at birth, late puberty and primary amenorrhea. Spontaneous menses (due to hormone-secreting tumor) and breasts development occur in rare cases. With proper hormonal substitution, patients could carry pregnancies achieved through IVF with donor oocytes.

Case presentation

Female patient, aged 22, addresses endocrinology specialist for a routine examination. She mentions having first menses when she was 14, with spontaneous menses for the next 5 years followed by secondary amenorrhea, for which she started estroprogestative substitution after medical recommendation, resulting in regular menstrual cycles and normal breast development. She came to our clinic for amenorrhea after stopping the hormone substitution therapy. Clinical investigations contributed to the diagnosis of hypergonadotropic hypogonadism, with testosterone in normal range and low estradiol. A karyotype test was performed with the result of 46,XY genotype without structural or numerical abnormalities. FISH testing revealed the presence of SRY, DXZ1 and DYZ1, therefore, the patient was advised to seek further genetic analysis. MRI showed Mullerian structures, infantile uterus with Fallopian tubes but instead of gonads, fibrotic bands could be seen. Considering the risk of developing a gonadoblastoma or even a dysgerminoma in a patient with Disorders of Sexual Development, the patient was advised to present to the Surgical Department to undergo exploratory laparotomy and resection of dysgenetic gonads, followed by estroprogestative substitution. Histopathological examination and immunohistochemistry analysis revealed that one of the dysgenetic gonad was a dysgerminoma with Ki67 positive in 17% of tumor cells, and the other one was a testes having Wolffian and Mullerian structures with no tumor characteristics.

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AEP604

Hyperthyroidism on molar pregnancy about a case

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Introduction
Hyperthyroidism during pregnancy can be caused by an hydatiform mole in its partial or total form. The biochemical particularities between hcg (human corionic gonadotropin) and Tsh (thyreo-stimulating hormone) in gestational trophoblastic disease can explain the thyrostimulating effect in it. We report a case of hyperthyroidism on molar pregnancy through an observation.
Observation
Patient of 27 years old, with a history of an intrauterine fetal death 5 years ago, admitted for incoercible vomiting on pregnancy estimated at 11 weeks with partial hydatiform mole. At the examination agitated patient without exophthalmia. She presented tachycardia at 118 beats per minute, fine tremor of the extremities, and no goiter. Laboratory results showed a stunt TSH at 0.01 mui/ml; T4l: 28.3 pmol/l, T3:7.9 pmol/l, HCG 540984 or +1.9 N. An obstetrical echography conclude on uterus increased in size, fetus in flattened death, placenta abnormally large with snowflake image reminiscent of a partial mole. Thyroid echography was normal. EKG: sinus tachycardia at 120 bpm. The rest of the balance sheet is without particularities, in particular the Ac anti RTS and TPO. The management consisted in the initiation of carbimazol 30 mg/day and propanolol 40 mg/d to obtain euthyroidism before uterine extraction. At day 4 we had improved symptoms and biological euthyroidism with T4L at 13 pmol/l after uterine evacuation.
Discussion
Clinical hyperthyroidism is a common complication of a hydatiform mole, in our case presented by incoercible vomiting and tachycardia. The structural homology between the TSH and HCG subunits and between their receptors gives HCG a thyroid-stimulating action. The presence of intrauterine fetal death could be attributed to the direct effects of thyroid hormones on the fetus. The treatment of hyperthyroidism induced by hydatiform mole is an uterine evacuation although in our case we first particularly used ATS and blockers.
Conclusion
The diagnosis of hyperthyroidism secondary to hydatiform mole is retained before a low or undetectable TSH, T4l elevated after eliminating transient hyperthyroidism from the large ratio to term, TRACK negativity and cervical ultrasound without hypervascularization. This is a resolutive table after uterine extraction.

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AEP605

Primary amenorrhea due to hypogonadotropic hypogonadism

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A diagnosis of primary amenorrhea (PA) is always a clinical challenge. By definition, PA is a failure to reach menarche by age 14 with the absence of secondary sexual characteristics or absence of menses by age 16 years regardless of the development of secondary sexual characteristics. It may result from a number of different conditions and requires comprehensive evaluation to identify a cause, along with a regular patient follow-up. The aim of this case report is to emphasize the significance of early diagnosis accompanied with timely treatment in patients with hypogonadotropic hypogonadism (HH). A 21-year-old female was referred to endocrinologist due to PA and possible uterine agenesis. She was born prematurely at 36 week and soon diagnosed with strabismus and congenital cataract. Previously, her mother had two miscarriages. At physical examination, her weight was 70 kg, height 167 cm (BMI 25.1 kg/m^2), hair growth reduced, breasts Tanner stage I, pubic hair Tanner stage II and high-arched palate was present. Basal hormonal evaluation revealed low estrogen (E2 126 pm/l), low levels of gonadotropins (LH 0.00 mIU/l, FSH 0.07 IU/l) and total testosteron of 1.76 nmol/l. Levels of IGF-1, IGF BP3, thyroid hormones, prolactin, basal cortisol and androstenedione were all in reference range. Glucose tolerance was not impaired. Magnetic resonance imaging (MRI) showed normal anatomy and appearance of hypothalamic-pituitary region. Pelvic MRI revealed a hypoplastic uterus with uncertain ovarian demarcation (right ovary 16×8 mm, properly located). LHRH and Pregnyl tests were performed and, according to all data, a diagnosis of HH was established. Additional analysis included cytogenetics: 46XX with pericentric inversion of chromosome 9 (inv[9][p11q13]). The patient also underwent psychological assessment. A treatment with estrogens was initiated, followed by combined, estrogen-progesterone replacement. As a result, patient is now with regular menstrual cycles and further development of secondary sexual characteristics. In conclusion, the precise and early diagnosis of HH along with appropriate replacement therapy can restore fertility in affected patients, preserve normal bone mineral density and prevent negative physical and psychological sequelae.

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AEP606

Translation of OAT syndrome infertility into normozoospermia after short duration testosteron therapy – case report

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Introduction
Infertility associated with hypergonadotropism is usually an unpromising condition related to acheiving fertilization. We describe the patient presented as oligoasthenoteratozoospermia (OAT syndrome), with laboratory primary hypergonadotropic hypogonadism but normal male fenotype, including typical male hair dustribution.
Case description
male, born 41 year ago, presented when he was 29 year old, as infertility with oligozoospespermia of sperm count of 0.2–0.4×0^6/semen volume, total motility of 14%, testosteron without Clomifen stimulation 9–11.5 nmol/l, FSH 11.8–18 mIU/ml, LH 6.8–9.1 mIU/ml, regularly on Profertil® therapy. When he was 35 year old he gave his consent for gonadotropin supression therapy with testosteron depo preparation od 125 mg im per 2 weeks. After 4 months od such a therapy his FSH was 2.1 and LH 0.1 mIU/ml, and as expected azoospermia. We discontinued testosteron therapy and after 1 year he came with FSH 11.4 mIU/ml, sperm count of 36.5×10^6/semen volume. After that time he has intermitently been on Clomifen and Profertil therapy, and sperm parameters more or less in normal ranges. His testosteron values has been in low values, when without Clomofen stimulation. In 2019 year for the first time we measured several times dihitrotestosteron levels which was always in normal ranges 454–785 ng/ml (referent 250–990) while testosteron was low 5.68–10.19 nmol/l.
Discussion
The aim of this case report is to emphasize the constelation of low testosteron levels and normal dihidrotestosteron in patient with normal male habitus but initialy with OAT syndroma. Although at the moment we have not been maesured precursors of testosteron and dihidrotestosteron we are in thinking about the so called ''backdoor'' pathway of androgen synthesis, until this time described only in animals and considered in human male development.

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AEP607

Analysing by decade, testosterone undecanoat depot injectable does not increases prostate volume. Study during up to 13 years on hypogonadic patients. (January 2021)

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Aim
Re-Analysing (starting 2007) the effect of injectable testosterone undecanoat depot (TUD) in hypogonadic patients.
Material-method
A. Patients: at onset 333 men with hypogonadism (median: 62 y).
B. Distribution: by decade (starting with 20y->90y); no = 6, 18, 35, 80, 104, 67, 21, 2.
C. TUD (Nebido^R-Bayer) 1000 mg injected one/3 months i.m.
D. Prostate volume (PV) by per-abdominal ultrasound: 3.5–5 MHz probe, elliptical/3D (cm^3).
E. Analysis in time: before testosterone (T0 = 333), after ½ month (T1 = 332), 3m (T2 = 273), 6m (T3 = 212), 1y (T4 = 175), 2y (T5 = 121), 3y (T6 = 84), 4y (T7 = 66), 5y (T8 = 59), 6y (T9 = 50), 7y (T10 = 43), 8y (T11 = 34), 9y (T12 = 26), 10 y (T13 = 19), 11y (T14 = 11), 12y (T15 = 5), 13y (T16 = 3).
F. Maximum increment percent from T0 noted Δ**M**%. Average increment percent noted Δ**A**%.
G. Statistical analysis: Student test.

Results
I. A. Mean prostatic volume before testosterone increased by decade (significance vs 20y): 13.17; 16.83 (0.24,NS); 22.25 (P = 0.016); 29.54 (P = 0.0003); 36.19 (P = 0.000004); 40.53 (P = 0.0000002); 44.67 (P = 0.000003); 33.75 (P = 0.001). **B.** All average prostatic volume post testosterone by decade and time were tabulated (see pdf).
II. Maximum increment post testosterone (Δ M %) per decade: 54.76; 44.44; 56.41; 68.92; 53.85; 68.18; 54.55; 29.00.
III. The moment of ΔM% – per decade: T10; T5; T8; T8; T3; T7; T5; T2.
IV. Average increment (ΔA%) per decade: +4.69; −12.02; −14.75; −1.48; −13.33; −45.29; +14.69; +14.63.
V. Considering all observations, TUD did not increase PV significantly. **A.** The average of increment (%) in all patients was negative: −6.61%. **B.** Per decade significance vs beginning TUD was P = : 0.34; 0.12; 0.67; 0.29; 0.77; 0.98; 0.28; 0.17.
VI. In many patients, especially from 30 to 79 years, TUD could decrease slightly prostatic volume.
Comments
After 3 month, many patients give up treatment. At 1 year, around half patients withdraw. However, comparing with 2019 (Lyon) data, patient number increased by 16.22%. 19 patients were operated before starting testosterone, 4 patients were operated during treatment. 5 patients received the diagnosis of prostatic cancer; to them, TUD was administrated when PSA < 1, usually after 3 years anticancer treatment. Surprisingly, 16 patients died after withdrawing TUD at 2–3 years.
Conclusions
Considering the risk for prostate (in elderly), testosterone undecanoat 1000 mg depot injectable is a safe treatment, even after 13 years of administration. Precautions should be accorded to men over 80 y old, after the 5th year of administration. Under strict control, TUD could be administrated also in prostatic cancer.

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AEP608

After up to 13 years observation, testosterone undecanoat 1000 mg at 3 months did not increased Prostatic Specific Antigen level. Relation with prostatic volume (January 2021)

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Aim
We appreciate the effect of testosterone undecanoat 1000 mg intramuscular injection (Nebido®; Bayer) on both prostatic volume (see Peretianu, this congress) and PSA (this study) in hypogonadic patients after up to 13 years.
Material and method
A. PSA (ng/ml) was done in Bucharest accredited laboratories, appreciated at 1 year. **B.** Prostatic volume (PV): ultrasound, 3–5 MHz, per abdominal, in 3D (cm3).
C. Statistical analysis: Student test, simple correlation, multiple regression.
Results
A. Patients at onset: 309 men, age: 18–96 years, average: 61.02 years; median: 62.
B. Prostatic volume: average: 33.05 cm3.
C. Average PSA (no patients): before treatment = 1.52 (309); 1y = 1.66 (164); 2y = 1.48 (113); 3y = 1.47 (82); 4y = 1.67 (65); 5y = 1.58 (59); 6y = 1.71 (47); 7y = 1.68 (44); 8y = 1.58 (35); 9y = 1.76 (23), 10y = 1.75 (19), 11y = 2.06 (11), 12y = 0.77 (decreased)(5), 13y = 0.7 (decreased)(3).
D. Statistical difference of PSA averages from T0 to 11y: nonsignificant: P = between 0.29–0.87. T0 v 12y P = 0.04, T0 v 13y P = 0.002.
E. Correlation between age and PSA was significant at: T0: r = 0.33; 1y: r = 0.2 and 8y P = 0.05; and nonsignificant in rest. Significance is depending on group size.
F. Correlation between PSA and prostatic volume was significant, both before and after treatment at 1, 2, 3, 5, 6, 8, 9, 10 years (depending on group size, r = 0.13–0.54).
G. Multiple regression test between PSA before/after treatment, prostatic volume before/after treatment and the age. Statistical significance: P values < 0.01 for all years (except 6y-NS and 13 y-non 5 patients). P << 0.05: R^2 = 0.28–0.82, F = 6.67–12.48.
Conclusions
1. Testosterone undecanoat 1000 mg injectable i.m. at 3 months did not increased PSA level after up to 13 years administrations.
2. Based on multiple regression data, PV & PSA post testosterone does not depend on testosterone administration but on the age and the PV before treatment and depend on the initial PSA level, i.e. before testosterone administration.
Comments
Since PV and PSA level did not depend on testosterone administration, but on age we thing that: a. there could be a therapeutic window for testosterone, considered before 80 years old, b. the moment of testosterone administration should depend on testosterone decreased slope, c. therefore, testosteronemia should be performed every year from 20 years old.

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AEP609

Premature ovarian insufficiency associated with a small supernumerary marker chromosome 15: a case report

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Introduction
Premature ovarian insufficiency (POI) is characterized by the loss of ovarian activity before the age of 40. It is associated with hypoestrogenism, raised gonadotrophins and oligomenorrhea or amenorrhea. POI is a heterogeneous disease that can result from different etiologies, including genetic, autoimmune, and iatrogenic. Of the genetic causes, single-gene mutations and chromosomal imbalances involving X chromosome or autosomes have been associated with POI. Here, we report a case of a 36-year-old patient with POI associated with a small supernumerary marker chromosome 15 (sSMC(15)).
Case presentation
A 36-year-old woman with normal intellect and no particular past medical history, had menarche at age of 13 followed by regular menses. She had no pregnancies before and she presented a secondary amenorrhea evolving for 8 years. The physical examination was unremarkable especially she had normal height, normal secondary sex characteristics, and no dysmorphic features. Hormonal tests revealed normal FT4, TSH, prolactin, elevated FSH in the menopausal range (82.43 mUI/ml) and AMH was too low at 0.04 ng/ml (reference: 0.03–7.15). Therefore, the diagnosis of premature ovarian was made and the patient was treated with hormone replacement therapy. Pelvic ultrasound demonstrated a normally placed and normally developed uterus and the ovaries were small without follicles. Her karyotype showed in 86% of metaphases analyzed the presence of a small supernumerary marker chromosome. Fluorescence in situ hybridization (FISH) showed the sSMC to be originating from chromosome 15, dicentric and most likely containing only heterochromatic material [mos 47,XX,+mar[39]/46,XX[6]. ish idic(15)(q11)(D15Z4++,SNRPN-)]. Parental karyotypes were normal confirming the *de novo* occurrence of the sSMC.
Conclusion
Several studies reported an increased incidence of sSMC(15) in infertile males, whereas in females, relationship between SMCs and infertility is still debated. Further precise molecular studies on sSMC are needed in the future to characterize the implication of sSMC in POI.

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AEP610

Assessment of glycemic variability using the FreeStyle Libre flash monitoring system in pregnant women with gestational diabetes mellitus

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Background and aim
Early control of gestational diabetes mellitus (GDM) can reduce the likelihood of adverse maternal and fetal outcomes. Glycemic variability (GV) is a more accurate parameter for assessing the risk of developing diabetic complications than traditional parameters of assessing compensation. In most cases, diet therapy is used to treat GDM, meanwhile the glycemia in pregnant women with GDM should correspond to the glucose level in healthy pregnant women. The aim of our work was to compare biweekly

glycemic profiles and glucose variability in healthy pregnant women and pregnant women with GDM on diet therapy using the FreeStyle Libre flash monitor system.
Materials and methods
Analysis of the glycemic profile of 40 pregnant women aged 25.47 ± 5.83 using the FreeStyle Libre continuous monitoring system. Pregnant women were divided into 2 groups: 20 healthy pregnant women and 20 pregnant women with GDM on diet therapy. Each group was evaluated for ambulatory glucose profile monitoring over a two week period using the FreeStyle Libre system.
Results
Age and HbA1c levels were comparable in both groups, but body mass index (BMI) before pregnancy was higher in the GDM group (P = 0.026). Women with GDM had higher blood glucose levels than healthy pregnant women, but within the target range. In patients with GDM, who were compensated for carbohydrate metabolism during diet therapy, there was a low variability of glycemia according to standard indices. There were significant differences in mean glycemia and J-index, which characterizes the maximum peak of glycemia (Table 1).

Measures of Glucose Variability	Patient group		n	P
	GDM	Healthy pregnant women		
SD, mmol\l	0.911	0.884	0–3.0	0.61
CONGA	3.980	3.875	3.6–5.5	0.27
LI	1.450	1.256	0–4.7	0.28
J-index	10.291	9.564	4.7–23.6	<0.05
HBGI	0.647	0.762	0–7.7	0.54
LBGI	4.728	5.665	0–4.6	0.16
MOOD	0.963	0.935	0–3.5	0.64
MAGE	2.31	2.263	0–2.8	0.72
ADDR	3.007	1.935	0–8.7	0.27
M-value	7.677	10.088		0.14
Mean glucose	3.6	3.1		<0.02

Findings
In order to obtain more detailed information about the glycemic profile, especially when it is difficult to assess the degree of compensation for GDM, modern devices for Flash glycemic monitoring can be of great value. Continuous monitoring allows a more thorough assessment of the effects of GDM therapy, at the same time, further researches are required to assess the significance of these data.

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AEP611

Vitamin D and sex hormones levels in men of different ages

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Introduction
Vitamin D (VitD) is thought to be essential for adequate testosterone (T) secretion in men. In the absence of D-hypovitaminosis, their blood T levels and T to estradiol (E2) ratio values are higher relative to those with VitD deficiency. The correlation between VitD levels and androgenization indices in men of different ages has not been practically studied.
The aim
To study blood levels of T and the androgen-estrogen balance depending on the blood concentration of VitD in young and middle-aged men.
Material and methods
47 men aged 23–59 years were examined: 1 group – young males (32.3 ± 1.1) yrs, n = 20; 2 group – middle age (53.0 ± 1.0) yrs without Diabetes Mellitus Type2 (DM2), n = 15; 3 group – middle age (54.0 ± 1.1) yrs with DM2, n = 12. In all three groups, the mean values of body mass index (BMI) did not differ from each other. Blood levels of total T, E2, and 25-OH VitD were determined in the patients by enzyme immunoassay. VitD insufficiency and deficiency were established according to the Endocrine Society Clinical Practice Guideline (2011). The studies were performed in the fall-winter period of 2020-2021.
Statistical analysis
SPSS 19.0 statistical software (IBM Corp., Armonk NY, US) Student's t-test, χ^2 method and Pearson correlation (r).
Results
The mean values of blood VitD levels in young men were significantly higher than those of middle-aged individuals (P<0.05). At the same time, they did not differ between the patients with and without DM2. In middle-aged patients of both groups, there was a significant decrease in the average values of blood T and T/E2 values relative to young men. At the same time, the frequency of androgen deficiency was significantly higher in group 2 (χ^2 = 4.49; P <0.05) and in DM2 patients (χ^2 = 5.75; P<0.05) compared to young men. However, the incidence of D-hypovitaminosis (blood VitD levels < 30.0 ng/ml), was not significantly different in middle-aged individuals than in men in group 1. Meanwhile, there was found a positive correlation between the blood VitD level and the index of the relative androgenization – T/E2 values, (r = 0.321; P<0.05) in the general group of examined patients.
Conclusion
Blood VitD content in middle-aged men, regardless of the presence or absence of DM2, is significantly lower in comparison with young men. A decrease in the blood levels of VitD can be a predictor of androgen–estrogen imbalance in men regardless of age.

Keywords
Vitamin D, sex hormones, androgen–estrogen balance.
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AEP612

Central hypothyroidism during pregnancy in a woman with Graves' disease

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Introduction
During pregnancy, women with Graves' disease are at risk of maternal and fetal hyperthyroidism caused by stimulating TSH receptor antibody. Here we report the unusual case of a woman with recurrent Graves' disease who developed central hypothyroidism transiently during pregnancy.
Case report and results
A 26-year-old woman was treated by antithyroid drug for a third episode of hyperthyroidism due to Graves' disease. At the beginning of her second pregnancy, cervical palpation showed a large vascular goiter. Thiamazole treatment was stopped in the first week of gestation. During the 3rd month, hormonal monitoring revealed central hypothyroidism: TSH = 1 mU/l (0.27–4.3), fT4 = 0.67 ng/dl (0.81–1.32), fT3 = 2.37 ng/l (2.47–4.1), in presence of anti-TSH receptor antibodies (3.5 UI/l) with stimulating activity (+ 285%) and elevated hCG levels (153 656 UI/l). During the second half of gestation, substitutive levothyroxine treatment restored an euthyroid state. Furthermore, anti-TSH receptor antibodies titers decreased progressively and were undetectable at the end of the second trimester. The woman gave birth to a healthy euthyroid baby girl (3.2 kg) without goiter. During the postpartum period, she breastfed normally. Her anterior pituitary function was investigated and shown to be normal: spontaneous menstrual periods, anterior pituitary hormones within normal range and normal pituitary IRM at 6-month *post-partum*. During *post-partum* follow-up, levothyroxine treatment was progressively decreased and the patient eventually developed 'classical' recurrence of Graves' disease with thyrotoxicosis 8 months after delivery.
Conclusion
We report the first case of transient central hypothyroidism during pregnancy in a woman with recurrent episodes of Graves' disease. Despite the presence of anti-TSH receptor antibodies with stimulating activity detectable during the first two trimesters of pregnancy, we suggest, as a unifying hypothesis to explain this highly unusual clinical and biological pattern, that this woman secreted a variant hCG molecule that binds both to the TSH receptor on follicular thyroid cells and on the folliculo-stellate cells of the anterior pituitary with inhibiting activity resulting in central hypothyroidism.

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AEP613

Bone metabolism in PCOS – influence of progestins

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Introduction
The polycystic ovary syndrome (PCOS) affects about 6–10% of women of reproductive age and is associated with oligomenorrhoea and anovulation. Recently, a possible impairment of bone accrual in women with PCOS due to the chronic inflammation disposition has been postulated [Kalyan, 2017]. The lack of progesterone due to anovulation may also have effects on bone metabolism [Seifert-Klauss, 2015]. A progestin test is a classic tool for assessing oligo- and amenorrhoea. The presented observational study monitors the effects of the progestin test for oligomenorrhoea on bone metabolism markers, LH and other hormones as well as ovulation rates in the following cycle.
Methods
60 premenopausal women (18–45 years), all pre-diagnosed with PCOS, without steroid treatment for at least 4 months are monitored for five visits in three consecutive cycles. Women with menstrual cycle lengths of ≥50 days, severe obesity (BMI >36 kg/m^2) and other endocrine diseases or metabolic disorders are excluded from the study. At baseline, medical history, hip and waist circumference, ovarian morphology and serum samples are taken in the early follicular phase of the cycle, before the participants take 10 mg dydrogesterone for 14 days for their progestin test. Serum samples are drawn at four defined follow-up time points (day 10–12 of the gestagen test, day 3–7 and day 19–26 of the following cycle as well as day 3–7 of the third cycle). Analytes determined in serum samples include CRP, progesterone, estradiol, LH, FSH, prolactin, testosterone, DHEAS and SHBG as well as the bone metabolism markers procollagen type I N-terminal propeptide, bone-specific alkaline phosphatase, osteocalcin, C-terminal collagen type I telopeptide and tartrate-resistant acidic phosphatase 5b.
Results
12 participants of the targeted 60 PCO-patients have completed the study to date. Whereas progesterone levels at day 3–7 of all cycles were below 0.4 ng/ml, 75% of the participants exceeded progesterone levels of 2 ng/ml during the progestin test (average 6.2 ± 3.6 ng/ml) and 42% at day 19–26 of the following cycle without exogenous progestin (average 12.7 ± 7.0 ng/ml). The luteal phase was missed in 3 patients (27%), who showed significantly elevated LH levels on the scheduled day of visit 4 (cycle days 22, 26 and 31), most likely due to delayed ovulation in the cycle following the progestin test. Bone metabolism parameters will be presented.
Discussion
This study systematically characterizes changes in bone metabolism which may be attributable to inflammation, ovulation vs. anovulation and/or progestin deficiency.

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AEP614

Peculiarities of cytokin levels in women with infertility living in iodine deficiency regions of Bukovina

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Introduction
The problem of ecologically caused iodine deficiency is acute in many countries around the world, including Ukraine, where the endemic zone for the development of iodine deficiency is Northern Bukovina. The possible participation of iodine in the induction or manifestation of autoimmune processes in the thyroid gland and their role in reproduction is discussed. Iodine deficiency is significantly higher in infertile women than in women with normal fertility. In addition, immune mediators, in particular cytokines, have a clear relationship with iodine metabolism and thus are important regulators of fertility.
The aim of the study
To determine the features of the peripheral blood cytokine profile in women with infertility living in iodine-deficient regions of Bukovina.
Materials and methods
The analysis was conducted on the basis of detailed clinical, anamnestic and laboratory studies of 32 women who lived in iodine-deficient regions of Bukovina and who appealed to the clinic with complaints about infertility. The control group consisted of 30 women with infertility living in regions that are prosperous in iodine content. The comparison group consisted of 30 healthy women. Determination of cytokine levels (TNF-α, IL-2, INF-γ, IL-4, IL-6) in blood serum was performed by ELISA.
Results
In women of the study group compared with the control, the studied cytokines of Th1 (TNF-α, IL-2, INF-γ) there was a significant difference only for TNF-α – anincrease of 0.82 times (P <0.05), with insignificant changes in IL-2 and INF-γ levels. At the same time, there was a probable increase in the levels of both studied cytokines of the Th2 type: both IL-4 (0.98 times, P <0.05) and IL-6 (0.45 times, P < 0.05). It should be noted, that in the both studied and control groups compared to healthy women the levels of all studied cytokines had the same trend.
Conclusion
Thus, endemic iodine deficiency in infertile women aggravates the production of TNF-α, IL-4 and IL-6, which may indicate on the role of iodine deficiency in immune homeostasis and infertility, mainly by reason of impaired Th2 type immune response.
Key worlds
Cytokines, women with infertility, endemic iodine deficiency.

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AEP615

Y chromosome in Turner syndrome: preventive management Case report and review of the literature

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Introduction
Turner syndrome (TS) is one of the most common types of aneuploidy; its etiology is associated with total or partial X-chromosome monosomy. In 5–12% of patients, mosaicism for a cell line with Y chromosome is identified. The presence of Y-chromosome increases the risk of gonadal tumors, especially gonadoblastoma and subsequent dysgerminoma. Here we report on the case of a girl with a rare 45X0/46XY mosaic TS exhibiting a primary amenorrhea and delayed puberty; she received preventive surgical treatment by resection of the ovarian strips under laparoscopy and hormonal supplementation.
Case report
The patient was diagnosed with TS at the age of 16 years, upon a diagnostic work-up for a primary amenorrhea, a delayed puberty and short stature without dysmorphic syndrome. Chromosome analysis revealed a mosaic karyotype (45X0/46XY). A physical examination revealed a Tanner stage I for breast and Tanner stage II for pubic hair development. Psychological evaluation showed normal global developmental with highschooler level, together with emotional and social maturity. Her bone age was 13 years. Pelvic magnetic resonance imaging and ultrasound demonstrated a small uterus with unseen ovaries. A laparoscopic exploration was performed which revealed a hypoplastic uterus with normal tubes with ovarian strips; preventive resection of the strips was performed with histology related to bilateral gonadal dysgenesis. In addition, a substitute hormonal treatment based on estrogen and progesterone was instituted to improve pubertal development.
Conclusion
Turner syndrome and Y chromosome material mosaicism is associated with an increased risk of gonadal tumors, prophylactic gonadectomy is recommended at the time of diagnosis.
Keywords
Turner syndrome, Y-chromosome, gonadoblastoma, preventive gonadectomy.

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AEP616

Phenotypic expression of a defects in androgen synthesis of action

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Sexual differentiation is a sequential process where several genes are involved, therefore a defect at any stage can lead to a divergence between genetic, gonadal and phenotypic sex. The objective of our work is to analyze the clinical and hormonal characteristics of 13 XY patients, explored between 1989 and 2007 and belonging to 10 different families. The average age of our patients was 18.9 years (2–33 years). The reason for consultation was sexual ambiguity in two cases, puberty delay in 5 cases, primary amenorrhea in 5 cases and inguinal hernia in the remaining case. Consanguinity was found in 50% of cases and the notion of similar cases in the family in 70% of cases. Insensitivity to androgens was suspected in 5 cases with elevated testosterone levels averaging 4 ng/ml (extreme 6–12 ng/ml) with a high LH level averaging 20 mIU/ml (extreme 32–63 mIU/ml). The molecular study confirmed the presence of a P752Z androgen receptor mutation (at exon 5 of the gene) in the 2 familial cases. A gonadotropin receptor abnormality was suspected in 5 cases with elevated LH levels on average at 15 mIU/ml (range 27–43 mIU/ml) and FSH levels at 11 mIU/ml (range 12–24 mIU/ml) contrasting with low testosterone level on average at 0.3 ng/ml (extreme 0.01–0.9 ng/ml) not stimulable by HCG. The absence of Leydig cells in the histological study of the testes confirmed the diagnosis in the 5 patients. The molecular study confirmed the presence of a Q525X missense mutation in the second extracellular loop of the LH receptor in 3 cases, among them two with familial incidence. The female phenotype in 46, XY DSD patients is a rare phenomenon of various etiolgies. Its management is a medical, social and psychological emergency and depends as much on the genetic anomaly and hormonal profile but also on the age of diagnosis, the sex of breeding and the psychological profile.

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AEP617

The prevalence of NAFLD in menopause: A systematic review

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Introduction
The prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) varies according to age, gender and nationality. In the general population, the incidence is about 15–25%. Liver disease increases with age and its prevalence is higher in menopausal women suggesting that steroid sex hormone metabolism may play a role in the pathogenesis of NAFLD.
Aim
The purpose of this systematic review was to investigate the prevalence and association of NAFLD in menopause.
Method
An extensive literature search was conducted until January 2021 through electronic databases (PubMed, Scopus, Cinahl) with the Medical Subject Headings and entry terms of "menopause", "non-alcoholic fatty liver disease" and "prevalence". The search yielded 56 results, 5 of which fulfilled the inclusion requirements according to the PRISMA checklist.
Results
One Brazilian study investigated the prevalence and risk factors of NAFLD in 188 postmenopausal women. A higher prevalence of NAFLD was detected among postmenopausal women. The presence of metabolic syndrome, abdominal obesity, and insulin resistance appeared to be risk indicators for developing NAFLD. A Chinese study demonstrated that obese and postmenopausal women had a high prevalence of NAFLD with severe metabolic disorders. Similarly, a study of 197 premenopausal, postmenopausal women, and women with PCOS found that NAFLD had a higher prevalence among postmenopausal women and women with PCOS than in premenopausal ones. Another study that examined the relationship between menopause and the prevalence of NAFLD in 1.559 middle-aged women stated an increased prevalence of NAFLD in the late stages of menopause as well as in the postmenopausal stages, regardless of the potential confounders. A Korean study in 1793 postmenopausal women, evaluated the relationship between vascular motor symptoms and NAFLD in this population. Moderate to severe vascular motor symptoms were found to be significantly associated with a higher prevalence of NAFLD in otherwise healthy postmenopausal women.
Conclusion
In this systematic review, the prevalence of NAFLD in menopause was highlighted. However, these results were based upon data from a limited number of studies and it is unclear if this association is valid. Large randomized controlled trials and meta-analyses could provide more definitive evidence regarding the association of NAFLD and menopause. Due to the lack of an adequate number of studies and the heterogeneity of the study population, a meta-analysis was not possible to be performed at this time.

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AEP618

Effects of mitochondrial dynamics during myocardial differentiation in 3D model

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Mitochondria, which are essential organelles for endocrine health, plays an important role in various physiological functions including hormonal biosynthesis, cell metabolism, proliferation and differentiation. Thus, mitochondrial toxicity can affect a variety of organs, such as liver, heart, muscle, kidney, and central nervous system. Mitochondrial toxicity is recognized as a contributor to drug-induced toxicity of various drugs such as hydroxytamoxifen, valproic acid, acetaminophen, doxorubicin, and amiodarone. Here we describe *in vitro* assay using 3D culture in embryonic body (EB) state and establish a novel model of idiosyncratic toxicity based on mitochondrial impairment. The EBs were cultured in 3D model, and exposed to chemicals for 4 days. This study aims to investigate mitochondrial dynamics during myocardial differentiation in mouse embryonic stem cells(mESCs). In the result, ID50 values under 10-3M each toxic chemical in EB state were obtained; the expression levels of mRNA associated mitochondrial complex were decreased in high concentration group. We also compared mitochondrial DNA copy numbers to examine the effect on the number of mitochondria in mESCs-derived cardiomyocytes. Taken together, the results suggest that mitochondrial toxicity of unknown chemicals can be estimated with our alternative *in vitro* assay.

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AEP619

Leydig cell tumor in childhood: a case report

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Background
In the pediatric population, the Leydig cell testicular tumor (TCL) is rare. It manifests communally in childhood with isosexual precocity gonadotropin-independent due to excess testosterone production.
Case report
We admitted a case of an 8.5 years old boy with the complaint of sexual precocity dating back to 4 years, which manifested by acne, hyper seborrhea, stature advance, penile enlargement, pubic hair development, and enlarged left testis. The testosterone level was 2.24 ng/ml. LH was 0.22 UI/l. Ultrasonography demonstrated a left testis increased in volume by presenting a well-limited central nodule of 20 mm, with scattered microcalcifications. An inguinal radical orchiectomy managed this mass. The pathological diagnosis was a benign Leydig cell tumor. Three months after surgery, the testosterone levels stayed high, facing an LH level of 3.26 UI/l.
Discussion and conclusion
The incidence of Leydig cell tumor is 1% of testicular neoplasms[1]. Its prognosis is not tumoral because they are benign in 90% of cases [2], but it has repercussions in terms of stature growth by accelerating the growth rate as they are associated with increased sex steroid production that caused the

LH-independent precocious puberty like in our case. Radical orchiectomy was performed. Post-orchiectomy surveillance showed pubertal levels of gonadotropins, which are thought to be likely triggered by hypothalamic–pituitary axis activation due to long-term sex steroid exposure. Further explorations are in progress.

Keywords
precocious puberty, Leydig cell tumor, stature advance.

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AEP620

Selected steroid hormones – their physiological effects and use in diagnostics and research

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The determination of steroid hormones and subsequent interpretation of results is accompanied by a range of difficulties. The amount of information that current technology can provide on the circulating concentrations of more than a hundred various steroid compounds can lead to problems with interpretation. The aim of this study is to help provide orientation in this maze of data on steroid hormones. First, we focus on specific aspects arising from the pre-analytical phase of steroid determination that need to be considered when planning sampling, whether for diagnostics or research. Then, we provide a brief summary of the characteristics and diagnostic relevance of several steroid hormones and/or their metabolites: (pregnenolone, 17ά-hydroxy-pregnenolone, dehydroepiandrosterone, hydroxyderivatives of dehydroepiandrosterone, androstenedione, testosterone, estrone, estradiol, estriol, cortisol, cortisone), which in our institute are determined with validated LC–MS/MS methods. For these steroids, we also provide newly calculated reference values in fertile women according to the phase of their menstrual cycle.

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AEP621

Experience of the transgender care unit

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Objective
Health care for transsexuals has changed in Andalucia since 2014. Our unit of attention to transsexual people began in 2015. The objective of this study is to analyze our experience.
Patients and methods
Retrospective study by reviewing the medical records of the transsexuals treated in our unit.
Results
145 transsexual people. Transsexual man to woman (TMW): 44.1%, Transsexual woman to man (TWM): 55.9%. 27.97 ± 8.14 years old. Start cross hormonal treatment 88.3%, 5 people have abandoned the treatment (4.8%): 1 planned pregnancy, 2 repentance, 2 another disease. Treatment complications have not been detected. Sex reassignment surgery: 41.5% (n = 54). TMW: 10 hysterectomy-oophorectomy and mastectomy, 16 hysterectomy-oophorectomy and mastectomy at same time (uncomplicated and preferred by people), 1 hysterectomy-oophorectomy, mastectomy and phalloplasty, 22 only mastectomy. TWM: 11 mammoplasty, 5 mammoplasty and feminizing genitoplasty. Private surgical intervention: 66.7%.
Conclusions
TWM is slightly more frequent in our series. Most people consult in the second decade of life, and most of them start cross hormonal treatment. Abandonment of cross hormonal treatment is uncommon. Treatment complications have not been detected. Only half of the people who start treatment have undergone sex reassignment surgery, half in the public health system. Hysterectomy-oophorectomy and mastectomy at same time has not more complications and it´s preferred by people.

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AEP622

Mayer-Rokitansky-Kuster-Hauser Syndrome type 2 – A case report

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Introduction
Mayer-Rokitansky-Küster-Hauser (MRKH) type 2 or MURCS (Müllerian duct aplasia, unilateral renal agenesis and cervicothoracic somite anomalies) syndrome is a congenital disease with an incidence of 1 in 4000–5000 female live births, with unknown etiology. Several chromosomal abnormalities were associated with the disease, with a normal 46XX karyotype and familial members to share the same associated anomalies as sporadic cases have been reported. Associated malformations include unilateral renal agenesis (23–28%) and one- or both kidney ectopia (17%) and the incidence of abnormally located ovary is significantly increased in patients with MRKH syndrome.
Case report
A 16-year-old girl presented for renal ectopia detected on a pelvic ultrasonography. We found out she was having primary amenorrhea, with normal breast and pubic pilosity development over the past three years (BVPV Tanner stage) and positive family history of renal and cardiac congenital anomalies. The abdomino-pelvic MRI described uterine and upper two-thirds vaginal agenesis, right kidney agenesis, ectopic left kidney, ovaries with abnormal morfology and topography, tubular aspect and situated high in the abdominal cavity. The karyotype was 46 XX and she had normal ovarian function. A diagnosis of Mayer-Rokitansky-Kuster-Hauser Syndrome type 2 was made.
Discussions
Here we describe a case of a young lady who presented with a renal anomaly that was diagnosed as a case of type 2 MRKH syndrome. The absence of obvious signs and symptoms and the normal development of secondary sexual traits and normal external genitalia causes the syndrome to be diagnosed most often in adolescence, with primary amenorrhea as the first symptom. Considering the renal, skeletal, hearing or cardiac congenital anomalies associated and the increased levels of psychological distress, the multidisciplinary approach of these patient is very important.

Keywords
primary amenorrhea, renal agenesis, Müllerian duct aplasia, Mayer-Rokitansky-Küster-Hauser type 2 syndrome

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AEP623

Perrault Syndrome, a case study

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Introduction
Perrault syndrome is a rare recessive autosomal degenerative disease defined by the combination of ovarian dysgenesis 46XX with sensorineural deafness. Other manifestations can expand the clinical picture, particularly a cerebellar degeneration and/or peripheral neuronal sensitivo-motor.
Observation
We have reported a 14 years old patient case, from a 2nd degree consanguineous marriage with perceptive bilateral deafness history, who has consulted for impuberal primary amenorrhea, the clinical examination did not show a particular dysmorphic syndrome nor retardation, Limitation of the laterality of the gaze in abduction, hyper ligamentous laxity of the fingers. The biological exploration revealed a hyper gonadotropic hypogonadism as well as normal 46 XX karyotype, this eliminates Turner’s syndrome. The abdominal ultrasound showed ovarian atrophy with a prepubescent tubular uterus.

Discussion
The diagnosis of Perrault syndrome has been made in the presence of hyper gonadotropic hypogonadism, an ovarian imaging atrophy, a normal karyotype with bilateral congenital neurosensory deafness; however, the spectrum of the disease is wide, the neurological exploration must be systematic to the search for neuronal and/or cerebellar degeneration, for this reason, an EMG as well as a brain MRI are programmed for our patient. In the absence of gene therapy, hormone replacement therapy represents the only hope today, the patient has received oestrogen treatment then oestroprogestative with a good clinical evolution.

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AEP624

Systematic review and meta-analysis of the observational trials evaluating the functional impact of COVID-19 on sexual health

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Background
Natural disasters resulting in psychosocial stress and endocrine imbalances are implicated for impacting sexual health. We postulate COVID-19 for its longer duration and global lockdown has implications on the sexual health
Methods
We analysed contemporary protocols of six ongoing trials through WHO International Clinical Trials Registry Platform and www.clinicaltrials.gov trials registry database. The latest evaluation was done on September 27, 2020 for trials registered from April to June 2020, evaluating the impact of COVID-19 on sexual health. Two researchers independently analysed the study designs.
Results
The trials evaluate female sexual behavior, marital and sexual health problems, sexual fantasies, postpartum sexual function, sexual function among healthcare workers, qualitative and quantitative aspects for fertility, urinary function, and STD. Six trials are cumulatively recruiting 868 participants; with two trials each in Turkey (n = 198) and Egypt (n = 520) and one each in Italy and France. Mean number of participants being enrolled is 145 (S.D. ± 130, maximum 400, minimum 50, range 350, 95% CI 8.4 to 281). Two trials enrol exclusively females (n = 198) and one trial only evaluates males (n = 50), with highest age 80 years and longest evaluation planned for one year. Interventions include questionnaire-based evaluation and diagnostic work-up. Established tools including IIEF-5, IPSS, SECRET questionnaire, Male Sexual Health Questionnaire (MSHQ), FSFI (Female Sexual Function Index), dyspareunia scale are utilised. SARS-CoV 2 RNA PCR evaluation in urine and semen and interleukin assessment in semen are being done
Conclusions
The utilisation of validated tools across varied spectrum of participants, for evaluation for impact of contagiousness of the virus to confinement due to lockdown is a collective strength of ongoing observational studies. Varied novel approaches are being explored to understand the implications of COVID-19 on sexual health and function.

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Thyroid

AEP625

Mycophenolate mofetil in sight threatening Graves' ophthalmopathy: a case report

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Introduction
Graves ophthalmopathy (GO) is an inflammatory autoimmune disorder of the orbit which is associated with autoimmune thyroid disease. The medical treatment of severe and sight threatening GO remains a challenge, it generally implies the use of glucocorticoids with others treatments. Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid that prevents T-cell and B-cell proliferation and the production of cytotoxic T-cells and antibodies. Furthermore, an antiproliferative effect on orbital target cells has also been considered. We report the case of a patient presenting with sight threatening GO treated with glucocorticoids and MMF.
Case presentation
A 44-year-old man with hypertension, presented since November 2019 Graves' disease diagnosed following the onset of bilateral proptosis. The evolution was marked by the worsening of his ophtalmopathy in July 2020. Emergency ophthalmological examination showed a visual acuity at 7/10 on the right eye and < 1/10 on the left eye, superficial punctate keratitis in both eyes, lazy photomotor reflex and slight papillary pallor in the nasal area of the left eye, limitation of the abduction and the presence of inflammatory signs in both eyes more accentuated on the left eye. Orbital MRI showed Graves' orbitopathy with bilateral exophthalmia grade III with greater compression of optic nerve on the left eye. The patient received methylprednisolone intravenously for three days (1 g/day) followed by oral corticosteroid therapy at a dose of 1 mg/Kg/day with improvement in inflammatory signs without improvement in visual acuity. The management was to combine mycophenolate mofetil at a dose of 1 g*3/day. The outcomes were favorable with resumption of vision on the left eye (8/10) and improvement of the visual acuity on the right eye (10/10) without serious adverse events.
Conclusion
The combination of MMF and glucocorticoids seem to be promising since it shows beneficial effect in sight threatening Graves' orbitopathy without major toxicities.

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AEP626

Inoperable papillary thyroid carcinoma with metastasis pulmonary: therapeutic alternative

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Summary
Papillary thyroid carcinoma is rare in children and adolescents, most often discovered late by lung metastases. It is generally of good prognosis but can present cases difficult to operate requiring a targeted therapeutic approach. We report the case of a 15-year-old patient from a non-consanguineous marriage, with no history of irradiation, followed for Hashimoto's hypothyroidism since the age of 6 under Levothyrox 25 µg. Admitted for a multi-nodular goiter evolving for 3 years of progressive increase complicated 6 months before its admission by exertional dyspnea without signs of compression. On clinical examination we note a slight cyanosis of the lips, a polypnea at 30 cycles, an 80% SaO2, bilateral snoring rales, a firm grade 2 goiter, with 2 right and left nodules of 1.5 cm, not very mobile with lymphadenopathy left jugulo-carotid of 1 cm. A thyroglobulin at 4035 ng/dl. The cervical ultrasound describes a nodular goiter with endothoracic embedding, voluminous on the right of 32.5 mm, TIRADS 5. On the CT there is bilateral pulmonary carcinosis, a tracheal deviation to the right on the chest X-ray, on the RFE a tight restrictive syndrome with 39% FEV1. Fine needle aspiration concludes with papillary carcinoma. Faced with the risks associated with the surgery, the patient was put on Sorafenib 150 mg/m^2/day, i.e. 200 mg/day for 6 months with good tolerance and a respiratory improvement of 92% SaO2, thyroglobulin controlled at 500 ng/dl, stabilization of pulmonary metastases with reduction in the volume of the goiter. Surgery was performed, noting a fixed, adherent thyroid mass that could not be resected. Several biopsies were taken confirming the papillary carcinoma. In multidisciplinary discussion, the patient was put back on Sorafenib titrated at 400 mg not tolerated then put back at 200 mg/day, radiotherapy was started in addition to therapy. Sorafenib represents in our context a major asset in the management of inoperable papillary thyroid carcinoma.

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AEP627

Laser ablation versus radiofrequency ablation for benign non-functioning thyroid nodules: twelve-month results of a randomized, parallel-arm, open-label trial

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Background
Radiofrequency ablation (RFA) seems to achieve a significantly larger nodule volume reduction rate (VRR) than laser ablation (LA) in benign non-functioning thyroid nodules (BNTNs). We compared the efficacy and safety of both thermal ablation treatments at the 12-month follow-up in patients with solid or predominantly solid BNTN.
Methods
This 12-month, single-use, randomized open-label parallel trial compared the following primary endpoints between the RFA and LA groups 12 months post-treatment: (a) nodule volume reduction, expressed as a percentage of the nodule volume at baseline and (b) proportion of nodules with more than 50% reduction (technical success rate). We enrolled patients with a solitary BNTN or dominant nodule characterized by pressure symptoms/cosmetic problems or asymptomatic patients who experienced a volume increase of >20% within 1 year. This trial was registered with ClinicalTrials.gov (NCT02714946).
Results
Sixty patients were randomly assigned (1:1 ratio) to receive either RFA or LA, and 29 patients per group completed the study. Both groups had similar basal nodule volume, thyroid function, histology, and symptoms/cosmetic score, whereas a larger quantity of energy was delivered to patients who underwent RFA. At 12 months, the nodule volume reduction rate was 70.9 ± 16.9% and 60.0 ± 19.0% in the RFA and LA groups, respectively (P = 0.024). This effect was confirmed in the linear regression model that was adjusted for age, sex, and nodule baseline volume and proportion of cellular components (RFA treatment: β = 0.390; P = 0.009). No significant between-group difference was observed in the technical success rate at 12 months post-treatment (RFA: n = 26, 89.7%; LA: n = 22, 75.9%; P = 0.149). A statistically significant improvement was observed from the baseline to the 12-month follow-up for compression (RFA: 4.6 ± 2.6 and 1.3 ± 0.8, P<0.001 and LA: 4.6 ± 2.1 and 1.6 ± 0.8, respectively, P<0.001) and cosmetic (RFA: 3.4 ± 0.6 and 1.3 ± 0.5, P<0.001 and LA: 3.4 ± 0.5 and 1.4 ± 0.6, P<0.001) scores although the between-group differences were not significant.
Conclusion
RFA achieved a significantly larger nodule volume reduction at 12 months; however, the technical success rate was similar in the RFA and LA groups.

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AEP628

Graves' disease in patients with autoimmune polyendocrine syndrome type 3

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Introduction
Type 3 autoimmune polyendocrine syndrome (APS-3) is defined by the presence of an autoimmune thyroid disease and another autoimmune illness, excluding Addison's disease; this is a frequent combination. Graves' disease (GD) is an autoimmune disorder affecting approximately 0.5% of general population. It's occurrence in autoimmune polyendocrine syndrome (APS) is less common than Hashimoto thyroiditis. The aim of our study was to describe clinico-biological findings, therapeutic management and progess of GD in patients with APS type 3.
Methods
We analyzed clinical and biological findings of 10 patients with GD and APS. Data were gathered from files collected in internal medicine and/or endocrinology department from January 2000 to December 2017.
Results
Ten patients (21.7%) among 46 with APS had GD. GD was suspected face to clinical manifestations of hyperthyroidism in 8 cases and fortuitously in 2 cases. It was about 7 male and 3 female. The mean age of our population was at 31.5 years [14–50]. Among complaints, we found excessive sweating in 8 patients, weight loss with increase appetite in 6 cases, asthenia and tremor in 5 patients each. Diarrhea and nervousness were reported in 1 case each. Physical examination showed protruding eye ball in 6 patients, tachycardia in 5 cases and amyotrophy in 4 cases. Neck examination showed enlarged thyroid gland in all cases. Hyperthyroidism was complicated by cardiothyreosis, neuromuscular signs in 4 cases each and metabolic disorders in 6 cases. Thyroid function tests revealed a suppressed TSH level and elevated levels of serum T4 at 68.3 pmol/l [24.5–116]. Immunologic analysis found anti-TSH receptor antibodies in all cases, anti-thyroid-peroxidase antibodies in 8 cases and thyroglobulinin 3 cases. All patients presented mellitus Type 1 diabetes (DT1). DT1 was diagnosed after GD in 5 cases, before and at the same time of GD in 2 and 3 cases respectively. Anti GAD and anti IA2 antibodies were positive in 8 and 1 cases respectively. APS type 3 was retained in all cases. Treatment by anti thyroid drugs with beta-blokers was used in 9 cases. Radioactive Iodine Therapy (RAI) was performed in 7 cases. Surgical treatment by total thyroidectomy was indicated 1 case. Progress demonstrates remission in 8 cases with average follow-up of 90.5 months [25-156].
Conclusion
Patients with GD are at high risk to develop auto-immune disorders especially APS 3 type like our study. Screening of autoimmune diseases (DT1, Addison disease, celiac disease, pernicious anemia, connectivities…) in patients with GD should be done early and regularly in order to take appropriate action.

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AEP629

Long-term outcomes of radioiodine therapy in toxic solitary thyroid nodules

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Introduction
The toxic solitary thyroid nodule is a major cause of hyperthyroidism, especially in iodine-deprived regions. The most widely used therapy is iodine-131, which is effective in achieving normal thyroid function and reducing nodule dimensions, however, it may induce hypothyroidism. The aim of this study was to evaluate the outcomes of radioiodine therapy in patients with toxic solitary nodules and to determine predictive factors for the development of hypothyroidism.
Methods
A retrospective analysis of medical records of patients with toxic thyroid nodule submitted to radioiodine therapy between 2008 and 2018 in our center was conducted.
Results
During the study period, 100 patients received radioiodine therapy for toxic solitary nodule, with a minimum follow-up of one year (77% female, age at diagnosis 63±14 years). The most used doses were 20 mCi (61%) and 15 mCi (35%). The therapy was effective in reversing hyperthyroidism in 99% of patients. However, 56% developed hypothyroidism, 79% of them being diagnosed within 6 months after therapy. The evolution to hypothyroidism was greater in women and the hypothyroidism group were younger, had smaller nodule size and thyroid volume and higher doses of iodine per thyroid volume. Logistic regression confirmed female sex (OR 2.90, P = 0.034), nodule size [OR 0.95 (mm), P = 0.026], thyroid volume [OR 0.94 (ml), P = 0.013] and radioiodine dose per volume [OR 4.47 (mCi/ml), P = 0.039] as predictive factors for hypothyroidism. There were no differences regarding the previous TSH value, use of antithyroid drugs, total iodine dose or iodine dose per kilogram of weight. In ultrasound reevaluation, within four years after treatment, there was a significant absolute and relative nodule reduction of 10 mm (5–14) and 33% (24–49), respectively (P<0.001). Higher absolute and lower relative reductions were found in larger nodules (R = 0.26, P = 0.014 | R = –0.29, P = 0.006). There was an absolute and relative reduction in thyroid volume of 10 ml (6–17) and 53% (32–73) (P<0.001). The patients who developed hypothyroidism showed higher reductions in thyroid volume (72% vs 37%, P<0.001). There were no differences in nodule or thyroid volume reduction regarding sex, use of antithyroid drugs or total dose of radioiodine.
Conclusion
Radioiodine therapy is effective in the treatment of hyperthyroidism caused by toxic thyroid nodules, and induces significant reductions in nodule and thyroid dimensions. However, this treatment may induce hypothyroidism, found in more than half of the cases in the present study. Female sex, lower nodule size and thyroid volume and higher radioiodine dose per volume are predictive factors of its development.

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AEP630

Adverse childhood experiences and negative emotional responses : risk factors for thyroid autoimmune diseases?

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Stressful condition and negative emotions can contribute to the overproduction of proinflammatory cytokines and promote immune dysregulation, which, in turn, increases the risk of various diseases, including autoimmune disorders. The present study was aimed at evaluating the relationship, if any, between psychological and individual characteristics (stress, coping and emotional intelligence) and thyroid autoimmunity.

Method

We enrolled 174 HT patients (gender: 157 female; 12 male; age: M = 47.01; s.d. = 13.36) and 133 euthyroid subjects (gender: 111 female, 21 male; aged M = 45.56; s.d. = 12.69) as controls. All subject had no personal and/or familial history of psychiatric disorders. All participants fell a set of psychological self-report questionnaires in order to measure psychological stress (MSP), coping strategy (Coping Inventory for Stressful Situations, CISS), trait emotional intelligence (TEIQue-SF) and Adverse Childhood Experiences (ACEs questioner).

Results

We found significant differences between patients and controls. MSP test showed greater levels of overall stress ($P = 0.001$) and stress subcategories, including psycho-physiologic sensations ($P = 0.000$), effort and confusion ($P = 0.02$), depressive anxiety ($P = 0.01$), pain and physical problems ($P = 0.000$), in HT patients than controls. Also, HT patients showed minor wellbeing ($P = 0.020$) and self-control ($P = 0.047$) compared to controls at TEIQue Test. Concerning coping strategies, HT patients seem to have more difficulties in adequately managing the emotional area ($P = .004$), which involves greater emotional responses, self-preoccupation, and a fantasizing tendency. Noteworthy, it emerged that HT patients have had a greater number of traumatic experiences in childhood ($P = 0.01$) than controls, with particular reference to physical abuse ($P = .001$), parental divorce ($P = 0.02$) and presence in the family of subjects suffering from mental illness ($P = 0.05$) or substance abuse ($P = 0.38$). The patha analysis on HT patients confirmed that the total stress is influenced by adverse childhood experiences ($\beta = .12$, $P = .04$) and by trait emotional intelligence ($\beta = -.16$, $P = 0.02$). It is conceivable that traumatic events occurring early in life might have had an influence on the subsequent development of autoimmune disease.

Conclusions

Our data suggest a correlation between psycho-social and immune factors. HT patients seem to have a very delicate psycho-affective equilibrium, difficulties in emotion regulation and impulse control, as well as in managing stress. Traumatic experiences in childhood and negative emotional responses may favor the subsequent development of autoimmunity, acting as an exogenous trigger in susceptible subjects. Autoimmunity, even in conditions of euthyroidism, can in turn negatively impact the psychological well-being of patients, who in fact appear less confident and optimistic.

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AEP631

Features of Subacute Hhyroiditis in COVID 19

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The Sars-COV-2 virus is a recognized endocrine disruptor, which determines the possibility of endocrine dysfunctions associated with COVID 19. One of the endocrine diseases associated with COVID 19 is subacute thyroiditis (STh), which develops regardless of the severity of manifestations of the underlying disease. The aim of the study: to evaluate the clinical manifestations, therapy, and outcomes of STh in unvaccinated COVID 19 patients.

Materials and methods

The diagnosis of STh was established on the basis of generally accepted clinical criteria. As a result 26 patients from April to October 2020 were included in the study: group1 – with STh without COVID 19 in medical history ($n = 8$); group2 – COVID 19 convalescents who received glucocorticoids (GCs) in complex therapy (in the diagnosis of PT, the daily dose in terms of prednisone was 20 mg) ($n = 10$); group3 – COVID 19 convalescents who did not use GCs in COVID 19 therapy ($n = 8$). The levels of erythrocytes (Er), hemoglobin, leukocytes, lymphocytes, erythrocyte sedimentation rate, thyroid-stimulating hormone, free thyroxine, thyroid peroxidase antibodies, C-reactive protein (CRP) in the peripheral blood were determined; ultrasound examination of the thyroid gland, thyroscintigraphy with 99mTc-pertechnetate, with the calculation of the uptake index of the radiopharmaceutical were conducted as well.

Results

Comparison of indicators of the complete blood count revealed differences in the levels of Er, leukocytes, the proportion of lymphocytes, which were associated with the characteristics of treatment (use of GCs). The thyroid status at the time of STh establishment indicated a thyrotoxic phase, confirmed by thyroid status. For the treatment of STh in groups1, 3, a non-steroidal anti-inflammatory drug (NSAID) (nimesulide 200 mg/day) was prescribed. In 50% of patients in group1, 87.5% of patients in group3 required the addition of GCs using the average dose in terms of prednisolone (30 mg/day). Group2 required an increase in the GCc dose to 40 mg/day in terms of prednisone (NSAIDs were't). Beta-blockers were used to minimize hyperthyroidism's symptoms in individual doses. The duration of therapy up to resolution in group1 averaged 25 days, in group2 – 51 days, in group3 – 44 days and depended on the relief of symptoms, indicators of complete blood count, CRP. In 3 months hypothyroidism developed in 25% of patients from group1, in group2 – in 90% of the cases, in group3 – in 37.5% of the cases.

Conclusion

The results indicate a higher incidence of hypothyroidism after STh in COVID 19-patients to compare ordinary STh.

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AEP632

The use of Thyroid Uptake scan in non-malignant thyroid disease; a multicentre audit

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Thyroid uptake scan is a widely used thyroid investigation that provides valuable information regarding the structure and function of the gland and helps in differentiating some of the common thyroid pathologies. We present a multicentre audit of thyroid uptake scans done for non-malignant thyroid pathologies and try to analyse the usefulness of this investigation in different situations.

Methods

This audit includes thyroid uptake scans from two centres (King's Mill Hospital Sherwood Hospitals NHS Foundation Trust Nottinghamshire UK and Hospital Central de la Defensa Gómez Ulla Madrid Spain) done over two years (2018 and 2019). Medical and electronic records were examined to get the data on presenting thyroid functions, TSH receptor antibodies (TrAB), clinical neck examination, thyroid uptake scan results, final diagnosis and management.

Results

A total of 117 cases were analysed; 27 from UK and 90 from Spain. 113 of these patients were hyperthyroid. 26 patients had positive TrAB (TrABs not available in 7). Clinical examination data was available for 98 patients; 27 normal, 38 diffuse goitre, 21 single nodule, 12 multiple nodules. Final diagnosis was Graves' disease in 27, thyroiditis in 11, toxic multinodular goitre in 30, toxic nodule in 19 and 10 patients had other diagnoses. 20 patients were found to have non nodular hyperthyroidism with negative TrABs. We also performed subgroup analyses to see whether thyroid uptake scans significantly altered diagnosis or management. Unsurprisingly, there was no significant benefit from the thyroid uptake scan in those with hypothyroidism (4) or secondary hyperthyroidism (2). In those with TrAB positive hyperthyroidism (Fig 1) and a non-nodular thyroid examination, thyroid uptake scan did not add any significant information to aid in diagnosis or management; merely confirming the diagnosis of Graves' disease in all patients.

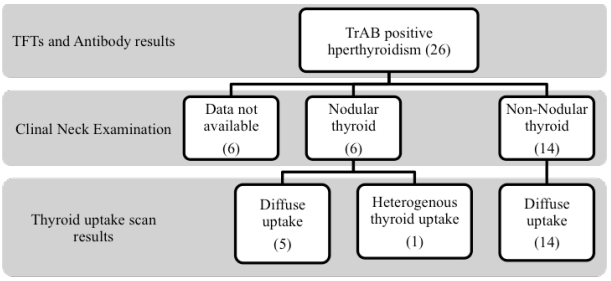

Fig 1: Sub group analysis of TrAB positive hyperthyroidism.

In those with TrAB negative hyperthyroidism (fig 2), thyroid uptake scan significantly altered the pre scan probable diagnosis but whether it changed the eventual management in all of these patients is not entirely clear.

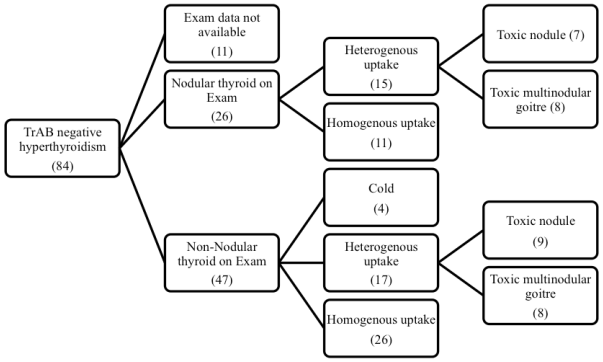

Fig 2: Sub group analysis of TrAB negative hyperthyroidism.

Conclusion

Our results show that thyroid uptake scan can be useful in patients with TrAB negative hyperthyroidism and TrAB positive hyperthyroidism with a nodular thyroid on examination. Amiodarone induced thyrotoxicosis is also an accepted indication of thyroid uptake scan. Clinicians should evaluate each case on an individual basis to see if uptake scan will significantly alter the diagnosis or management before requesting.

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AEP633

Efficacy of transcutaneous laryngeal ultrasonography (TLUS) in the diagnosis of vocal cord function in an endocrine surgery referral center.

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Introduction

Thyroid diseases affect a large population worldwide and total thyroidectomy (TT) is the most common curative treatment [1]. Recurrent laryngeal nerve (RLN) lesions are the most dangerous complication [1]. The intraoperative neuromonitoring (NIM) is a useful tool in reducing the incidence of nerve injury, but a preoperative examinations of vocal cords function through flexible fiberoptic laryngoscopy (FFL) is recommended [1]. FFL is uncomfortable and expensive evaluation, so transcutaneous laryngeal ultrasonography (TLUS) has been proposed as alternative indirect examination of vocal cords function [2].

Materials and methods

We conducted a retro prospective on 100 consecutive patients with benign and malignant thyroid disease underwent to TT and preoperative and postoperative evaluation with FFL and TLUS. All TLUS was performed by one experienced investigator.

Results

Demographic data and results are showed in Tables 1 and 2, respectively.

Table 1. Patients' demographic and clinical information

	Population
Mean age ± s.d.	50.63 ± 12.15
Gender, %	
Male	24 (24%)
Female	76 (76%)
Diagnosis, %	
Benign	68%
Malignant	4%
Indeterminate cytology	28%
Preoperative FFL, %	
Normal	100%
Vocal Impairment	0%
Preoperative TLUS, %	
Normal	100%
Vocal cord impairment	0%
Correct correlation with FFL	100%
Incorrect correlation with FFL	0%
Normal visualization	91%
Lateral visualization	9%
Postoperative FFL, %	
Normal	80%
Unilateral vocal cord hypomobility	12%
Unilateral vocal cord paralysis	8%
Postoperative TLUS, %	
Normal	80%
Unilateral vocal cord hypomobility	8%
Unilateral vocal cord paralysis	8%
Normal visualization	98%
Lateral visualization	2%
Correct correlation with FFL	98%
Incorrect correlation with FFL	2%
Postoperative diagnosis, %	
Benign	76%
Malignant	24%

Table 2. Statistical data (PPV+, predictive positive value; PNV, predictive negative value).

	CI of 95%
Sensitivity	0.833 (0.743–0.898)
Specificity	1.000 (0.954–1.000)
Prevalence	0.120 (0.066–0.204)
PPV+	1.000 (0.954–1.000)
PNV–	0.978 (0.919–0.996)

Discussion

In the literature, there are discordant data that give a sensitivity greater than 90% and others a 33%, while the specificity is always greater than 90% [1,2]. Our study showed a sensitivity of 83.3%, a specificity of 100%, PPV+ of 100% and a PNV– of 96.7%. TLUS is safe in recognizing healthy patients but has some limitations in recognizing patients with chordal hypomobility, particularly in male patients with prominent and/or calcific thyroid cartilage.

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AEP634

Evaluation of fetuin-A levels in patients with autoimmune thyroiditis

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Background
Hypothyroidism due to autoimmune thyroiditis (AITD) leads to atherogenic lipid profile and therefore might increase the cardiovascular risk of patients. Fetuin-A is a hepatokine with a role in the regulation of mineralization, metabolism and the cardiovascular system. Fetuin-A levels are known increased in obesity-linked diseases. To date, the role of fetuin-A in autoimmune thyroiditis has not been thoroughly investigated.
Subjects and methods
In our study we investigated the association between thyroid hormone levels, thyroid antibodies, the components of lipid metabolism, anthropometrical parameters and fetuin-A. We enrolled eighty-six patients (7 men, 79 women, mean age 43 ± 13 years, median BMI 25.3 (23.4–30.5) kg/m^2) from the outpatient clinic of Endocrine Department of University of Debrecen, Faculty of Medicine. All patients had autoimmune thyroiditis with various thyroid hormone status from hypo- to hyperthyroidism. Serum fetuin-A concentrations were determined with enzyme-linked immunosorbent assay (ELISA). Thyroid hormone levels, anti-thyroperoxidase (aTPO) concentration and lipid parameters were measured by routine laboratory methods.
Results
Median serum fetuin-A level was 929.7 (822.0 – 1038.3) mg/l, LDL-C was 3.2 (2.6–3.8) mmol/l, HDL-C was 1.5 (1.3–1.8), triglyceride was 0.84 (0.49–1.45) mmol/l, while mean total cholesterol level was 5.3 ± 1.1 mmol/l. Mean fT3 and fT4 were 4.67 ± 0.67 and 17.8 ± 3.6 pmol/l, respectively. Significant positive correlation was found between fT3 and fetuin-A levels (r = 0.273, P = 0.013). There was a significant negative correlation between age (r = −0.406; P<0.001), daily levothyroxine dose/body weight (r_s = −0.370, P = 0.001), total cholesterol (r = −0.287, P<0.01), ApoB100 (r = −0.300, P<0.01) and fT3. However, we could not find correlation between fetuin-A and aTPO levels. Among patients receiving levothyroxine substitution, a correlation between CRP and fT3 was present (r = −0.251, P = 0.047).
Conclusions
The significant correlation between fetuin-A and fT3 levels might indicate a regulatory effect of T3 on metabolism. However, further clinical investigations are needed to clarify this relationship.

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AEP635

Long term outcomes of Graves' Orbitopathy treatment; a clinic's experience

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Introduction
In this study we present data on the long-term outcomes of treatment of patients with moderate and severe GO.
Methods
98 patients with GO attending our clinic for the last 13 years and received treatment for moderate to severe GO were evaluated for their long-term response to treatment. Initial decision for treatment was based on activity and severity of the disease, assessed by CAS-score and NOSPECS respectively and the presence of ocular muscle edema (OME) at the MRI–STIR imaging. Patients with moderate to severe disease received iv corticosteroids according to the EUGOGO protocol (totally 4.5 g methylprednisolone for 12 weeks), and those with persisting disease continued with per os prednisolone (30 mg daily, tapered over 3 months). Response to treatment was evaluated based on changes of both CAS-score and OME at the MRI–STIR. Thyroid and liver function, and smoking status were also assessed.
Results
The patients' mean age was 52.08 ± 13.11 years. 30/98 patients (30.61%) had mild GO (mean CAS-score 2.58 ± 0.47, no or mild OME at the MRI-STIR) and received no treatment. 68/98 patients (69.38%) had moderate to severe GO (mean CAS-score 4.13 ± 1.26, intense OME at the MRI–STIR) and received iv treatment. 20/68 patients (29.41%) had a significant improvement (mean CAS-score 3.04 ± 0.07, mild to moderate disease, and no or mild OME at the MRI–STIR) and received no further treatment. The rest 48/68 patients (70.58%), due to persisting disease (mean CAS-score 3.30 ± 1.21, and intense OME at the MRI–STIR), continued with the per os protocol and were improved at the end of treatment (mean CAS-score 2.27 ± 1.14, no or mild OME at the MRI–STIR). Only 3/68 patients (4.41%) who received iv corticosteroids developed mild transaminasemia. All patients were euthyroid at the initiation of treatment and 6/68 continued smoking. Recurrence observed in 11/68 patients (16.17%) who had prior treatment, with mean CAS-score 3.64 ± 1.28 and intense OME at the MRI–STIR, at a mean 21.5 ± 32.3 months (range 1–108 months). They received additional iv treatment (1.5 g methylprednisolone for 6 weeks) and all improved significantly (mean CAS-score 2.97 ± 0.95, no or mild OME at the MRI–STIR).
Conclusion
Treatment with iv corticosteroids followed by oral corticosteroids in those with persistent disease based on CAS and MRI–STR findings is effective for patients with moderate to severe GO, minimizing the recurrence rate and has no serious side effects. MRI–STIR imaging of the ocular muscle is a useful tool for treatment initiation and evaluation of response.

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AEP636

Comparison of metabolic parameters between women with autoimmune thyroiditis on levothyroxine replacement therapy and euthyroid healthy women

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Introduction
The association between thyroid function within the normal range and body weight and related metabolic parameters has been the subject of numerous studies with inconsistent results not only in euthyroid healthy population but also in treated patients with autoimmune hypothyroidism.
Objective
To compare body mass index (BMI), blood glucose and serum lipids between women with autoimmune thyroiditis on levothyroxine replacement therapy and euthyroid healthy women.
Patients and methods
127 women with autoimmune thyroiditis receiving levothyroxine therapy (42.6 ± 1.9, 20–64 years) and 361 age-matched healthy women (40.6 ± 0.6, 19–65 years) were included in this retrospective study. All women were euthyroid with TSH and FT4 levels within reference range. TSH and FT4 levels were measured using ECLIA, fasting blood glucose, total cholesterol, HDL, triglycerides were measured and LDL was calculated using Friedewald's formula. Women in the study did not have any significant comorbidities, diabetes mellitus, did not take metformin, lipid-lowering or estrogen-containing medications.
Results
Women on levothyroxine had higher levels of TSH (2.38 ± 0.09 vs 1.98 ± 0.05 mIU/l, P<0.01) and FT4 (11.50 ± 0.12 vs 10.89 ± 0.07 pmol/l, P<0.01) compared to healthy women. No significant differences between treated hypothyroid and healthy women were found in terms of BMI (26.7 ± 0.5 vs 27.3 ± 0.3 kg/m^2, P = 0.30), blood glucose (5.12 ± 0.05 vs 5.20 ± 0.03 mmol/l, P = 0.162), total cholesterol (5.21 ± 0.09 vs 5.27 ± 0.06 mmol/l, P = 0.638), HDL (1.43 ± 0.03 vs 1.43 ± 0.02 mmol/l, P = 0.483), LDL (3.27 ± 0.07 vs 3.32 ± 0.05 mmol/l, P = 0.681) and triglycerides (1.13 ± 0.06 vs 1.14 ± 0.03 mmol/l, P = 0.956) after adjustment for TSH and FT4. In women on levothyroxine TSH had positive correlation with HDL and FT4 was negatively associated with total cholesterol and LDL after adjustment for age and BMI. In healthy women TSH had positive association with total cholesterol and LDL and FT4 showed negative correlation with total cholesterol, HDL and triglycerides.
Conclusion
Women with autoimmune thyroiditis receiving levothyroxine have similar BMI, blood glucose and lipids compared with healthy euthyroid women provided that TSH is within reference range. Since there is no relationship between TSH and metabolic risk characteristics in euthyroid women on levothyroxine replacement therapy there would be no benefit in adjusting levothyroxine dose to achieve low-normal TSH.

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AEP637

Persistently elevated procalcitonin levels in Covid-19 pneumoniae leading to medullary thyroid cancer diagnosis

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Objective
We report a case of acute respiratory syndrome coronavirus 2 (SARSCoV2) pneumonia in which persistently high procalcitonin (PCT) allowed the diagnosis of sporadic medullary thyroid cancer (MTC).
Methods
We describe the history of 43-year-old male with bilateral Sars-Cov-2 pneumoniae, in whom persistent increased PCT despite reduction of C reactive protein lead to investigate other causes of high PCT. Serum calcitonin (CTN) was measured and a painless, right latero-cervical swelling as well as thyroid nodules were found.
Results
Serum PCT and CTN were 94 ng/ml and over 2000 pg/ml, respectively. A thyroid ultrasound and cytological examination by fine needle aspiration confirmed the diagnosis of MTC. The patient underwent total thyroidectomy with bilateral cervical lymph nodes dissection. Histological analysis confirmed MTC of right thyroid lobe and metastasis at lymph nodes of the central right midneck area.
Conclusions
Although CTN represents the gold standard biochemical parameter for the diagnosis and follow-up of MTC, it can be affected by physiologic and pathologic conditions. PCT has recently been regarded as potential marker of MTC achieving high sensitivity and specificity. In the present case, high levels of PCT in the absence of signs of bacterial infection, allowed to diagnose MCT. Hence, in the absence of any other sign of infection, a complete clinical assessment, including neck palpation, calcitonin measurement and thyroid ultrasound should be performed in the presence of persistent elevated PCT. PCT could be a new diagnostic tool or a supplementary biomarker in the management of MTC.

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AEP638

Graves' disease presenting with hypercalcaemia, thymic hyperplasia and lymphadenopathy

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We would like to report an interesting case of Graves' disease which presented with thymic hyperplasia, bilateral generalised lymphadenopathy and hypercalcaemia, along with other typical manifestations of hyperthyroidism. A 53 year old lady was admitted following an opioid overdose as she was suffering from depression after a recent slipped disc injury which had resulted in poor mobility. She suffered an out of hospital respiratory arrest, underwent cardiopulmonary resuscitation including treatment with nalaxone and was subsequently admitted. History revealed weight loss, anxiety, sweating and palpitations and she was noted to be in atrial fibrillation. She was found to have hyperthyroidism with TSH <0.01 mU/l (normal range 0.3–4.2 mU/l) and FT4 of 39 pmol/l (normal range 12–22 pmol/l) with positive TSH receptor antibodies. Bloods also showed mild hypercalcaemia with adjusted calcium of 2.72 mmol/l (normal range 2.20–2.60 mmol/l) and supressed PTH of 4 ng/l (normal range 16–65 ng/l) with normal vitamin D. CT thorax, abdomen and pelvis done to rule out malignancy showed generalised small volume lymphadenopathy in the neck, mediastinum and left axilla, nodules in the lung fissures bilaterally and some anterior mediastinal soft tissue. Myeloma screen and tumour markers were negative. She was started on carbimazole and anticoagulation with rivaroxaban and was referred to the Lung and Lymphoma MDTs for imaging review. The MDT discussions suggested a diagnosis of thymic hyperplasia, hypercalcaemia and lymphadenopathy secondary to thyrotoxicosis and did not recommend a biopsy. She responded well to antithyroid drug treatment with resolution of thyrotoxicosis and hypercalcaemia and an interval CT scan at three months showed complete resolution of the thymic hyperplasia and lymphadenopathy. Her symptoms of anxiety have also improved. Thymic hyperplasia is a known but rare manifestation of Graves' disease which is thought to be caused by the action of TSH receptor antibodies on thyrotropin receptors in the thymus. Similarly, hypercalcaemia has also been reported in severe untreated Graves' disease. This is thought to be an affect of thyroid hormones causing increased bone resorption. Generalised lymphadenopathy is also described with Grave's disease. Hypercalcaemia, generalised lymphadenopathy and a neck mass on a background of weight loss would otherwise suggest a malignancy, such as lymphoma, but all of these are known features of severe untreated Graves' disease. This complex case demonstrates the importance of a multidisciplinary approach to ensure that the patient is not subjected to unnecessary invasive investigations and is managed optimally.

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AEP639

Importance of lymph extranodal extension to therapy outcomes in patients with thyroid follicular epithelial cell-derived carcinoma evaluated at one year

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Introduction
The number of lymph node metastasis (NM) and the existence of extranodal extensión (ExEx) are not included among prognosis variables used in the most common staging systems for differentiated thyroid cancer as AJCC and ATA risk systems.
Objective
In patients with NM at diagnosis, to analyze the association between the number of NM and the presence of ExEx with response to therapy.
Patients and methods
Patients were included if they had undergone surgery at our center between december 2011 and january 2018 with a definitive diagnosis of thyroid follicular epitelial cell-derived carcinoma (TC) with NM and had had at least one follow-up after 12 months except for those died from TC. At one year, patients were classified in two groups according to the response to therapy: the group of Adequate Responders (AR) if they matched the definition of Excellent or Indeterminate Response and the group of Incomplete Responders (IR) in case of Biochemical or Estructural Incomplete Response based on the definitions endorsed by ATA. The variables evaluated at diagnosis for their potential relation to IR included: number of NM, ExEc and traditional factors as sex, age, presence of cancer (incidental or clinical), tumour size, unfavorable histology, distant metastasis (DM), multifocality, macro and microscopic extrathyroidal extension and incomplete surgical resection.
Results
103 patients (men: 26.2%) were included (median age of 49 ± 15.8 years) with a median of 3 (p25-p75: 2-6.25) resected MN. ExEx was demonstrated in 26.7 % of cases. Presence of Clinical cancer, incomplete resection, distant metastasis and macro and microscopic EE were found in 62.4%, 16.1%, 4.9%, 7.8 and 38.8% respectively. At one year, 19.6% of patients were classified into the IR group. Severals factors were clearly associated with IR: median tumoral size, presence of ExEx (18.8% in AR versus 62.5% in IR, $P< 0.05$) and DM (1.2% in AR versus 15% in IR, $P<0.05$). Multivariate analysis showed ExEx as an independent factor for IR (OR 5.6, IC 95% [1.2–26.3]). Specific mortality (3 cases) was associated with age (8.1 % versus 0 % in patients younger or older than 55 years of age respectively, $P < 0.05$) and unfavorable histology.
Conclusion
In CT patients with NM, the inclusion of ExEx to the variables frequently known at diagnosis could improve the prognosis value on mortality and recurrence of traditional AJCC and ATA risk systems.

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AEP640

Efficacy of multidisciplinary approach in thyroid nodules: analysis of factors used for predicting malignancy

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Background
To date, numerous molecular tests have been developed for preoperative evaluation of thyroid nodules. Nevertheless, these tests cannot be administered in many centers due to their imprecise diagnoses and high costs. The present study aimed to investigate the effect of making surgical decisions in a council through a multidisciplinary approach after clinical, ultrasonographic, and pathological evaluation of nodules on the accuracy of the decisions.
Materials and methods
The retrospective study included patients with thyroid nodules who underwent preoperative ultrasonography (USG) followed by FNAB, which was confirmed by postoperative pathological examinations between January 2017 and January 2019. Relationship between USG features of nodules and malignancy was analyzed. A comparison was performed between patients that were referred for surgery through the multidisciplinary versus non-multidisciplinary approach.
Results
A total of 255 nodules in 211 patients were evaluated in the study. The prevalence of malignancy was 100% in nodules with hypoechogenicity + microcalcification + margin irregularity (P<0.001). The likelihood of malignancy was significantly higher in dual combinations of these three adverse conditions (P<0.001 for all) (Table 1). Margin irregularity was found to be the most predictive model for malignancy (CI: 1.9–13.8, OR: 5.249, P<0.001). The multidisciplinary approach was superior to the non-multidisciplinary approach in the detection of malignancy (P = 0.008)(Table 2).
Conclusion
Margin irregularity had the highest predictive value for the detection of malignancy. Employing the multidisciplinary approach in preoperative evaluation of thyroid nodules can be highly effective in detecting malignancy and preventing unnecessary surgery.

Table 1. Multivariate Logistic Regression Analysis for Independent Factors for Predicting Thyroid Malignancy

Us Features	Beta Coefficient	Odds Ratio	95% Confidence Interval	*P* Value
Hypoechogenicity	1.336 ± 0.329	3.804	1.996, 7.250	<0.001
Irregüler margin	1.658 ± 0.495	5.249	1.989, 13.856	0.001
Microcalcifications	0.998 ± 0.358	2.713	1.344, 5.476	0.005
Macrocalcifications	–0.268 ± 0.470	0.671	0.335, 1.343	0.569
Type III vascularity	–0.399 ± 0.354	0.765	0.305, 1.923	0.260

Table 2. Comparison of Multidisciplinary approach and Non-Multidisciplinary approach

	Multidisciplinary approach		Non-Multidisciplinary approach	
	Benign Histology	Malignant Histology	Benign Histology	Malignant Histology
	No. %	No. %	No. %	No. %
Non-diagnostik I	–	1 (100.0)	31 (86.5)	5 (13.5)
Benign II	8 (88.9)	1 (11.1)	64 (92.8)	5 (7.2)
AUS/FLUS III	7 (43.8)	9 (56.2)	37 (72.5)	14 (27.5)
Follicular neoplasm IV	2 (66.6)	1 (33.3)	5 (62.5)	3 (37.5)
Suspicious of malignancy V	–	8 (100.0)	2 (10.0)	18 (90.0)
Malignancy VI	–	4 (100.0)	–	30 (100.0)

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AEP641

Percutaneous laser ablation of metastatic lymph nodes, role of minimally invasive thyroid treatment in center of reference of endocrine surgery.

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Background
The incidence of papillary thyroid cancers is increase in last decades due to easier ultrasound diagnosis. The papillary thyroid cancers metastasize via lymphatics to the lymph nodes of the central and later cervical neck compartment. According to 2015 ATA guidelines, the recurrence rate is less 1–2% [2]. The treatment of choice in lymph node recurrences is surgery, but it is burdened by a higher rate of complications (25% of recurrent laryngeal nerve palsy) [2]. Therefore, laser ablation of recurrent lymph nodes has been recognized as an alternative treatment with minimal invasiveness, low complication rate and curative effect [3].
Cases presentation
We report 6 cases of patients undergoing total thyroidectomy for papillary thyroid cancer diagnosed with fine needle aspiration cytology (FNAC) positive for malignant cells. All patients underwent metabolic radiotherapy, as indicated in the ATA guidelines, and experienced a lymph node recurrence 12–18 months after therapy. The diagnosis of relapse was made with ultrasound suspicion, FNAC with dosage of Thyroglobulin in the eluate. Three patients had a recurrence in the IV compartment, one in Vb compartment and two patients had a recurrence in the III compartment. The patients were treated with ModìLite™ laser ablative session using a multisource laser system (EchoLaser, Elesta SpA, Calenzano, Italy) with 1064 nm wavelength. The laser energy per each patient was delivered by a single 300 µm flat tip fiber introduced in target tissue through 21G Introduce needle. Hydrodissection of the lesion with 9% saline was performed in all patients. The energy delivered was 1560.28 ± 3213.84 Joule (Power, 3W). No major or minor complications were reported. At one-month follow-up, a volumetric reduction of the lesion of 39.67 ± 3.07% was reported. At 3 months of 48.83 ± 2.63% and at 6 months of 58.67 ± 3.07%. At 6 months, a fine needle aspiration was performed, negative for malignant cells and with a negative dosage of Thyroglobulin in the eluate.
Conclusion
Our experience has shown that laser ablation is an effective alternative to surgical treatment.
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AEP642

Estimating risk of recurrence of differentiated thyroid cancer patients: a real-world multicenter validation of the american thyroid association initial risk stratification and dynamic re-assessment after 5 years of follow-up.

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Background
Most Differentiated Thyroid Cancer (DTC) cases typically show indolent biological behavior and a low mortality rate. Various prognostic systems are used to assess disease recurrence risk, to tailor treatment and follow-up strategies. The initial Risk Stratification System (RSS) and dynamic Response to Therapy Re-stratification (RTR) system, recommended by the 2015 American Thyroid Association (ATA) Guidelines, are the most employed. Still, they have been validated only in retrospective cohorts of single tertiary referral centers. This study aimed to verify their real-world ability to predict disease recurrence five years after initial treatment and to clarify the specific weight of the dynamic RTR system compared to the initial RSS.
Methods
A prospective and multicentric cohort of DTC patients collected by the Italian Thyroid Cancer Observatory was analyzed. The inclusion criteria were: (i) histological diagnosis of DTC: (ii) complete information on initial treatment and 1- and 5-year follow-up visits. Patients were grouped by the RSS and RTR criteria. The correlation between risk group and structural evidence of disease was evaluated by univariate and multivariate logistic regression. The predictive performances of the two systems were also compared.
Results
Seven hundred eighty patients from 24 centers were included. The risk of recurrent disease, based on the RSS, was classified as low in 450 (57.7%), intermediate in 278 (35.6%), and high in 52 (6.7%) patients. One-year response to treatment was excellent in 576 (81.2%), indeterminate in 98

(13.8%), biochemical incomplete in 12 (1.7%) and structural incomplete in 23 (3.2%) patients. At the 5-year follow-up visit, structural evidence of disease was observed in 25 patients (3.2%): 1.1% of low, 4.7% of intermediate and 13.5% of high-risk patients; 0.3% of patients with 1-year excellent response, 6.1% with an indeterminate response, 8.3% with a biochemical incomplete response and 56.5% with a structural incomplete response (χ^2 test, *P*-value <0.0001). Multivariate logistical models showed statistically significant predictive performance for both RSS (intermediate risk: OR 4.37; 95% CI 1.54–12.38; high risk: OR 13.84; 95% CI 4.22–45.41) and RTR (1-year indeterminate response: OR 18.72; 95% CI 3.72–94.14; biochemical incomplete response: OR 26.09; 95% CI 2.20–309.54). Moreover, the dynamic stratification showed better predictive power, especially when combined with the initial risk.

Conclusions

Both ATA initial risk estimation and dynamic risk re-stratification systems effectively predict DTC recurrence, in a real-world, heterogeneous, and multicenter cohort. The dynamic stratification showed better predictive power, and it is even better when the two systems are combined.

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AEP643

Assessment of hearing impairment in adult patients with euthyroid Hashimoto's thyroiditis

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Introduction

Hearing loss may be associated with autoimmune diseases, but it was less studied in Hashimoto's thyroiditis (HT). We aimed to evaluate hearing impairment by audiometric assessments in adults with euthyroid HT.

Materials and Methods

Adult patients with euthyroid HT (normal thyroid functions, positive AntiTPO/AntiTg and sonographic findings) were compared with controls. We excluded pregnant or older patients (>50-year-old), those with history of otological/audiological disease or surgery, otitis media, acoustic trauma, chronic illnesses, use of alcohol, cigarette, medications, rheumatoid factor, antinuclear, antimitochondrial, antiparietal, antineutrophil cytoplasmic, anti-smooth muscle, or antigliadin antibodies, abnormal biochemical or otological findings. Tympanometry which indicated tympanic peak pressure (TPP, daPa), acoustic reflex testing (ART), pure tone average (PTA), and transient evoked otoacoustic emission (TEOAE) were performed. We grouped the participants according to ART (positive/negative), TEOAE (normal/undetected), PTA (≤20/>20 dB).

Results

Air conduction thresholds on right ear at 500, 4000, 6000, 8000 Hz, PTA average, and left ear at 250, 4000, 6000, 8000 Hz were higher in euthyroid HT ($n = 36$) than in controls ($n = 40$) ($P<0.05$). We found less negative TPP and a higher ratio of negative ART in euthyroid HT ($P<0.05$). Euthyroid HT predicted undetected TEOAE and increased hearing threshold on right ear at 500 and 8000 Hz ($P<0.001$). TEOAE detected hearing impairment at a higher rate. AntiTPO level was positively correlated with TPP and air conduction thresholds except right ear at 8000 Hz.

Conclusions

Hearing may be impaired in euthyroid HT. We recommend close monitoring of hearing functions in these patients. TEOAE more specifically indicates hearing impairment.

Table 1. Logistic regression analysis showing the association between categorical parameters and HT.

Parameters	Univariate		Multivariate	
	OR(95% CI)	*P* value	OR(95% CI)	*P* value
fT4(normal-high/normal-low)	8.000(2.832–22.72)	<0.001	11.20(3.10–40.35)	<0.001
ART L ipsilateral(positive/negative)	2.250(1.738–2.913)	0.046		
ART L contralateral(positive/negative)	2.250(1.738–2.913)	0.046		
TEOAE(normal/undetected)	2.666(1.941–3.663)	<0.001	NA	<0.001
Hearing threshold (≤20/>20 dB)				
R PTA average	2.252(1.739–2.915)	0.030		
R air 500 Hz	2.252(1.739–2.915)	0.030	NA	<0.001
R air 4000 Hz	2.288(1.757–2.985)	0.015		
R air 6000 Hz	2.427(1.828–3.225)	0.002		
R air 8000 Hz	2.597(1.912–3.533)	<0.001	NA	<0.001
L air 250 Hz	2.252(1.739–2.915)	0.030		
L air 4000 Hz	2.252(1.739–2.915)	0.030		
L air 6000 Hz	2.380(1.805–3.134)	0.003		
L air 8000 Hz	2.427(1.828–3.225)	0.002		

R:right L:left

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AEP644

Assessment of clinical burden and practice patterns in patients with chronic hypoparathyroidism in the united states (us): a claims data analysis using diagnosis-based criteria

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Objectives

There is a paucity of real-world studies analyzing comorbidities, lab testing and treatment patterns of patients with chronic hypoparathyroidism (cHP). This study describes a large cohort of cHP patients identified using a diagnosis-based approach from a US claims database.

Methods

This retrospective study was conducted using a large (130 million individuals) claims database (HealthVerity Closed Payer Claim Medical and Pharmacy databases: Private Source 20) from Oct 2014 to Dec 2019. Patients were eligible if they had ≥2 diagnosis claims of HP that were 6–15 months apart, a prescription claim for either active vitamin D, calcium, PTH or thyroid replacement therapy between the first HP claim and within 30 days of the second HP claim, and were continuously enrolled for one year before the index date (the date of the first of two qualifying HP diagnosis claims) and ≥16 months after. Patients were followed up to two years after the index date. Demographics, comorbidities, lab testing and treatment patterns were analyzed.

Results

Out of 43 640 patients with a diagnosis claim for HP, 4118 met the eligibility criteria. In this cohort, the mean age was 56.5 years ± 18.6 (S.D.), and 76.4% were females, similar to data from other large cohort studies. The most common comorbidities during the 1-year follow-up were hypertension (56.0%), hypocalcemia (38.7%), cancer (30.5%, of which 24% were thyroid cancers), diabetes (29.4%), chronic pulmonary disease (24.1%), cardiac arrhythmias (17.4%), CKD stage 3–5 (17.0%), osteoporosis (9.6%) and neuropsychiatric disorders, including depressive disorders (22.0%), anxiety (21.6%), and sleep-wake disorders (18.4%). During the 1-year follow up, commonly ordered lab tests included serum calcium (89.9%), eGFR/creatinine (85.7%), 25-hydroxy vitamin D (61.1%), and intact PTH (43.9%). Serum phosphorous (36.3%), serum magnesium (35.4%) and 24 h-urine calcium (10.5%) were evaluated much less frequently. In addition, BMD was measured in 10.9% patients. During the same follow-up period, 67.1% of patients had a prescription claim for thyroid replacement therapy, 60.5% for calcitriol, 15.7% for ergocalciferol, and 3.4 % for PTH.

Conclusion

This study highlights the high comorbidity burden in cHP patients which is aligned with the observed monitoring patterns. Kidney health appears to be a key concern in this population, and may be an important consideration in therapeutic intervention. The comorbidities and practice patterns observed are consistent with the results found using a surgery-based approach to identify cHP patients within the same claims database. Future analyses will include the economic burden of cHP.

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AEP645

Phenotypical changes of thyroid disease in a patient with Turner Syndrome

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Introduction
Turner syndrome (TS) is among the most common chromosomal abnormalities in females, resulting from structural or numeric abnormalities in the X chromosome. Autoimmune disorders, especially thyroid diseases have a high prevalence among these patients. Usually Hashimoto's thyroiditis (HT) is the most frequent one, whilst the association between this syndrome and Graves' disease (GD) has been less often reported. Here we report a case of patient with TS who has developed both autoimmune thyroid diseases over the course of her follow-up.
Case report
A 16-year-old female patient was referred to our endocrinology department for symptoms of hyperthyroidism. The patient was diagnosed with TS at the age of 9 when she had consulted for short stature. The diagnosis was confirmed with a karyotype showing a deletion in the short arm of the X chromosome: 46, X del(p12). Shortly after, she developed hypothyroidism and was put under levothyroxine. The patient has a family history of hyperthyroidism in her mother and her uncle. The antithyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies were negative at the time. At the age of 15, the patient started showing signs of hyperthyroidism such as weight loss, exophthalmia and tachycardia, with a thyroid stimulating hormone (TSH) level at 0.010 mUI/l (0.51 – 4.94 mUI/l). The immunological tests were positive this time with an anti-TPO level at 1300 UI/ml (<60 UI/ml), an anti-TG level at 354.9 UI/ml (<100 UI/ml) and a TSH receptor antibody level at 33 UI/l (<2 UI/l). A neck ultra-sound was performed and showed a hyper vascular goiter. All these exams confirmed the GD in our patient. A treatment with benzyl thiouracil was started for almost a year and the patient thyroid function became normal. At her last consultation, she presented signs of hypothyroidism even after stopping benzyl thiouracil for more than a month and the TSH level was high >100 mUI/l. Therefore, the patient was put again under levothyroxine to eventually achieve normal thyroid function.
Conclusion
Autoimmune thyroid diseases may begin in early childhood in patient with TS, and its prevalence increases with age. HT and GD are caused by two distinct paradigms. Nevertheless, it has been sporadically reported that GD and HT may follow one another in the same individuals, due to a sequential phenotypic conversion from HT to GD, or vice versa. In fact, patients with TS and associated HT were found to be at higher risk of progressing toward GD than the general population.

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AEP646

Hypothyroidism causing acute kidney injury (AKI)

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AKI is a potentially a life threatening condition and it is extremely crucial to investigate the root cause it order to manage the patient appropriately.
Case report
A 30 years old female presented with complaints of generalized muscle weakness, lethargy and mood changes. She was found to have raised creatinine with significant drop in her GFR to 41. Rest of her electrolytes and full blood count were within normal range. She was commenced on Intravenous fluids with strict input/output monitoring. No obvious trigger for her decline in renal function could be found. In order to find the cause for renal deterioration and in view of her clinical presentation, thyroid function tests and creatinine Kinase was done subsequently. Her blood tests revealed TSH >100 mU/l with T4 <1.0 pmol/l. Creatnine Kinase was minimally raised around 322 u/l. Provisional impression of hypothyroidism induced myopathy and AKI was made. She was treated with levothyroxine 100 µg. Her Thyroid peroxidase AB -TPO (303 IU/ml) was positive. Rest of the renal investigations were normal. Renal team were in agreement of concluding that acute kidney injury was perhaps due to severe undiagnosed Autoimmune hypothyroidism. Following adequate rehydration and after commencing thyroxine, she improved significantly both clinically and biochemically. Her creatinine gradually decreased over time with reciprocal improvement in her GFR.
Discussion
Hypothyroidism causing acute kidney injury is a very rare presentation. The exact mechanism for kidney failure still remains unknown. It has been postulated that absence of thyroid hormone alters mitochondrial oxidation and reduces glycogenolysis resulting in muscular atrophy leading to decreased number of fast-twitching (Type 2 fibers) Subsequently, increased deposition of glycosaminoglycan and hypertrophy of slow muscle fiber occurs causing myopathy and increased fatigue. It has also been proposed that T4 deficiency alters muscle permeability resulting in release of muscle enzymes, known as creatnine kinase. Its accumulation, known as rhabomyolysis is a well-known attribute of AKI. Some studies have shown effect of Thyroid hormone on renal perfusion (Renal plasma flow) which can subsequently alter GFR and affect kidney function. It is also noteworthy that majority of the rare cases reported demonstrates rhabdomyolysis as major cause of AKI in Hypothyroidism. However, in our case, patient had minimally raised levels of CK and was found to be in AKI. This is the first case to be reported that doesn't meet the criteria for rhabomyolysis in presence of AKI.

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AEP647

Graves' disease; relapse or fake news with Biotin

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A 41 year old lady presented to emergency department with tremors and palpitations. Her examination and routine bloods were normal but ECG showed sinus tachycardia (heart rate = 141 bpm). She was treated with propranolol and discharged. She was readmitted in emergency department with ongoing palpitations, lethargy and tremors. On examination, she had a diffuse goitre but no signs of Graves' eye disease. The blood tests showed overt thyrotoxicosis (TSH<0.01 mU/l, FT4 = 49.1 pmol/l, FT3 = 27.7 pmol/l) with positive anti TSH receptor antibodies (Anti-TRAb levels = 11.3 IU/l) and a thyroid ultrasound revealed a diffusely enlarged goitre. She was started on treatment for Graves' disease with carbimazole 15 mg BD along with propranolol. She was on 8 weekly endocrine follow up to monitor thyroid function tests (TFT). Within 4 months, her weight increased from 86.5 kg to 93.5 kg. She had the anticipated mild iatrogenic subclinical hypothyroidism (TSH = 7.35 mU/l, FT4 = 5.8 pmol/l, FT3 = 5 pmol/l). The dose of carbimazole was reduced to 5 mg once daily. Six months later, there was mild relapse of Graves' disease (TSH<0.01 mU/l, T4 = 24.2 pmol/l, T3 = 9.2 pmol/l). Carbimazole was increased from 5 mg to 20 mg again. Her thyrotoxicosis went into remission (TSH = 1.56 mU/l, T4 = 9.9 pmol/l) 11 months after initial diagnosis, but the anti-TRAb was still positive (3.7 IU/l). Carbimazole was continued at 5 mg. Her TFTs started to show an unusual pattern of remission with normal TSH but raised FT4 and FT3 whilst being on carbimazole 5 mg.

- TSH = 2.05 mU/l, T4 = 19.1 pmol/l and T3 = 8.1 pmol/l
- TSH = 1.08 mU/l, T4 = 26.9 pmol/l and T3 = 14 pmol/l

This was discussed with the biochemist as it wasn't the common pattern of early relapse with fully suppressed TSH(<0.01 mU/l). Hence it was thought to be an interference with biotin. On direct enquiry, the patient confirmed taking a variety of over the counter supplements containing biotin to help improve her hair and nail growth. This correlated well with the timing of unusual pattern of TFT. The carbimazole was stopped and her TFT on repeat check were completely normalised. Graves' disease has a relapsing remitting course. It is not unusual to make frequent changes of carbimazole dosages based on TFT results every 6–8 weeks. The usual duration of treatment of Graves' disease is 12–18 months to achieve remission and normalization of Anti-TRAb. Biotin has been reported to interfere with thyroid hormone assays and also give falsely elevated anti-TRAb levels. This can lead to inadvertent use of carbimazole in a patient with Graves' disease in remission. This case highlights the importance of identifying use of supplements like biotin which can interfere with TFT results.

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AEP648

Case report : A rare case of leucinosis decompensated by hyperthyroidism

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Leucinosis also called Maple syrup urine disease (MSUD) is a rare inherited disorder of branched-chain amino acid metabolism classically characterized by poor feeding, lethargy, vomiting and a maple syrup odor in urine with an evolution to encephalopathy and central respiratory failure if untreated. When diagnosed at birth, treatment is based on nutrition therapy aiming at rapidly reducing of toxic metabolites through dietary restriction, shifting towards and preventing or minimizing endogenous protein catabolism. Any state of catabolism can cause leucinosis' decompensation: intercurrent infectious disease, fever, anorexia, vomiting, surgery, excess protein instake. We report a case of MSUD decompensated by hyperthyroidism with complex management. A 20 years old woman had a family history of leucinosis and a diagnosis of MSUD at birth. At 13, an hyperthyroidism caused by Graves' disease was diagnosed. She was treated by carbimazole for 7 years with relapses when decreasing treatment. Between September and October 2020, she experienced 3 successive hospitalizations for middle to major leucinosis decompensations due to thyrotoxicosis occurring despite an increase to maximal doses of carbimazole and use of ursodeoxycholic acid. Therapeutical options were limited by formal contraindication to use corticoid, poor experience with radioactive iodine therapy and difficulties to organize surgery with strict metabolic conditions. However, after a multidisciplinary discussion, surgery was chosen as a radical treatment due to the major risk of new decompensation. Leucinosis is a very rare disease and its association to hyperthyroidism was never reported before.

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AEP649

Hyperthyroidism and exophthalmos in a patient with Erdheim–Chester disease

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We present extremely rare case of a female patient with the coincidence of hyperthyroidism, exophthalmos and Erdheim–Chester disease (a rare form of non-Langerhans cell histiocytosis, positive BRAF mutation). The patient was hospitalized due to exacerbations of the primary disease and symptoms of thyroid dysfunction. For about two months, the patient has reported increased feeling of heat, sweating, palpitations, weight loss of about 10 kg for 3 months, significant intensification of exophthalmos, pain in the eyeballs, lacrimation, feeling of sand under the eyelids. In addition, the patient has been taking amiodarone for 1.5 years (due to ventricular arrhythmias). The medical history also revealed central diabetes insipidus, progressive retroperitoneal and peraortic fibrosis involving the adrenal glands, aorta, inferior vena cava, spreading into the mediastinum, condition after insertion of JJ catheters into both ureters due to stagnation in the calicapelic system, multiple osteosclerotic changes. During the diagnostics and treatment, it was found that the exacerbation of eye symptoms (bilateral exophthalmos) was caused by the masses of fibrous tissue formed in the course of the underlying disease – the patient was referred to orbits decompression. During the observation, due to the diagnosed hyperthyroidism, the patient was qualified to radical treatment with radioiodine – it was obtained euthyreosis with substitution treatment with l-thyroxine. This case illustrates the importance of careful attention of diagnostics, treatment and monitoring even despite the most typical course of hyperthyroidism – and if necessary to accelerate and extend the treatment with additional tests.

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AEP650

Myxedema coma in a COVID-19 patient

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Introduction
Myxedema coma is a rare condition with an estimated incidence of 0.22 per million per year in the western world and a mortality rate around 30–50%. It can occur as the result of severe longstanding hypothyroidism or be precipitated by an acute event, such as infection. We present a rare case of myxedema coma in an elderly woman with SARS-CoV-2 infection.
Case report
An 82-year-old woman, with no previous history of hypothyroidism, presented with signs of breathing difficulty for the past 2 days associated with progressive lethargy and constipation. She had history of arterial hypertension, dyslipidaemia, and chronic kidney disease (KDIGO 4 stage). She had a uterine neoplasm discovered in contrasted CT scan but refused to undergo further studying. Her chronic medication included simvastatin, clopidogrel, furosemide, irbesartan and hydrochlorothiazide. In the physical examination, she was pale and dehydrated. Glasgow coma scale (GCS): 9 points. Blood pressure was 84/56 mmHg, heart rate of 60 bpm, temperature 36.2ºC and peripheral oxygen saturation of 94% at room air. Cardiopulmonary auscultation was normal. Her abdomen was diffusely tender to palpation and she had no peripheral oedema. Her initial blood work showed anaemia (10.3 g/dl), hyponatremia (126 mmol/l), hyperkalemia (5.7 mmol/l) and acute kidney injury (creatinine 1.67 mg/dl and urea 113 mg/dl). SARS-CoV-2 PCR testing was positive. Chest roentgenogram demonstrated signs of bilateral pneumonia. Head CT showed no recent vascular events. She was admitted and started fluid resuscitation with 0.9% saline. On the second day of hospitalization, she became unresponsive (GCS: 3 points) and presented oxygen desaturation, needing supplemental oxygen therapy with FiO2 80%. She was hypotensive (90/56 mmHg), bradycardic (45 bpm), and hypothermic (32.4ºC). She showed signs of inadequate perfusion of extremities, with barely palpable peripheral pulses. Her blood work evidenced pancytopenia, elevated transaminases, hyponatremia (132 mmol/l), hyperkalemia (5.3 mmol/l), PCR 24.5 mg/dl, procalcitonin 0.22 ng/ml, free T4 <0.25 ng/ml and TSH 52.67 µU/ml. She was diagnosed with myxedema coma triggered by SARS-CoV2 infection and treated with 200 mg hydrocortisone and 200 µg L-thyroxine intravenously. Despite these measures, she showed no signs of response and died within a few hours.
Discussion
Myxedema coma diagnosis requires a high level of clinical suspicion. This is the second described case of myxedema coma in a COVID-19 patient. In this patient, factors favouring this diagnosis were the coma status, hypoventilation, hypotension, bradycardia, hyponatremia and hypothermia. The SARS-CoV2 infection, a virus with known neurological tropism, might have impaired the ventilatory response even more.

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AEP651

Evolution of SARS-CoV-2 related atypical thyroiditis

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Background
We provided the first description of thyrotoxicosis due to atypical thyroiditis in patients hospitalised for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic disease (Covid-19), not associated with neck pain, more common in men, correlated with disease severity and coexisting with non-thyroidal illness syndrome. Classic viral subacute thyroiditis is often followed by permanent thyroid dysfunction and autoimmunity, thus we have started a longitudinal thyroid study, also including patients newly infected with SARS-CoV-2.
Methods
Baseline (at hospital admittance) and longitudinal (quarterly) study of patients hospitalised for moderate-to-severe Covid-19 disease, without known history of thyroid disorders, assessing serum thyroid function and autoantibodies, inflammatory markers and thyroid ultrasound scan (US).

Patients showing US focal hypoechoic areas suggestive for thyroiditis also underwent subsequent thyroid ^{99m}Tc or I^{123} uptake scan.
Results
To date 185 Covid-19 patients have been studied, of whom 53 (29%) already evaluated at follow-up. At baseline, 44/185 (24%) had low serum TSH concentrations and 23/185 (12%) thyrotoxicosis (low TSH and/or high free-thyroxine). TSH positively correlated with lymphocyte count (0.38, P<0.001) but not with C-reactive-protein (−0.12, P = 0.09) and interleukin-6 (0.01, P = 0.936). Thyroid US performed during hospitalisation showed one or more focal hypoechoic areas suggestive for thyroiditis in 8/20 (40%) patients. At 3 months of follow-up the serum median (IQR) TSH concentrations were increased in all patients (n = 53) compared with baseline: 1.6 (1.0–2.2) mIU/l versus 0.9 (0.5–1.8) mIU/l, respectively (P<0.001). Serum free-thyroxine, free-triiodothyronine and inflammatory markers also normalised compared with baseline. Seven patients (13%) had positive anti-thyroglobulin (TgAb) and/or anti-thyroid-peroxidase (TPOAb) autoantibodies and were excluded from the thyroid imaging study. Thyroid US showed focal hypoechoic areas of thyroiditis in 14/46 (30%) patients; thyroid ^{99m}Tc/I^{123} scintigraphy resulted normal in 3/12 (25%), focally reduced in 8/12 (67%) and diffusely reduced in 1/12 (8%). The prevalence of thyroid focal hypoechoic areas at US was 53% and 27% in patients with low or normal TSH at baseline, respectively (P = 0.05). At 6 months of follow-up the thyroid function remained normal, no patients developed TgAb/TPOAb and the thyroid US and ^{99m}Tc/I^{123} scintigraphy studies are ongoing.
Conclusions
Thyroid dysfunction during moderate-to-severe Covid-19 disease is mild and transient, however atypical areas of focal thyroiditis at US persisted at 3 months in about one third of patients and long-term consequences are still unknown. The association of low serum TSH concentrations with both lymphocytopenia and focal areas of thyroiditis at US supports the hypothesis of thyroid gland involvement in SARS-CoV-2 infection.

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AEP652

Pre-operative vitamin D deficiency is a risk factor for post-thyroidectomy hypoparathyroidism: a systematic review and meta-analysis of observational studies

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Context
Whether pre-operative vitamin D deficiency (VDD) contributes to post-operative hypoparathyroidism (hypoPT) risk is unknown.
Objective
To meta-analyze the best available evidence regarding the association between pre-operative vitamin D status and hypoPT risk.
Data Sources
A comprehensive literature search was conducted in PubMed, CENTRAL and Scopus databases, up to October 31, 2020.
Study Selection
Patients undergoing thyroidectomy with pre-operative vitamin D status and post-operative hypoPT data.
Data Extraction
Two researchers independently extracted data from eligible studies.
Data synthesis
Data were expressed as risk ratio (RR) with 95% confidence interval (CI). The I^2 index was employed for heterogeneity.
Results
Thirty-nine studies were included in the quantitative analysis (61 915 cases with transient and 5712 with permanent hypoPT). Patients with VDD demonstrated a higher risk for transient hypoPT compared with those with pre-operative vitamin D sufficiency (RR 1.92, 95% CI 1.50–2.45, I^2 85%). These results remained significant for patients with pre-operative 25(OH) D concentrations ≤20 ng/ml (mild VDD; RR 1.46, 95% CI 1.10–1.94, I^2 88%) and ≤10 ng/ml (severe VDD; RR 1.98, 95% CI 1.42–2.76, I^2 85%). The risk of permanent hypoPT was increased only in cases with severe VDD (RR 2.45, 95% CI 1.30–4.63, I^2 45%). No difference was evident in subgroup analysis according to study design or quality.
Conclusions
Patients with pre-operative VDD are at increased risk of transient hypoPT following thyroidectomy. The risk for permanent hypoPT is increased only for those with severe VDD.

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AEP653

Metabolic effects of levothyroxine as a part of multicomponent therapy in patients with a combination of arterial hypertension, type 2 diabetes mellitus and subclinical hypothyroidism

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Objective
To establish the association of the dynamic changes in carbohydrate, lipid metabolism parameters and blood pressure (BP) profile in patients with combined course of arterial hypertension (AH), type 2 diabetes mellitus (DM) and subclinical hypothyroidism (SH) and to determine the efficacy of the applied scheme. We examined 106 patients – 45 women and 61 men aged 45–55 years with AH stage II grade 2 and type 2 DM which were divided on SH presence into two groups: gr.1 – with SH which additionaly to the main antihypertensive scheme received levothyroxine (n = 47) and without SH (n = 59) – gr.2. Levothyroxine was administered in an individually selected dosage by titration in accordance with the obtained laboratory parameters.
Methods
BP profile, HOMA-insulin resistance (IR), glycated hemoglobin (HbA1c), lipid metabolism parameters (LDL-C, HDL, TG), thyroid-stimulating hormone (TSH) levels.
Results
Analysis of patients monitored during the year with multimorbid pathology – gr. 2 showed more expressed disorders of carbohydrate metabolism – fasting glucose, HbA1c, compared with similar indicators in gr.1, which demonstrates more significant metabolic changes, and subjectively indicates an increase in cardiovascular risk. Patients of gr. 2 are characterized by more pronounced manifestations of dyslipoproteinemia in the form of increased LDL-C (P<0.05) and hypertriglyceridemia and lower levels of HDL. In the dynamics of combined antihypertensive treatment in patients from gr. 1 and gr. 2, a sufficient antihypertensive effect was found, which was to achieve the target BP levels of 76.43 % and 69.27 % of those surveyed, respectively. Significant differences after 12 months of therapy were reached by the value of systolic BP in all examined groups (P<0.05). Diastolic BP was significantly reduced in all groups compared to the initial values (P <0.05). Administration of levothyroxine led to a significant reduction in proatherogenic lipids, in group 2, where LDL-C from (3.6 ± 0.33) mmol/l to (2.5 ± 0.27) mmol/l, P <0.05, and TG from (3.3 ± 0.44) mmol/l to (1.85 ± 0.31) mmol/l, P <0.05, whereas SH promotes the development and progression of atherosclerosis despite hypolipidemic therapy.
Conclusions
Additional administration of levothyroxine to the standard combined scheme in patients with AH, type 2 DM and SH improve lipid, carbohydrate metabolism and hemodynamics in the form of a significant reduction in dyslipidemia, normalization of fasting glucose levels and HbA1c which definitely reduces the risk of cardiovascular events in this category of patients.

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AEP654

Autoimmune polyendocrine syndrome in patients with thyroid autoimmunity

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Introduction
Autoimmune Polyendocrine Syndrome (APS) is defined by the presence of 2 or more autoimmune induced endocrine failures in a single patient. There are 4 types of APS: type1 including chronic muco-cutaneous candidiasis,

hypoparathyroidism, Addison disease (AD) and ectodermal dystrophy, APS type 2 and 3 containing autoimmune thyroide disease (AITD), type1 diabetes (DT1) with (type2) or without adrenal failure (type3) and type 4 not falling into the above categories. The aim of our study was to precise the prevalence of APS in a group of patients with AITD and their clinical and serological evaluation.
Methods
Retrospective study including 46 patients suffering from APS among 113 with AITD was performed in internal medicine and/or endocrinology department hospital from January 2000 to December 2017.
Results
46 patients (40%) with AITD had APS. 60% of population was female (sex-ratio = 1.87). The mean age was 34.13 years [14–65 years]. We noticed history of thyroid disease in 26% of cases and family auto-immune disorder in 8.6%. In our study, we identified 7 cases of APS type2 and 39 cases of APS type3. AITD was type Grave's disease in 10 cases, Hashimoto thyroiditis at hypothyroidism stage in 23 cases, hyperthyroidism stage in 6 cases and euthyroidism in 7 cases. On clinical presentation, APS manifests itself as one of the major autoimmune diseases: adrenal failure and/or DT1 and/or hypo/ hyperyroidism in all cases. Diabetes preceded APS in 50% of cases. Minor autoimmune disorder type Vitiligo was diagnosed preceding the development of APS in 2 cases and concomitantly in 1 case. Thyroid gland was enlarged in 67% of cases. Serum analysis showed diabetes in 56.5%, hypothyroidism in 50%, hyperthyroidism in 35%, euthyroidism in 15% and adrenal insufficiency in 15.2% of patients. Immunologic investigations showed Thyroid peroxidase autoantibodies in 91%, thyroglobilin-autoantibodies in 43%, Glutamic-Acid-Decarboxylase autoantibodies in 67%, TSH-receptor autoantibodies in 21.7%, adrenal autoantibodies in 16.2%, antinuclear antibodies in 6.5%, antigliadin antibodies in 4.3%, anti-ovarian, antiparietal-cell and anti-transglutaminases auto antibodies in 2.1% respectively. Multiple autoimmune syndrome (type3) was retained in 6 patients (13%). Extra endocrine auto-immune disorders founded were: vitiligo (3 cases), lupus, celiac disease and pernicious anemia (1 case each).
Conclusion
Prognosis of APS depends on individual glandular failures. Considering the high incidence of APS in patient with family and/or personal autoimmune history, regular screening in specialized centers must be performed. In our series containing 46 cases of AITD with APS, type3 was more observed (84.8%) unlike other studies in which APS type2 was more prevalent.

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AEP655

Vitamin D deficiency is associated with increased thyroid autoimmunity in Georgian adults

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Introduction
Recently, apart from its main physiologic role, the active form of vitamin D has also been recognised to have anti-inflammatory and immune-modulating properties. Accumulating evidence suggests that Vitamin D deficiency is associated with increased prevalence of various autoimmune diseases, and in particular, with autoimmune thyroid disease. Despite contradicting evidence, the balance is tipping towards inverse correlation between vitamin D deficiency and autoimmune thyroid diseases. To the best of our knowledge, this association has not been studied before in South Caucasia, a large geographical area spanning across four countries, including Georgia. Therefore, this study aimed to investigate whether vitamin D deficiency was associated with increased prevalence of autoimmune thyroiditis among Georgian adults.
Methods
Study population consisted of patients aged >18 years with measurements of both serum vitamin D (25OHD) and thyroid peroxidase antibody (TPOAb) levels in two medical centres in Georgia from July 2016 to August 2020. The participants were divided into cases (vitamin D deficient) and controls (vitamin D sufficient/insufficient). 25OHD and TPOAb baseline levels were compared using Kruskal–Wallis rank-sum test. The strength of association was quantified by odds ratio. The strength and direction of association between vitamin D and TPOAb were measured with Spearman's rank-order correlation. Statistical significance was accepted at 95% confidence interval (P<0.05).
Results
170 patients had measurements of both 25OHD and TPOAb, and were included in the analysis, with a mean age of 43.9 ± 15.49 years (male to female ratio of 1:4.28). 59.4% (n = 101/170) had vitamin D deficiency and 53.5% had positive TPOAb (n = 91/170). In the case group, 60.4% (n = 61/101) had positive TPOAb, compared to 43.5% (n = 30/69) in controls. TPOAb baseline levels were higher in cases (mean: 191.0, S.D.: 53.9), compared to the controls (mean: 102.7, S.D.: 155.4) (P = 0.0328). TPOAb was significantly higher in the case group (P = 0.0439) with an odds ratio of 2.0 (OR>1, 95% CI: 1.1–3.7, P = 0.0308). When adjusted for age, gender, and BMI, a percentage change of 14.8% was observed, increasing the odds ratio to 2.3 (OR>1, 95% CI: 1.2–4.5, P = 0.0169). A significant inverse correlation was observed between vitamin D and TPOAb levels (rho = –0.16, P = 0.0367).
Conclusion
Our findings suggest a significant and inverse correlation between vitamin D deficiency and thyroid autoimmunity among Georgian adults. Further prospective studies are warranted to ascertain a causal relationship between vitamin D deficiency and autoimmune thyroiditis in our population.

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AEP656

Features of large intestinal microbiota of patients with diffuse toxic goiter

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It is well known that the range of disorders of various organs and systems in thyroid dysfunction is diverse, due to the scale of the impact of thyroid hormones on the body. One of the most characteristic clinical manifestations of thyrotoxicosis is changes in the gastrointestinal tract in the form of dysbiosis. Some studies have found inconsistencies in the association of these filotypes with the presence of thyrotoxicosis. In addition, there is no data in the literature on the change in the content of the main filotypes of the intestinal microbiota depending on the state of compensation of thyrotoxicosis.
The purpose of the work was to study the species composition and population level of microflora of the intestinal cavity in patients with diffuse toxic goiter, as well as to study the content of the main filotypes of intestinal microbiota in these patients.
Material and methods
We examined 40 patients with accidents (15 men and 25 women) aged 30 to 73 years (mean age 47.8 + 8.9 years) in the stage of compensation and decompensation of the disease and 51 almost healthy donor who formed the control group. The first group (20 patients) consisted of patients in a state of compensation, the second group (20 patients) – in a state of decompensation of the disease.
Results and discussion
Analysis of changes in the species composition and population level of the microflora of intestinal cavity made it possible to establish that in all examined patients with accidents revealed intestinal dysbiosis. Grade IV dysbiosis was found in 27.5% patients, grade III dysbiosis in 22.5% patients, grade II dysbiosis in 18 patients 45% and grade I dysbiosis in 5% patients. Imbalance developed due to elimination and deficiency of autochthonous anaerobic and aerobic obligatory bacteria (*Bifidobacteria, Lactobacteria and Enterococci*), contamination of the large intestine with hemolytic *Escherichia*, opportunistic pathogenic enterobacteria, life expectancy and increase in staphylococci and yeast-like fungi of the *Candida* type.
Conclusion
Thus, the content of Firmicutes in patients with accidents was significantly higher, and the content of Bacteroidetes – significantly lower than in healthy individuals (P<0.05). Analyzing the content of the main microbial filotypes depending on the state of accident compensation, it was found that in patients in state of compensation and decompensation of accident the content of Firmicutes was significantly higher (P<0.05) and the content of Bacteroides – significantly lower in patients in the state of compensation and healthy individuals (P<0.05).

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AEP657

A case of Grave's disease following SARS-Cov 2 infection

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Introduction
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that caused a global pandemic in 2020. The virus has infected more than 100 million people worldwide and the pandemic is still spreading. It can affect practically all organs. Data on the impact of SARSCoV-2 on the thyroid gland are very scarce. Two patients with Graves' disease (GD) and COVID-19 have been recently published(1). We present a case GD occurring after SARS-CoV-2 infection.
Methods
We describe the clinical findings, thyroid function tests, and neck ultrasound of a patient presenting with thyrotoxicosis signs.
Results
A 38-year-old, Tunisian female, having a medical history of autoimmune diseases, had been hospitalized on september, 2020, at COVID-19 department (a naso-pharyngeal swab test for SARS-CoV-2 was positive, and chest high resolution computed tomography without iodinated contrast agents) showed bilateral ground glass areas typical of SARS-CoV-2-related interstitial pneumonia. Due to persisting asthenia and onset of tremor and palpitations, thyroid function was assessed on November, 2020, showing suppressed serum TSH (<0.01 mU/ml) with increased serum-free thyroxine (FT4 31.6 pmol/l). Physical examination revealed a non-tender goiter. TSH receptor antibodies were positive (14.1 IU/l). Therapy with corticosteroid and propranolol was started with improvement of symptoms and thyroid function. Anti-thyroid drugs were not started because the patient has leukopenia contraindicating this treatment. Clinical presentation and positive TSH receptor antibodies are compatible with a diagnosis of GD (autoimmune hyperthyroidism). Our cases of hyperthyroidism were diagnosed 2 months after the clinical onset of COVID-19.
Conclusion
In conclusion, we report a case of Graves' disease after COVID-19, with no previous known thyroid disease. Of course, with Graves' disease being the most frequent cause of hyperthyroidism, especially in middle-aged women, the association might be casual. However, the increasing number of publications on autoimmune diseases related to COVID-19 suggests that SARS-CoV-2 could act as a trigger of latent or new-onset autoimmunity. Physicians working in COVID-19 departments should be aware of possible connections between SARSCoV-2 and thyroid dysfunction, both subacute thyroiditis and Graves' disease, which should be investigated by future prospective studies.

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AEP658

Neurogenesis pathway-focused gene expression analysis in patients with primary hypothyroidism and autoimmune thyroiditis

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Abstract
Important regulators of metabolism are thyroid hormones. They play an important role in the development and maturation of the central nervous symptom and their failure in the prenatal period leads to irreversible brain damage, however, their effect on the brain of an adult has not been fully studied. On the other hand, Hashimoto encephalopathy is associated with autoimmune thyroiditis. With the discovery of neurogenesis in the adult brain many recent studies have been focused on understanding the basic mechanisms controlling this process. Many neurogenesis regulatory genes not only transcribed but also translated into blood cells. The focus of our study was to analyze the transcriptional activity of neurogenesis regulatory genes in peripheral blood cells in patients with thyroid pathology.
Methods
We used the pathway-specific PCR array (Neurotrophins and Receptors RT^2 Profiler PCR Array, QIAGEN, Germany) to identify and validate neurogenesis regulatory gene expression in patients with thyroid pathology and control group.
Results
The results showed that GDNF, GFRA3, NGFR, NRG1, NTF3, NTRK1, NTRK2 significantly decreased their expression in patients with autoimmune thyroiditis with rising serum autoantibodies. The patients with primary hypothyroidism as a result of autoimmune thyroiditis and postoperative hypothyroidism had significantly lower expression of BDNF, CBLN1, FGF2, NGFR, NRG1, NTF3. The mRNA level of CNTFR, MEF2C was markedly decreased in the group of patients with postoperative hypothyroidism. ARTN, CNTF, PSPN, TFG, MT3, NELL1 did not change their expression in all groups of patients.
Conclusion
The finding indicates that a decrease of thyroid hormones and a high level of autoantibodies such as anti-thyroglobulin antibody and anti-thyroid peroxidase antibody influence the expression mRNA neurogenesis-regulated genes in patients with thyroid pathology.

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AEP659

Outcome of Long Term Antithyroid Therapy in Patients with Graves' Hyperthyroidism

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Graves' disease is an autoimmune thyroid disease which, untreated, carries a significant morbidity risk. Treatment options for Graves's disease have changed over the decades.
Aims
To evaluate the outcome and risk factors for relapses of patients with Graves's disease treated with antithyroid drugs for at least 2 years.
Methods
A retrospective, analytic study on 360 consecutive patients admitted between Jan 2011–Oct 2019 and evaluated at diagnosis, after restoring of euthyroidism and at final visit. Clinical evaluation, thyroid function tests, TRAb (TSH receptor antibodies), goiter volume were obtained.
Results
There were 296F/64M, age at diagnosis: 44.5 ± 13.78 [13–81 years], freeT4 = 41.8 ± 22.68 pmol/l (N = 12–22), 226(62.8%) with ophtalmopathy, 34 (9.4%) with atrial fibrillation, 41 (11.4%) with heart failure. After diagnosis, all received methimazol, 28.15 ± 20. 52 mg/day. Normal free T4 was obtained after 9.37 ± 16.2 months and normal TSH after 12.97 ± 17.8 months. Patients were treated by thyroid surgery (109 pts, after 51 ± 46 months), radioiodine therapy (58 pts, after 58 ± 52 months), radioiodine and surgery (n = 9 pts) and 193 pts received longterm thionamides (55.64 ± 38.5 months). 6/193 patients only medically treated were cured at final visit. 228/360 patients had relapses. Risk factors for relapses were: young age (P = 0.002) and heart failure at diagnosis (P = 0.004). Serum levels of TRAb >10 ng/ml predicted active disease at final evaluation (Sn = 61.3%, Sp = 51%, P = 0.03).
Conclusions
Patients with Graves's disease have longer duration of antithyroid treatment before ablation, with frequent relapses. Young patients with severe disease at diagnosis (TRAb >10 ng/ml, heart failure) should receive thyroid ablation, because only 5% medically treated became cured.

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AEP660

Factors affecting development of hypothyroidism at patients with subacute thyroiditis

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Introduction
The aim of the present study was to determine the possible factors contributing to the development of hypothyrodisim in patients who had a subacute thyroiditis (SAT) attack.
Methods
Medical records of patients who were diagnosed with SAT between September 2014 and January 2020 were analyzed retrospectively in one center in Trabzon city of Turkey. The medical records of the patients were searched with ICD-10 code E06.1. There were 283 patients recorded with ICD-10 code E06.1; 119 of them had appropriate records and enough data to be involved into the study. Patients known to have previous thyroid disease were excluded. Patients who were followed at least 6 months after SAT attack cured were included. The demographic data of the patients; laboratory results including erythrocyte sedimentation rate (ESR), C reactive protein (CRP), thyroid stimulating hormone (TSH), triiyodotronine (T3), thyroxine (T4), anti-thyroid antibodies; the character and spread of neck pain; ultrasonography (USG) findings; the medications; the need to steroid therapy and the duration of steroid therapy; presence of hypothyroidism; occurrence and frequency of recurrences were recorded. The relationship between these parameters and development of permanent hypothyroidism were searched.
Results
The mean age of the patients was 42.3 ± 10.9 (24–78 year). The frequency of SAT was higher among women than men (93 women vs 26 men; 78.2% vs 21.8%, respectively). SAT was more frequent during spring and summer, but there were no statistical differences in means of the months or the seasons (P= 0.329, 0.534, respectively). Eighty-eight (69.7%) of the patients described a viral/flu-like disease before neck pain started. Almost half of the patients (n = 68, 57.1%) had gone to a different specialty other than endocrinology; 55 (46.2%) to otorhinolaryngology, 10 (8.4%) to internal medicine, 2 (0.02%) to emergency clinic and 1 (0.01%) to infectious disease until taking a SAT diagnosis. Thirty-four (28.6%) of the patients had been prescribed antibiotics for misdiagnosis of an upper tract infection. There were 10 patients (8.4%) who developed hypothyroidism after SAT attack. Mean steroid using time was longer at patients with hypothyroidism (17.7/16.4 vs. 8.9/5.9 weeks; P = 0.021). Hypothyroidism was more frequent among patients who did not have thyrotoxicosis during SAT attack; p= 0.004 and who had recurrent SAT attacks p= 0.035.
Conclusions
Patients who need steroid for a longer period, who have recurrent SAT attacks and who did not have thyrotoxicosis during SAT attacks should be closely monitored in means of developing hypothyroidism.

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AEP661

Iodine excretion in schoolchildren of Vilnius

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Iodine deficiency is the main cause of preventable mental retardation in children. Urinary iodine excretion is a marker of recent iodine intake and is used to monitor the iodine status of population. Iodine excretion in Lithuanian schoolchildren was previously investigated in 2001. The main objective of this study was to evaluate iodine excretion in children, ages 6–12, living in Vilnius, Lithuania.
Methods
Urine samples were collected from June 2019 to January 2021 at 3 outpatient clinics during "NATRIJOD" – a national program conducted to evaluate sodium and iodine status in Lithuania. Parents signed informed consent forms. Questionnaires about the child's gender, age, height, dietary habits, use of medications and dietary supplements were collected. Urinary iodine was measured spectrophotometrically by a method based on the Sandell–Kolthoff reaction. The method was approved by the Ensuring the Quality of Urine Iodine Procedures quality assurance program. Urinary creatinine was measured enzymatically by Architect (Abbott, USA) analyser. Urinary iodine concentration (UIC, µg/l) was measured in spot urine samples and estimated 24hour urinary iodine excretion (UIE, µg/day) was calculated dividing UIC by creatinine and multiplying by expected 24h creatinine excretion referenced from values of German children with the respective gender and height.
Results
Data of 117 subjects were analysed. Median UIC was 214.68 µg/l and median UIE was 128.92 µg/day. 69.2% of children had UIE within the recommended range. 30.8% of participants had iodine deficiency (UIE <100 µg/day) with a higher rate among girls (40.7%) compared to boys (22.2%) (P = 0.030). 37.8% of 6–7 year-olds, 33.3% of 8–9 year-olds and 22.7% of 10–12 year-olds had iodine deficiency. Median UIE in 6–7 year-olds and in 8–9 year-olds was lower compared to children aged 10–12 (respectively 121.54 µg/day vs 173.15 µg/day, P = 0.049 and 124.23 µg/day vs 173.15 µg/day, P = 0.008). Iodine deficiency rate in children with no diet restrictions was lower than in those who had diet restrictions (25.8% vs 55.0%, P = 0.010). UIE in children who mainly ate home-cooked food was higher compared to those who ate at school or processed food from stores (137.61 vs 99.71 µg/day, P = 0.011).
Conclusion
Compared with the data from 2001 the iodine intake of schoolchildren has increased. However, a considerable portion of children remain at risk of iodine deficiency. Continued monitoring of iodine intake using 24-h urine samples is needed to ensure that the actual iodine intake of schoolchildren is sufficient.

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AEP662

An audit of thyroidectomy in Graves' Disease, in a large UK tertiary centre

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Background
Thyrotoxicosis with Graves' Disease is treated with thionamide, radio-iodine treatment and thyroidectomy. Surgery is an important choice, especially when Graves' Disease is complicated by thyroid orbitopathy. Pre- and post-operative protocols for thyroidectomy are imperative.
Aims
1) To assess pre-operative preparation of patients, with potassium iodide, vitamin D, beta blockade, and the pre-operative thyroid function.
2) To assess the post-operative monitoring and complications.
Method
The patient cohort came from a large UK tertiary centre from 2014-19. Every thyroidectomy is recorded in the BAETS database which facilitated ascertainment of subjects. The anonymised data were analysed to calculate percentages for each parameter within the aims of the audit.
Results
Ninety-two patients were included in the cohort, aged 19–74 years. It was found that 85% of patients were euthyroid pre-operatively, with 2% hyperthyroid pre-operatively and 13% hypothyroid. 48% received pre-operative vitamin D; 49% received pre-operative potassium iodide; and 53% were on a beta-blocker or alternative. Post-operative calcium checks took place the same and following days, performed in 99% and 100% respectively. Post-operative parathyroid checks took place the same and following days, performed in 97% and 98% respectively. Post-operative hypocalcaemia occurred in 26% but was temporary in 92%. Vocal cord palsy was reported in 11%, but in all cases was a temporary neuropraxia. The rate recorded in the BAETS 2017 national database is 7.8% for temporary vocal cord palsy, although the database notes that this is likely an underestimation due to lack of post-operative laryngoscopies (1). The national rate for persistent vocal cord palsy, over 6 months, is 1.2% for total thyroidectomy (1).
Discussion
The results show low complication rates in this cohort, with the majority of complications being temporary. Post-operative investigation for calcium and parathyroid hormone was achieved in almost all cases. Pre-operative optimisation with vitamin D, potassium iodide and beta blockers was not always achieved in more urgent cases. A proforma is presented, to ensure not only that pre-operative optimisation occurs, but that it is also clearly documented for each patient. This audit would suggest that if done by experienced surgeons, surgical management of Graves' Disease confers low complication rates and can be an effective option in the management of Graves' Disease.
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AEP663

Thyroid-receptor antibodies, immunoglubulin E and antinuclear antibodies in patients with Graves' disease and their association with Graves' orbitopathy and smoking habits

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Introduction
Thyrotropin-receptor antibodies (TRAb) play a key role in the pathogenesis of Graves' disease (GD) and Graves' orbitopathy (GO) and are important for the diagnosis of both diseases. Elevated levels of immunoglobulin E (IgE) and antinuclear antibodies (ANA) were also found in GD patients. Smoking is a risk factor for GD and GO development and GO progression. We aimed to assess the associations between TRAb, IgE and ANA, and the presence and severity of GO and smoking in GD patients.
Material and methods
A total of 103 GD patients (mean age 51.2, 84 females) were divided into three subgroups: moderate-to-severe GO (n = 36), mild GO (n = 32) and "only GD" subgroup (n = 35). Forty healthy controls (HC) (mean age 51.2, 36 females) were also included. TRAb were measured in all GD subgroups by a thyrotropin-binding inhibitory immunoglobulin (TBII) assay. TBII<2 IU/ml were considered negative. All subjects were tested for IgE- and ANA-positivity and were categorized as smokers (current and ex-smokers) and non-smokers according to their smoking habits.
Results
The GD group had significantly higher number of smokers (P<0.01), higher IgE-positivity rate (P = 0.04) and a similar percentage of ANA-positivity compared to HC. The moderate-to-severe GO subgroup had significantly higher TBII (P<0.01) and significantly lower TBII-negativity rate (P<0.01) compared to the other two subgroups. The percentage of positive IgE did not differ significantly between GD subgroups, but the moderate-to-severe GO subgroup was the only subgroup, whose IgE-positivity rate was significantly higher than HC (P = 0.01). The moderate-to-severe GO subgroup also had the highest ANA-positivity rate amongst the three subgroups (P = 0.02). Mild GO and "only GD" patients did not differ significantly in terms of TBII level, TBII-negativity rate, IgE and ANA. Both GO subgroups had significantly higher smoking rate than the "only" GD subgroup (P = 0.01). There was a positive correlation between smoking and TBII (ρ = 0.245, P = 0.02) and between smoking and IgE (ρ = 0.23, P = 0.03).
Conclusions
GD patients exhibit different immunological patterns depending on the presence and severity of GO. Smoking might affect the clinical and immunological manifestations of GD, but is not the only factor involved.

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AEP664

How Does Age Influence Disease Outcome in High Risk Papillary and Follicular Thyroid Cancer Patients?

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Background
The 2015 American Thyroid Association (ATA) Risk Stratification System for differentiated thyroid cancer (DTC) is designed to predict response to therapy and recurring disease. Although age is not incorporated as a risk factor, recent research suggests that the addition of age can improve this system. However, these studies comprised low number of patients with ATA High Risk, low numbers of patients with follicular thyroid cancer (FTC), and did not distinguish between papillary thyroid cancer (PTC) and FTC. The aim of our study was therefore to investigate the influence of age on disease outcome in ATA High Risk patients with a focus on differences between patients with PTC and FTC.
Methods
We retrospectively studied adult patients with DTC who were diagnosed and/or treated at a Dutch university hospital between January 2002 and December 2015. All patients fulfilled the 2015 ATA High Risk criteria. Logistic regression and Cox proportional hazards models were used to estimate the effects of age and several age cutoffs (per five years increment between 20 and 80 years) on four disease outcomes: (i) response to therapy, (ii) developing no evidence of disease, (iii) recurrence, and (iv) disease specific survival (DSS).
Results
We included 236 patients with High Risk DTC (32% FTC) with a mean age of 56 years and a median follow-up of 6 years. During follow-up, 14% of the 79 patients that achieved excellent response developed a recurrence. For both PTC and FTC, age had a significant influence on having an excellent response after initial therapy, developing NED, recurrence, and DSS. For FTC, an age cutoff of either 65 years or 70 years seemed to be statically optimal for the different disease outcomes, while this was either 50 years or 60 years for PTC.
Conclusion
In a population of patients with High Risk DTC, age has a significant inverse influence on disease outcomes. Slightly different optimal age cutoffs were identified for the different outcomes, and these cutoffs differed between PTC and FTC. Therefore, age should be considered to be included as a risk factor in the ATA Risk Stratification System, and when doing this, PTC and FTC should be treated as separate entities.

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AEP665

Could ultrasound characteristics guide us on the presence of malignancy in thyroid nodules with Bethesda III cytology?

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Background
Thyroid nodules with indeterminate cytology represent a therapeutic challenge. The probability of malignancy had been established between 5 and 15%, but it varies among the published data. Nowadays we have molecular tests to help in therapeutic decisions, but they are not available at all centers leaving uncertainty regarding appropriate management.
Objectives
– To know the percentage of malignancy in thyroid nodules with Bethesda III (AUS/FLUS) cytology in our center.
– To establish whether there is an association between the ultrasound characteristics of the B. III nodules and malignancy.
Materials and methods
WECe selected Bethesda III nodules from 1034 FNAs performed in our center between May 2012 – October 2016. Age, sex, ultrasound suspicious characteristics (central vascularization, microcalcifications, taller than wide shape, irregular margins and hypoechogenicity), TIRADS score and definitive histology were registered. The association between malignancy and the cited variables was analyzed.
Results
6.96% (102/1034) of cytologies were B.III. 46.2% (47) of these nodules B.III had surgery, while 20.5% (21) are waiting for surgery and 33% (34) are in clinical ultrasound follow-up. *Results in operated patients (n = 47):* 76.6% were women; Age 54 [10–75] years. 48.9% (23) had 1 single B.III cytology and in the remaining 51.1% (24) the FNA was repeated (5 B.III, 7 unsatisfactory, 6 benign, 3 suspicious of malignancy and 3 Follicular neoplasm). 42.6% (20) of the B.IIIs nodules operated were thyroid carcinomas: 75% (15) papillary carcinoma, 5% (1) Hurthle cell carcinoma, 10% (2) minimally invasive follicular carcinoma, 5% (1) medullary carcinoma and 5% (1) were anaplastic carcinoma. Within TIRADS 2 nodules, the percentage of malignancy detected was 0%, while in TIRADS 4a was 28.6% and it rises to 75% in TIRADS ≥4b (P = 0.008). The only ultrasound characteristic that was associated with malignancy by itself was irregular margins (P = 0.039). The risk of malignancy increased with the addition of suspicious ultrasound characteristics, without detecting statistical differences here (P = 0.09): 3 or more = 72.7% malignancy; 2 = 50%; 1 = 27.8%; 0 = 0%.
Conclusions
The percentage of malignancy in B.III nodules in our center in these preliminary results is between 34-46.2%. Both the TIRADS and the addition of suspicious ultrasound characteristics correlate well with the presence of malignancy and constitute a helpful tool when considering whether surgery or clinical follow-up is the best option (high percentage of malignancy when there are 2 or more ultrasound data of suspicion or score ≥4b on the TIRADS scale).

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AEP666

Increased gene expression of TIMP1 and CHI3L1 in fine-needle aspiration biopsy washouts from papillary thyroid cancer

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Aim
To assess the relative expression of tissue inhibitor of metalloproteinase-1 gene (TIMP1) and chitinase-3-like protein 1 gene (CHI3L1) in fine-needle aspiration biopsy (FNAB) washouts and the serum levels of their protein products (TIMP-1 and chitinase-3-like protein 1 also known as YKL-40) in patients with histologically confirmed papillary thyroid cancer (PTC) and with benign nodules. Further, we evaluated the correlation between the gene expression and the circulating protein product.
Materials and methods
Eighty subjects (72 females, 8 males, mean age of 40.6 ± 11.3 years) were recruited from the routine patient flow referred for FNAB of thyroid nodules in one tertiary center. Forty patients with cytology Bethesda V and VI were operated and PTC was confirmed. The other 40 patients were with benign cytology (Bethesda II) and were considered a benign group. TIMP-1 and YKL-40 serum levels were measured in all subjects. The gene expression of TIMP1 and CHI3L1 was assessed in cytological specimens from 20 patients with PTC and 20 benign cases using quantitative real-time PCR.
Results
The PTC group was sex-matched with the benign group and the male-to-female ratio was 1:9. There was no significant difference between the mean age in the study groups (P = 0.922). The relative expression of TIMP1 and CHI3L1, assessed in FNAB washouts, was significantly higher in the PTC group than in the benign nodule group (P <0.001 for TIMP1; P = 0.018 for CHI3L1). The serum level of TIMP-1 was significantly higher in the PTC group compared to the benign group (82.0 ng/ml; 48.2–133.6 ng/ml *vs.* 91.8 ng/ml; 38.1–164.5, P = 0.036). We did not find significant difference in YKL-40 levels between the two study groups (71.4 ng/ml; 42.0–206.4 ng/ml in the benign group *vs.* 71.0 ng/ml; 20.4–229.2 ng/ml in the PTC group, P = 0.447). There was no correlation between TIMP1 and CHI3L1 expression and the serum levels of their protein products TIMP-1 and YKL-40 (P = 0.089, P = 0.517, respectively). TIMP1 relative expression showed better diagnostic value compared to CHI3L1 gene (P = 0.037) and to serum TIMP-1 (P = 0.004).
Conclusions
The increased expression of TIMP1 and CHI3L1 implies a possible role of these genes in the PTC carcinogenesis. Their identification in FNAB washouts could be used as additional diagnostic marker.

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AEP667

Molecular landscape of the multiple endocrine neoplasia type 2 syndrome in the Belarusian population

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Background
The multiple endocrine neoplasia syndrome type 2 (MEN-2) is characterized by medullary thyroid cancer (MTC) as a permanent feature; the combination with pheochromocytoma and parathyroidism is referred as MEN-2a syndrome. The reason for hereditary forms of MTC is mutations in the proto-oncogene RET (RE-arranged during Transfection).
The aim of the study was to establish the molecular determinants frequency of MEN-2 syndrome in patients with MTC in the Republic of Belarus.
Materials and methods
The study included 194 patients with MTC diagnosis. The selection was made according to the Cancer Register of the Republic of Belarus and the medical documentation of the Republican Center for Thyroid Tumors. Testing of 5, 8, 10, 11, 13–16 exons of the RET gene was performed by the method of molecular sequencing according to Sanger on the ABI 3500 genetic analyzer.
Results
From 1987 to 2017 years 26930 new cases of thyroid cancer were detected (4899 men and 22 031 women), the share of MTC was 2.2% (591 people). Genetically determined MTC with various clinical manifestations (MEN-2A, MEN-2B, familial MTC) was detected in 18.6% of cases (36/194). Pathogenic mutations were detected in exons 11, 13, and 10 of the RET gene (78%). Analysis of the gene disorders spectrum showed predominance in codon 634 of exon 11 of the gene (C634R\F\W\Y), which is associated with the development of familial MTC or MEN-2A syndrome. Rarer alterations are presented by polymorphisms Y791F, C620GW, L790F, S649L, V804M/L, S904F, R912P, M918T. The pathogenic variants L790F and C611Y were compiled for one case. Pathogenic variants in 634 codons were detected in 27.8% of cases (n = 10). The penetrance of pheochromocytoma was 50.0% (n = 5), the average age was 31.9 years. Among patients with mutations in other codons of the RET proto-oncogene, pheochromocytoma was found in one case (2.7%) in a patient with variant M918T. The penetrance of pheochromocytoma in patients with this pathogenic variant (n = 2) was 50.0%. A genotype–phenotype correlation was found between the presence of pheochromocytoma and mutations in exon 11 of the RET proto-oncogene (P = 0.009).
Conclusions
High frequency of occurrence of hereditary forms of MTC was found in the Republic of Belarus, similar to the spectrum of mutations in the RET proto-oncogene described in the literature, and the presence of a genotype-phenotype correlation in identifying various variants of gene alterations. The presented data are intermediate and will be clarified in the course of further implementation of research work.

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AEP668

Characteristics of medullary thyroid cancer in the Republic of Belarus and prognosis factors

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Background
Medullary thyroid cancer (MTC) is a calcitonin-producing C-cell tumor and accounts about 5% in the structure of thyroid malignancies. There are sporadic and hereditary variant of MTC, which is a mandatory component of endocrine neoplasia syndrome type 2. The aim of the study was to determine the relationship between the aggressiveness of the clinical course of MTC and demographic characteristics.
Materials and methods
The study is carried out of the state program "Oncological Diseases" on the assignment "To develop and implement effective technologies for the diagnostic detection and monitoring of patients with multiple endocrine neoplasia type 2a syndrome." Patient inclusion criteria for the study: morphologically verified diagnosis of MTC, written informed patient's consent, ability to follow instructions throughout the study.
Results
The data obtained from the Belarusian cancer-register during 1987–2017 years. The research included the information about 591 patients with MTC. The MTC incidence index in the Republic of Belarus is constant, makes 0.2 per 100 thousand population. The number of MTC cases increased by 3.6 times, annually increased from 5 to 30 cases. It is explained by the improvement of diagnostics' quality and the of average population's life expectancy. The increase of MTC incidence was observed after the age of 40 with subsequent increase by the age of 60. MTC was more often observed among women (71.1%), than among men (28.9%). The essential difference in incidence among city residents and villagers wasn't revealed in the last decade. It confirms equal opportunities of diagnostics for the both of groups. The distribution of patients by region over the past 10 years has been uniform. There were 45.2 % patients with metastatic form of disease in this research, 44.8 % of them with neck lymph node metastases and 5 % had distant metastases. More common tumors were more often diagnosed in male. As a result of univariate analysis, prognostic factors influencing specific survival were revealed: male sex (P<0.05), extrathyroid tumor

growth (P<0.001), the presence of metastases in regional lymph nodes (P<0.05) and distant metastases (P< 0.001).
Conclusions
The incidence rate of MTC in the Republic of Belarus has increased more than 6 times over the past 30 years (0.03 and 0.2 per 100 000 population). Male sex, extrathyroid tumor growth, the presence of metastases in regional lymph nodes, distant metastases are prognostically unfavorable factors for the specific survival of patients with MTC.

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AEP669

Clinical and laboratory features of patients with medullary thyroid cancer in the Republic of Belarus

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Background
The management of patients with medullary thyroid cancer (MTC) has an important endocrinological aspect, because MTC can be a manifestation of multiple endocrine neoplasia syndrome (MEN), a genetically determined pathology with an autosomal dominant inheritance. MEN-2 syndrome is characterized by of MTC as a permanent feature, the combination with pheochromocytoma and/or adenoma of the parathyroid glands. The aim of the study was to determine the clinical and laboratory characteristics of patients with medullary thyroid cancer in order to form a database of patients with MEN2A.
Materials and methods
The research is carried out of the state program "To develop and implement effective technologies for the diagnostic detection and observation of patients with MEN2A." According to the Belarusian Cancer Register in 1987–2017 years 26930 new cases of thyroid cancer were identified (4899 men and 22 031 women), the share of MTC was 2.2% (591 people). Examination of 79 patients with MTC was carried out. Patients collected and recorded in the form of primary reporting data of anamnesis and general clinical examination.
Results
In 16.5% (13 patients) hyperplasia of regional lymph nodes was detected, a puncture biopsy was performed, and in 5.0% (4 patients) a relapse of the disease was revealed. No data were found for parathyroid hyperplasia. 91.1% (72 patients) underwent ultrasound of internal organs, revealed minor abnormalities. Computed tomography of the chest and internal organs was performed in 39.2% (31 patients). Data for tumor pathology and progression of the disease have not been established, but in 7.6% (6 patients) adrenal formations were revealed, which requires further examination. The TSH level was normal in 46.0% (36 patients). 8.9% (7 patients) simultaneously had two histotypes of cancer: medullary and papillary, so they had to receive a suppressive dose of levothyroxine. TSH was suppressed in 43.0% (34 patients), hypothyroidism was noted in 2.5% (2 patients). 55.7% (44 patients) take calcium and vitamin D supplements. Differences in the content of serum calcium in patients depending on the intake of calcium and vitamin D were not established (2.31 ± 0.04 vs 2.31 ± .03; P>0.05). Transient postoperative and manifest hypoparathyroidism was found in 19.0% (15 patients). In 7.6% (6 patients) calcium levels do not reach the lower limit of normal, which is associated with a lack of adherence to treatment.
Conclusions
Patients with MTC require a multidisciplinary laboratory and instrumental examination due to the possible combined pathology, which, in turn, determines the subsequent therapeutic and surgical treatment of patients.

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AEP670

Primitive thyroid Lymphoma: about two cases

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Introduction
Primary thyroid lymphomas (LTP) are a rare entity, characterized by their histological and clinical heterogeneity. They represent 5% of thyroid tumors and 2% of extra-ganglionic lymphomas. We report two observations of LTP by specifying the epidemiological, diagnostic and therapeutic features.
Observations
Observation 1
70-year-old patient, followed in internal medicine for Sd sec, having undergone a total thyroidectomy in 2004 with diffuse large B-cell anapathic malignant lymphoma (LMNH) on LMNH of MALT associated with a lymphocytic thyroiditis. The patient benefited from 4 chemotherapy sessions (CHOP), with Levothyrox 100 µg/day put on. Complete remission was obtained with a normal cervical ultrasound.
Observation 2
68-year-old patient with no particular history, in particular no thyreopathy, thyroidectomized in 2016 with a histological appearance compatible with a Hodgkin's lymphoma scleronodular form, the immunohistochemical study showed an intense and diffuse positivity of tumor cells to antibodies anti-CD15 and anti-CD30, the patient received 6 courses of chemotherapy (ABVD protocol) and radiotherapy on the tumor bed, the patient currently on Levothyrox 100 µg/day with clinical and radiological monitoring.
Conclusion
Despite its rarity and unusual location, lymphoma of the thyroid gland must be known and taken into account in the differential diagnosis of thyroid tumors. Early diagnosis and management allow favorable treatment results to be obtained.

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AEP671

Case report of multifocal papillary thyroid cancer in thyroglossal duct cyst.

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Papillary thyroid carcinoma is one of the important but rare differential diagnosis of midline neck masses in adults. Other causes include thyroglossal duct cyst (TGDC) which is the commonest, ectopic thyroid gland, lymph node enlargement, and dermoid cyst. We report a rare case of unusual presentation of papillary thyroid cancer in a TGDC.
Case report
A 40-years-old female patient presented with a midline mass in the upper part of the neck. It was neither associated with pain nor dysphagia, or dysphonia. The mass was hard, mobile, non-tender, measuring 1×2 cm. Thyroid function tests were normal. On bedside neck ultrasound, the mass was hypoechoic, heterogenous, hypovascular, measuring 0.7×1.2 cm with irregular margins and multiple microcalcifications. there were two small hypoechoic hypovascular nodules in the right thyroid lobe measuring 0.7×0.6 cm and 0.5×0.5 cm respectively. There was no significant cervical lymphadenopathy. Ultrasound guided FNA from the midline mass and from the thyroid nodules were both positive for papillary thyroid carcinoma (PTC). Thyroglobulin determination in the needle washout from the midline mass was significantly high. Patient underwent total thyroidectomy and level VI lymph node dissection in addition to surgical removal of the TGDC using Sistrunk's procedure. Histopathological assessment confirmed the diagnosis of PTC in the right lobe of the thyroid and in the thyroglossal duct cyst. Five lymph nodes out of eight were PTC metastasis. The diagnosis of a multi-focal PTC in the thyroid gland (2 foci) with extrathyroidal extension to the TGDC and central lymph nodes was made. Following surgery, therapeutic strategy was completed with radioactive I^{131} ablation and suppressive levothyroxine therapy. Radioactive iodine total body scans have revealed no remnant thyroid tissue. Thyroglobulin levels were undetectable 12 months after follow-up.
Discussion
The development of carcinoma in TGDC is very rare but well recognized. It is diagnosed in approximately 0.7% to 1% of thyroglossal duct remnants. Clinical examination of TGDC almost always fails evaluate for potential of malignancy within the cyst. TGDC carcinoma should be suspected if neck U/S revealed any suspicious sonographic features and US-guided-FNA should be done as the next diagnostic approach. In our case, we have decided to complete by a radioactive iodine therapy because of the disease multifocality. In the absence of clear guidance and recommendations, the

management of TGDC carcinoma depends on the clinical situation and the team experience.

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AEP672

Side-effects of calcitonin stimulation tests with calcium gluconate

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Introduction
Over time, different substances and protocols have been used and tested for stimulating calcitonin (CT). Some of them proved to be useful in diagnosing medullary thyroid carcinoma (MTC). However, these are associated with side-effects, with various duration, intensity and severity.
Objective
To report the side-effects observed during CT stimulation test with calcium (Ca) gluconate.
Materials and methods
A dose of 25 mg/kgBW (kilograms per body weight) of Ca gluconate was administered in 3–5 min (adjusted to the patient's ideal weight) after informed consent, with a total of 191 explorations: 124 in women (median age = 47 ± 13.3 years, range: 21–78) and 67 in men (median age = 54 ± 13.8 years, range: 22–79). We further classified the side-effects by severity after Food and Drug Administration (FDA) 21 312.32 Code of Federal Regulations in: Adverse event (AE), Life-threatening adverse event (LTAE) and Serious adverse event (SAE).
Results
21 types of side-effects were recorded, the most frequent being warmth in 175 tests (91.62%), altered taste in 37 tests (19.37%) and bradycardia in 11 tests (5.75%). No gender significant difference was noted regarding the occurrence of side-effects in general, but men were more predisposed to experience cardio-vascular side-effects than women: bradycardia/tachycardia, hypotension/hypertension, angina, atrial/ventricular extrasystoles, asystole, $P<0.02$. Cardio-vascular side-effects were not correlated with values of basal CT (normal/increased) or with peak-values of stimulated CT. Regarding FDA classification of severity, amongst 191 tests: no side-effects were noted in 9 (4.71%), AE in 160 (83.76%), SAE in 22 (11.51%) and LTAE was noted only in 1 test (0.52%). There was no link between patients' age, sex, weight or body-mass-index and severity.
Conclusion
Ca stimulation test is safe, with few mild side-effects. A specific protocol and cautions should be applied to minimize the possibility of a serious cardiac event, the most important being continuous cardiac monitoring during and after the test.

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AEP673

Graves' disease with spontaneous resolution following ocrelizumab in primary progressive multiple sclerosis

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Introduction
Immune reconstitution therapies (IRT), which include antibody-based cell-depleting therapies targeting CD52+ (alemtuzumab) or CD20+ (rituximab, ocrelizumab) leukocytes, are approved for the treatment of multiple sclerosis. Thyroid autoimmunity is a common adverse effect of alemtuzumab treatment, Graves' disease being the most prevalent manifestation. To date, thyroid autoimmunity events have not been reported with CD20 targeting monoclonal antibodies.
Case report
Fifty-nine-year-old woman with primary progressive multiple sclerosis, non-smoker, with no prior personal history of thyroid disease or autoimmunity (confirmed before the IRT initiation). She was started on ocrelizumab in July 2018; 6 months later, immediately prior to her second ocrelizumab administration, her thyroid function tests revealed an overt hyperthyroidism with strong positivity for TRAb, TPOAb and TgAb; she had no signs of ophthalmopathy. Due to the temporal association of Grave's disease (GD) diagnosis with ocrelizumab infusion, absence of symptoms and our experience with alemtuzumab-induced GD, with a frequently unpredictable course and occasional rapid evolution to hypothyroidism, we decided for an active surveillance strategy and antithyroid drugs were not started. On the following 6 months, she underwent spontaneous resolution of hyperthyroidism with TRAb negativity and a mild and transitory period of subclinical hypothyroidism, while she continued the biannually ocrelizumab administration schedule. To present date, she has maintained close clinical and biochemical surveillance with normal TSH, fT4 and fT3 levels and undetectable TRAb.
Discussion
To our knowledge, this is the first case of GD reported after ocrelizumab administration. The timing of diagnosis, onset and course of the reported case is similar to alemtuzumab-induced GD, usually interpreted as an "immune reconstitution syndrome"; however ocrelizumab cell count depletion is inferior in severity, cell population affected and duration of depletion. An older CD20-targeting therapy, rituximab, has been proposed for treatment of Graves ophthalmopathy; however, although it depletes B-cells it does not reduce TRAb levels making unlikely a sporadic GD ethology, incidentally detected and treated by anti-CD20- targeting therapy. This case highlights the importance of pre-screening and follow-up with thyroid function tests in patients treated with ocrelizumab. As a novel therapeutic antibody, further investigation is required to unravel underneath causes of thyroid autoimmunity with ocrelizumab.

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AEP674

A case of thyrotoxic periodic paralysis induced by super-stimulation of na–k–atpase in a competitive bodybuilder with thyrotoxicosis factitia.

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Thyrotoxic periodic paralysis (TPP) is a rare endocrine emergency where early diagnosis of both hypokalaemia and thyrotoxicosis are vital to allow prompt treatment to prevent life-threatening complications and prevent recurrences. We present the first reported case of TPP in which four known stimulants of Na–K–ATPase acted simultaneously to produce profound hypokalaemia. A 32 year-old competitive body-builder took thyroxine supplements & a long-acting β2 agonist, Clenbuterol and followed a strict diet, in preparation for a body-building competition. Following this, he went on an extreme food-binge lasting several hours. Several hours later, he developed bilateral lower limb weakness, which progressed over the next 15 hours. He attended the emergency department 24 hours after the onset of symptoms, with severe bilateral, symmetrical weakness of the lower limbs. He had no family history of thyroid disease or intermittent paralysis. Hypokalaemia of 2.3 mmol/l was found, dropping to 1.9 mmol/l in the presence of primary respiratory alkalosis (pH-7.44, pCO2-5.2). ECG showed features of hypokalaemia, including prolonged QT/QTc-intervals of 520 msec/640 msec, respectively. Hyperinsulinaemia was confirmed (276 pmol/l), with blood glucose of 7.4 mmol/l. TSH was suppressed (<0.02 mIU/l) indicating biochemical thyrotoxicosis, with normal free-T4 (12 pmol/l) and slightly reduced total-T3 (1.02 nmol/l). FSH & LH were both suppressed (<0.5 IU/l), total testosterone was normal (23.7 nmol/l) but oestradiol was elevated (224 pmol/l. Urine was screened using ultra-performance-liquid-chromatography, mass-spectrometry (UPLC-TOF-MS) for over 1300 drugs and metabolites & was positive for Clenbuterol & the anabolic steroids Trenbolone and Oxandrolone. From simultaneous samples we were thus able to document that hyperthyroidism, hyperinsulinaemia, β-agonist activity and alkalosis were all acting in concert in this patient, to stimulate Na–K–ATPase and cause significant hypokalaemia and profound muscle weakness. All four elements were entirely self-induced. Serum potassium normalised within 12-hours with parenteral potassium and fluid replacement, with return of full muscle power and normalisation of the ECG. The patient discontinued his thyroxine supplements and at outpatient review 1 month later, his thyroid-function tests were normal. This case outlines the vital necessity of checking thyroid-function tests & doing full medicines reconciliation in any patient presenting with hypokalemia and muscle weakness. It also highlights the possibility that competitive bodybuilders

may constitute a unique 'at-risk' group for TPP by virtue of the supplements they take, which often include thyroxine and β-agonists.

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AEP675

Multiple endocrine neoplasia type 2a (men 2a) case with bilateral medullary thyroid carcinoma and papillary thyroid carcinoma presentation

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Introduction
MEN 2A is an autosomal dominant disease,a familial syndrome with a mutation at RET proto-oncogene. %25 of medullary thyroid carcinoma (MTC) is a part of MEN 2A. Herein, we presented a patient with MEN 2A who was found to be heterozygos for RET mutation cause of the association of MTC and papillary thyroid carcinoma (PTC) is very rare.
Case
63 year old patient was admitted to the endocrinology clinic after total thyroidectomy as the thyroid tissue contains both MTC and PTC focuses in each thyroid lobe. As there was family history of MEN syndrome, the patient was evaluated for MEN syndrome. Abdominal MRI revealed a mass in the left adrenal, 28×23 mm in size, showing heterogeneous signal loss in the external phase sequence,and heterogeneously enhanced pheochromocytoma in the arterial phase. The dopamin level in the 24 hour urine collection measured at two different occasions were 442.91 and 536.98 µg/day (65–400) respectively. The level of calcium,phosphorus and parathyroid hormone (PTH) were normal. On postop neck USG, an appearance compatible with residual throid tissue with dimensions of 22×15 mm in the localization of the left throid gland was detected. Calcitonin level was 33.6 pg/ml (<8.4). Thyroglobulin level was <0.1 mcg/l (1.15–50.03), anti-thyroglobulin level was < 0.9 IU/ml (0–4). One alelle (heterozygous) had c.23706>T(*P*.L790F) due to RET mutation. With these results,the patient was evaluated as MEN 2A. Left adrenalectomy and reoperation of residual thyroid tissue were recommended. Patient wanted to go another center for surgery.
Conclusion
The other components of MEN 2A should be investigated for all patients diagnosed with MTC. Family screening, serum calcitonin level, neck USG, existence of RET mutation and biochemical panel for pheochromocytoma should be investigated. Coexistence of MTC and PTC is very rare. There is no sufficient data to prove this association. However, it is assumed that the RET proto-oncogene would lead to the thyroid kinase activation.

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AEP676

Rare association of two primary carcinomas: papillary and pulmonary thyroid, due to a BRAF mutation

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Introduction
The coexistence of pulmonary adenocarcinoma and papillary carcinoma of the thyroid is a rare event. The relationship between these two cancers is still unclear; Far from being a coincidence, it's most often attributed to a genetic mutation (of which that of BRAF's the most common). The management must focus on the most aggressive carcinoma. In this case, it's pulmonary adenocarcinoma since the latter carcinoma is known for its indolent evolution and a better prognosis than the first.
Observation
A 45-year-old patient, with a family history of malignant thyroid neoplasia, underwent total thyroidectomy with central and lateral lymph node dissection for a thyroid nodule initially classified as Tirads 5. The histopathological examination was in favor of invasive papillary carcinoma of 3 cm, with the presence of vascular embolism, classified pt3bN1Mx. Radioiodine ablation therapy was performed. The postoperative evaluation objectives a dry cough that has been around for more than 3 months with a deterioration of the general condition; a chest X-ray supplemented by a CT scan revealed a pulmonary masse of 7 cm localized at the left lower lobe, scintigraphy was performed, and showed an absence of uptake by the pulmonary tumor. An echoguided biopsy of the mass showed pulmonary adenocarcinoma. Faced with the coexistence of these 2 primary tumors, we suspected a BRAF mutation that we confirmed its presence by the genetic study, and we completed the screening of other possible cancers. the CA 19 9 returned x5 the normal limit, the somatic examination found a naveus of 3 cm without malignancy signs. Our patient underwent a left lobectomy.
Discussion
BRAF represents one of the most frequently mutated protein kinase genes in human tumors. BRAF mutation can be observed in melanoma, papillary thyroid carcinoma, colorectal carcinoma, leukemia… In these cancers, various genetic aberrations of the BRAF proto-oncogene, such as different point mutations and chromosomal arrangements, have been reported. The most common mutation is BRAF V600E which can be detected by DNA sequencing and immunohistochemistry on fixed formalin, paraffin-embedded tumor tissue.
Conclusion
BRAF is one of the most frequently mutated protein kinases in cancer. Data to date support a role for BRAF as a driver of mutation that influences phenotype in different ways and indicates that it's an important therapeutic target for patients with cancer.

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AEP677

Importance in monitoring and treatment of thyroid cancer with new third-generation thyroglobulin assays

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Introduction
Up by 30% of patients have recurrence in the first years after treatment of differentiated thyroid cancer (DTC) so it is necessary to have highly sensitive assays that allow adequate long-term follow-up. Nowadays, the measurement of serum thyroglobulin (Tg) is used as a tumor marker to monitoring DTC and must be determined along with levels of antithyroglobulin antibodies, since they can interfere in Tg immunoassays. Therefore, it is recommended to determine both using the same method and equipment.
Objective
The aim of this study was to evaluate the interchangeability between the Tg-ultrasensitive results using two types of immunoassays.
Materials and methods
Parallel determination of serum Tg concentration in 80 samples of patients with thyroid pathology, using the analyzers Modular E-170® (electrochemiluminescence; Roche-Diagnostics) and Architect i4000SR® (chemiluminescent-microparticle-CMIA; Abbott-Diagnostics). The statistical analysis has been developed with the Method-Validator software (v1.19), following the recommendations of the Spanish Society of Laboratory Medicine (SEQCML) for comparison of measurement procedures, performing the analysis of the agreement by Bland-Altman plot and regression by the methods of Deming and Passing-Bablok.
Results

Pearson's correlation coefficient (r): 0.999			
Method agreement analysis			
Bland-Altman	Confidence Interval (CI) 95%	–0.288 a 0.508	
	Dm	0.11	
Regression Analysis		CI 95%	Mean
Deming	Slope	0.976 a 1.02	0.998
	Ordinate	–0.092 a 0.355	0.131
Passing-Bablok	Slope	1.057 a 1.15	1.109
	Ordinate	0.00 a 0.01	0.007

Conclusions
By the data obtained, both methods would be interchangeable according to Bland–Altman analysis (the value 0 is included within CI) and Deming's method (value 0 for the ordinate at the origin and the value 1 for the slope are within their respective CI). As well as the regression analysis can be performed ($r \geq 0.975$). However, Passing-Bablok method indicated the presence of a systematic proportional difference since the value 1 is not within the CI for the slope, although it is very close. This type of error could be due to the fact that both assays have different methodology in their immunoassays and could be associated with the presence of different interferences described in the literature (Streptavidin/Biotin technology), thus the patients should always be tested with the same highly sensitive assay. It would be necessary to increase the number of samples in order to cover the dynamic range of both techniques. Although this minimal difference has no clinical relevance, it is a priority to guarantee highly accurate results at the detection limit, in order to detect tumor recurrence and/or persistence early.

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AEP678

COVID-19: a new trigger of subacute thyroiditis in pregnant women?

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Introduction
Recently, there has been an increasing number of reports about subacute thyroiditis (SAT) developing after COVID-19. SAT and transient gestational thyrotoxicosis constitute the majority of emerging thyrotoxicosis during pregnancy.
Case report
A 27-year-old, 34-week pregnant women complained of pain in a very small area on the anterior side of her neck and fatigue. Thyroid function tests performed four months ago were found to be in the normal range. A nasopharyngeal swab test for SARS-CoV-2 was negative but both IgM and IgG against SARS-CoV-2 were positive. On physical examination of the patient, there was no symptoms other than pain in the neck, and bilateral thyroid gland was large with tenderness. Thyroid function was assessed, showing suppressed TSH (0.1 mIU/ml, normal range 0.27–4.2), normal free thyroxine (fT4 – 1.6 ng/dl, normal range 0.93–1.7), and elevated free triiodothyronine (fT3 – 4.96 pg/ml, normal range 2.0–4.4), anti-thyroid peroxidase (anti-TPO) were negative (12.24 IU/ml, normal range <34.0), thyroid receptor antibody (TRAb) and thyroglobulin antibodies (anti-TG) were also positive (TRAb –5.78 IU/ml, normal range <1.75, anti-TG – 200 IU/ml, normal range < 138). C-reactive protein (CRP) were increased (10.49 mg/l, normal range <10.0), and D-dimer were normal (310 ngFEO/ml, normal range < 800.0). In the blood sample were increased white blood cells (WBC) – $9.8 * 10^9$ (normal range 4.0–9.0), red blood cells (RBC)- $4.95 * 10^{12}$ (normal range 3.7–4.7), erythrocyte sedimentation rate (ESR)- 46 mm/h (normal range <20.0). In the thyroid gland ultrasound both lobes were large and parenchymal blood flow was not increased. There was a distinct view of SAT. Paracetamol (daily dose – 1500 mg) was started because of the thyroid's pain. The subject's pain was significantly decreased 5 days later. Clinical and laboratory findings in pregnant woman was compatible with SAT. During 2 weeks pain and tenderness in the thyroid lodge was completely relieved. After repeated laboratory tests were normal levels and patient didn't experience any problem during pregnancy and when she was 38 weeks pregnant delivered a healthy girl who weighs 3560 g.
Conclusion
This case report demonstrates a new trigger of subacute thyroiditis in pregnant women due to COVID-19. When determining the differential diagnosis of gestational thyrotoxicosis, subacute thyroiditis should also be considered and detailed history and physical examination of the thyroid gland should not be neglected during pregnancy.

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AEP679

Subacute thyroiditis cases increasing in pandemic: 2 cases of covid-19 associated subacute thyroiditis

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Objective
Subacute thyroiditis (SAT) was first described by Fritz De Quervain in 1904 and is generally a self-limiting disease causing pain, fever and temporary hyperthyroidism. It generally develops as a result of postviral inflammatory response following viral upper respiratory tract infections, and it has increased since the covid-19 pandemic in March 2020. We aim to present 2 SAT cases associated with COVID-19.
Case Summary
We present 2 SAT patients associated with COVID-19 who are health workers.
Case-1
A 54-years old female patient was admitted to hospital with sore throat and fever in July 2020. Laboratory values were TSH:0.08 uIU/ml (low), freeT4:1.21 ng/dl (in normal range), freeT3:3.4 pg/ml (in normal range) and erythrocyte sedimentation rate (ESR):41 mm/h, c-reactive protein (CRP):5.76 mg/l.
Case-2
A 52-years old female patient was admitted to hospital with sore throat, fever and fatigue in August 2020. She was euthyroid but ESR:85 mm/h and CRP:74.81 mg/l. For both cases, there is no history of trauma, contrast agent exposure and infection in another part of the body. They did not have any comorbidities. Thyroid autoantibody levels were negative and ESR and CRP levels were very high. Ultrasonographic evaluation revealed decreased echogenicity and focal thyroiditis, no nodule was detected. Both of the patients stated that they had a mild upper respiratory tract infection a few months ago but didn't have a PCR test because they didn't have severe symptoms but laboratory values measured for COVID-19 antibodies were very high. Both of them didn't benefit from the nonsteroid antiinflammatory drugs, but improved with methylprednisolon. After 8 weeks, patients recovered without any symptom.
Conclusions
The COVID-19 pandemic was declared by the WHO in March 2020, thus healthcare professionals focused on COVID-19 patients who presents with respiratory symptoms, but over time, the multisystem effects began to be noticed. As clinicians, it was noticed that the number of patients with SAT increased during the pandemic period. Just few studies and case reports are known. In some patients genetic disposition such as HLA-B35 is recorded. Severe SAT can be observed even after asymptomatic COVID-19 disease as in our cases. Although these sypmtoms can be confused with COVID-19, it should be kept in mind that they may be associated with postcovid SAT.
Key Words
Subacute thyroiditis, COVID-19, Viral infection

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AEP680

Benign and malignant thyroid pathology in Albanians living in the Genoa district, Italy: a comparison with data from the Tirana district, Albania

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Background
In Liguria, a region of north-western Italy, the Albanian population is currently estimated to be around 20 000, constituting 15% of foreign citizens living in this area; approximately 50% of these Albanians reside in the Genoa district.
Methods
We retrospectively reviewed the medical records of all the outpatients of the Endocrine Unit of San Martino Polyclinic Hospital from 2002 to 2019. Data on subjects born in Albania and now living in the Genoa district were extracted and compared with that reported in a database registered in the same period in the district of Tirana, Albania. The International Classification of Diseases – 9th revision – Clinical Modification (ICDM-9) was used for diagnosis classification. The management of differentiated thyroid cancer (DTC) was also evaluated. The 8th edition of the AJCC was used for DTC staging.
Results
We identified 48 Albanian patients affected by benign thyroid pathology. Our data were compared with those recorded in 2915 people living in the Tirana district. Similar F/M ratios were found in both districts (Genoa: 5:1 and Tirana: 4:1). Excluding cases of congenital hypothyroidism, the median age at the time of first examination was the same (41 years). No statistically

significant differences in the incidence of simple and unspecified goitre, thyrotoxicosis with or without goitre, or other thyroid disorders were found between the Genoa and Tirana districts. Non-toxic nodular goitres were less frequently diagnosed in Genoa (29%) than in Tirana (64%, $P<0.0001$), while acquired hypothyroidism and thyroiditis were more often recorded in Genoa (29% and 19%, respectively) than in Tirana (3%, $P<0.0001$; 4% $P = 0.0003$). From 2002 to 2019, 401 DTC patients were followed up at our centre; 8% were not Italian and 19% of non-Italians were Albanian ($n = 6$; stage 1–2). The median age of the Albanians on diagnosis (59 years) was similar to that of the Italians (53 years). Structural disease was observed in 2 Albanian DTC patients, in whom initial surgery had been performed in Tirana and further treatments were needed in Italy. The rate of loss to follow-up was similar in Albanian subjects (19%) and in other patients (10%) of the DTC cohort. At present, all DTC Albanians in the Genoa district are alive.

Conclusion

A difference in nutritional iodine load and in facilities for laboratory evaluations could explain the significant differences observed in some ICDM-9 between Albanians living in Genoa and those living in Tirana. The diagnosis and surgical treatment of thyroid malignancy probably needs to be improved in Albania.

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AEP681

Thyroid function in adults with Prader-Willi syndrome.

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Introduction

Prader-Willi syndrome (PWS) is a complex genetic syndrome in which hypothalamic dysfunction leads to hyperphagia and pituitary hormone deficiencies (PHD), among others. The majority of patients have intellectual disability (ID) and use of psychotropic drugs is frequent. Due to hypotonia and the low muscle mass associated with the syndrome, adults with PWS have a low basal metabolic rate (BMR). Combined with hyperphagia, this results in high risk of obesity. Therefore, exercise is extremely important. However, PHD like hypothyroidism can cause fatigue and exercise intolerance. If left untreated, hypothyroidism can lead to a further decrease in BMR, an increase in Body Mass Index (BMI) and increased cardiovascular risk. As mortality in PWS is high (3% yearly) and often related to cardiovascular problems and obesity, it is important to optimize thyroid function and other factors affecting BMR.

Objectives

To investigate the prevalence of hypothyroidism in adults with PWS and to provide practical screening recommendations.

Methods

In 122 adults with PWS (median age 29 y [IQR 21–39], median BMI 29 kg/m^2 [IQR 26–36]), we measured TSH, free T4 and T3 and searched the medical history for use of medication and any pre-existing diagnosis of hypothyroidism. Moreover, we performed an extensive literature search and summarized the current literature on hypothyroidism, T3 and T4 levels in adults with PWS.

Results

Hypothyroidism was present in 17% and more prevalent in females (23%) than in males (10%), even though this difference was not statistically significant ($P = 0.06$). Although within the reference range, serum T3 levels (reference range: 1.3–2.3 nmol/l) were relatively high compared to free T4 levels (reference range: 13.5–24.3 pmol/l). T3 levels were significantly lower in patients that used psychotropic medication ($n = 45$) than in patients that did not (median 1.7 [IQR 1.5–2.0] vs 2.1 [IQR 1.7–2.3], $P = 0.013$).

Conclusion

We found a prevalence of hypothyroidism of 17% in PWS-adults (compared to 3% in the non-PWS population). Levels of the active thyroid hormone T3 were significantly lower in patients using psychotropic medication. Based on our findings, we recommend 1) yearly screening of thyroid hormone levels in adults with PWS to avoid negative effects of untreated hypothyroidism on BMR, BMI and cardiovascular risk and 2) extra monitoring of the active thyroid hormone T3 in patients using psychotropic drugs.

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AEP682

Relationship between vitamin D status and metabolic parameters in premenopausal women with autoimmune hypothyroidism

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Background

Vitamin D deficiency is a global health problem. Nowadays is intensively studied the influence of vitamin D on the course of autoimmune diseases of the thyroid gland.

Objective

To study the relationship between vitamin D status and metabolic parameters in premenopausal women with autoimmune hypothyroidism.

Methods

146 premenopausal women with autoimmune hypothyroidism were examined. The mean age of patients was 46.8 ± 0.73 years. All women underwent anthropometric, general clinical, biochemical examinations, including determination of lipid and hydrocarbon metabolism, assessment of the functional state of the thyroid gland: TSH level, free thyroxine (FT4), free triiodothyronine (FT3), thyroid antibodies (TPOAb, TGAb). The collected data were statisstically analyzed using the Statistica 12 ($p<0.05$).

Results

The average level of TSH was 4.40 ± 0.21 uIU/ml; fT3 –1.97 ± 0.09 pmol/l; fT4 – 12.96 ± 0.37 pmol/l; TPOAb –112.87 ± 5.61 IU/ml; TGAb –152.25 ± 5.04 IU/ml, $p<0.05$. The mean level of 25 (OH) D in women with hypothyroidism was 16.42 ± 0.57 ng/ml, which corresponds to vitamin D deficiency (<20 ng/ml). Vitamin D deficiency was found in 78.8%, insufficiency in 17.1% of premenopausal women with hypothyroidism. There was a significantly strong ($P<0.05$) negative correlation between 25 (OH) D and TPOAb ($r = –0.77$), TSH ($r = –0.72$), TGAb ($r = –0.33$). Positive correlations of medium strength were found between 25 (OH) D and the level of fT3 ($r = 0.46$) and fT4 ($r = 0.44$), $P<0.05$. The body mass index averaged 29.4 ± 0.29 kg/m^2. The mean level of glucose 5.49 ± 0.06 mmol/l, basal insulin level 28.63 ± 0.88 mIU/l, HOMA-IR 3.31 ± 0.08 ($p<0.01$). Hypercholesterolemia averaged 6.1 ± 0.12 mmol/l, cholesterol LDL 3.72 ± 0.07 mmol/l, cholesterol HDL 1.37 ± 0.02 mmol/l, TG 3.73 ± 0.09 mmol/l, atherogenic coefficient (AC) >3 was observed in 64%, $P<0.01$. Analysis of the relationships of metabolic parameters showed a significantly strong ($P<0.05$) negative correlation between 25 (OH) D with BMI ($r = –0.74$), AC ($r = –0.65$), the level of cholesterol HDL ($r = -0.72$), cholesterol LDL ($r = –0.58$), TG ($r = –0.46$), HOMA resistance index ($r = –0.57$).

Conclusion

Low vitamin D status is significantly associated with autoimmune thyroid dysfunction and determines the degree of metabolic disorders and cardiovascular risk in premenopausal women with autoimmune hypothyroidism.

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AEP683

ABSTRACT WITHDRAWN

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AEP684

Prevalence of thyroid dysfunction in untreated chronic hepatitis C

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In Ukraine, in 2017, an estimated 53000 people were living with chronic hepatitis C virus (HCV) infection, and its prevalence rate was 123.7 patients per 100000 citizens. Symptoms of at least one extra hepatic manifestations appear in more than 50% of HCV-positive patients, and thyroid abnormalities are rather common. The purpose of the study was to determine the prevalence of thyroid function tests and anti-thyroid autoantibodies abnormalities in the untreated patients with chronic HCV infection. This retrospective study included 58 HCV (RNA+) patients, 18 males (31.0%) and 40 females (69.0%), and 23 apparently healthy controls. The mean age of patients was 40.4 ± 5.9 years. Routine clinical assessment and tests, and thyroid gland sonography were performed at the baseline. Thyroid function tests, including serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), free

triiodothyronine (FT3), and antibodies to thyroid peroxidase (TPO) were performed by an ultrasensitive immune chemiluminescent noncompetitive assay. Ultrasound thyroid abnormalities included heterogenous parenchyma in 14 (24.1%) and grade 1 goiter in 16 (27.6%) cases. TPO were three times higher in HCV patients, 26.06 ± 1.23 IU/ml as compared to 8.69 ± 0.87 IU/ml in control. The mean TSH levels were significantly higher in HCV patients versus control, 3.78 ± 0.41 uIU/ml and 2.08 ± 0.54 uIU/ml respectively. FT4 and FT3 levels were not changed significantly. Mean FT4 concentration in HCV patients versus control was 1.18 ± 0.05 and 1.25 ± 0.08 ng/dl, and mean FT3 level – 4.95 ± 0.51 and 5.28 ± 0.47 pmol/l respectively. Increasing of TPO levels over upper normal limit was found in 15 (25.9%) cases, 11 (27.5%) females and 4 (22.2%) males. In 5 (12.5%) females observed clinically significant TSH rising. In 4 (10.0%) of them increased TSH was accompanied by high TPO and specific ultrasound abnormalities, thus autoimmune thyroiditis with hypothyroidism was diagnosed. In 1(2.5%) female patient subclinical hypothyroidism was diagnosed due to isolated TSH increasing in the subclinical range of hypothyroidism, and absence of clinical signs. Therefore, increasing of TPO levels was detected in more than 25%, and hypothyroidism was diagnosed in 12.5% untreated patients with HCV infection; HCV-associated thyroid dysfunction was specific for females.

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AEP685

Iodized salt is sufficient to obtain an adequate nutritional status of iodine in pregnant woman

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Introduction
Iodine is an essential micronutrient used by the thyroid gland to produce thyroid hormones. Iodine deficiency during pregnancy is related to impaired neurocognitive development of fetus and neonate. The WHO recommends iodization of salt as main measure to prevent iodine deficiency disorders. In pregnant population other international organizations recommend the use of iodine supplements to guarantee adequate nutritional status of iodine (median urinary iodine concentration [UIC] ≥ 150 µg/l). The objectives of the study are to know nutritional status of iodine in our pregnant women and its relationship with iodine intake.
Materials and methods
Descriptive and analytical observational study carried out in 2017 in 318 women in the first trimester of pregnancy at Hospital Universitario Central de Asturias, Spain. Pregnant women with diagnosis of thyroid disease before pregnancy or multiple gestations were excluded. Information on dietary habits was collected by midwives in the primary care centers. The questionnarie contained items related to consumption of iodized salt, dairy products and iodine supplements. UIC was determinated in a first morning urine sample. The statistical analysis was performed using the R program (R Development Core Team), version 3.6.0, applying the Chi-square and Student's T statistical tests.
Results
Mean age of pregnant women was 34.10 ± 5.45 years, with a mean gestation age of 7.19 ± 2 weeks.
Results of the iodine intake questionnaire were as follows
– Consumption of iodized salt: 51.10%
– Consumption of dairy products (≥ 2 servings day): 48.9%
– Use of iodine supplement: 87.08%
Median UIC (Q1–Q3) was 171.5 µg/l (116–265 µg/l). 60.4% of pregnant women had ioduria greater ≥150 µg/l.

	UIC ≥150 µg/l	UIC < 150 µg/l	*P*	Median UIC (Q1–Q3) µg/l	*P*
Iodized salt					
No	55 (48.7%)	58 (51.33%)	0.001	147 (102–206)	0.016
Yes	97 (69.3%)	43 (30.7%)		191.5 (131.5–285)	
Dairy products					
<2 servings/day	78 (56.1%)	61 (43.9%)	0.269	168 (96–258)	0.48
≥ 2 servings/day	84 (62.7%)	50 (37.3%)		172 (122.25–255.75)	
Iodine supplement					
No	21 (53.9%)	18 (46.1%)	0.455	158.5 (113–199.5)	0.027
Yes	157 (60.1%)	104 (39.9%)		172.5 (116–285.75)	

Conclusions
Our pregnant population presents an adequate nutritional status of iodine. In our sample, the intake of iodized salt was sufficient to obtain an adequate UIC, being the main measure to achieve it. The use of iodine supplements increases UIC but has no protective effect against UIC <150 µg/l. We agree with the WHO recommendation on the use of iodized salt in pregnant women.

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AEP686

Comparison of body composition and insulin sensitivity changes in patients with Graves disease after radioiodine or antithyroid drugs treatment

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Thyroid hormones (TH) are key regulators of basal metabolic rate and body weight. They increase resting energy expenditure by increased synthesis of uncoupling protein-1 (UCP-1) in brown adipocytes which stimulates energy dissipation as a heat. TH also increase appetite by central adrenergic stimulation. Body weight change is a key symptom of thyroid dysfunction especially the weight gain observed in patients treated for hyperthyroidism
AIM: To compare the influence of different methods of Graves disease treatment on body composition and insulin sensitivity.
Methods
Pairwise comparison of 50 patients with Graves disease treated with radioiodine or antithyroid drugs (ATDs) in hyperthyroid state and three months after euthyroidism was established. Body composition changes were determined with dual energy X-ray absorptiometry (DXA). Glucose and insulin serum concentration were measured and QUICKI index calculated. Body composition analysis was performed separately in women ($n = 43$) and men ($n = 7$).
Results
Independently of treatment method there was significant increase in body fat (BF) and lean tissue mass (LTM), with BF rise dominating in men whereas LTM increase being more pronounced in women. BF increased by 2.43 (0.58;3.0) kg in women and 4.18 (0.25; 8.09) kg in men, whereas LTM increased by 3.84 (1.75 ; 4.35) kg in women and 0.77 (0.2–6.10) kg in men. There was no difference in BF, trunk body fat, legs body fat and LTM in women treated with radioiodine ($n = 33$) as compared to ATDs treated women ($n = 10$) (2.57 vs 1.3 kg, $P = 0.711$; 1.37 vs 0.88 kg, $P = 0.702$; 0.68 vs 0.72 kg, $P = 0.596$; 3.68 kg vs 2.13 kg, $P = 0.910$ respectively) and in a small sample of men ($n = 7$). In radioiodine treated group insulin sensitivity improvement was observed. There was decrease in serum insulin and glucose levels {7.40 (5.28; 9.55) vs 5.05 (3.70; 6.4) uIU\ml, $P = 0.018$; 95.18 (91.77; 101.32) vs 92.06 (87.89; 96.47) mg%/ $P = 0.023$ respectively} and increase in QUICKI index (0.36 ± 0.04 vs 0.38 ± 0.04 ; $P = 0.014$). Insulin decrease was greater in radioiodine treated as compared to ATDs treated patients {−2.35 (−3.85; 0.35) vs 0.12 (−1.89; 2.14) uIU\ml, $P = 0.056$} however glucose, QUICKI and HOMA didn't differ significantly between groups.
Conclusions
There was no difference in BF and LTM changes between radioiodine and ATDs treated patients. In women body weight increase was predominately caused by LTM rise. Despite of body weight gain there was improvement of insulin sensitivity after radioiodine treatment.

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AEP687

Interconnection between obesity, thyroid function, insulin resistance, and cardiovascular risk factors in patients with subclinical hypothyroidism

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Background and aim
The epidemic of overweight and obesity presents a major challenge to chronic disease prevention and health across the life course around the world. The putative relationships between thyroid hormones, body weight, and adipose

tissue homeostasis have been the focus of several studies in recent years, but the causal relationships between these parameters have not been well established. Aim of the study: to investigate the relationship between serum *thyroid stimulating hormone* (TSH), insulin resistance (IR), and cardiovascular risk factors in a sample of obese persons with subclinical hypothyroidism.
Materials and methods
A retrospective, longitudinal analysis of 145 obese persons was performed. The TSH and free thyroxine (fT_4) levels, anthropometric measurements, and laboratory test results were analyzed. Euthyroid patients were also divided into two groups according to TSH levels. There has been some discussion about lowering the upper value of TSH to 2.5 µIU/ml. This discussion is based in some data that indicated that patients with TSH $\geq$ 2.5 may have different profiles than those with TSH < 2.5 µIU/ml
Results
35 individuals presented with TSH levels above the normal level (subclinical hypothyroidism). Their waist circumference (WC) was significantly higher than those of euthyroid individuals. Serum TSH was positively correlated with the homeostasis model assessment of insulin resistance (HOMA-IR) index, triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C). Using TSH and BMI as independent variables, TSH levels were shown to be independently related to HOMA-IR (P = 0.002) and triglycerides (P = 0.006). Among euthyroid subjects, individuals with TSH values <2.5 mIU/ml exhibited statistically significant decreases in waist-to-hip ratio, HDL-C levels, and HOMA-IR scores and a tendency toward lower WC values.
Conclusion
Subclinical hypothyroidism in overweight and obese persons appears to be associated with excess weight, especially visceral weight. In the present sample of obese persons, TSH levels appear to be associated with insulin resistance.
Keywords
subclinical hypothyroidism, obesity, cardiovascular risk factors.
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AEP688

Acoustic radiation force impulse elastography findings of achilles tendon in patients with hypothyroidism

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Introduction
There are very limited number of clinical studies and data on the effect of thyroid dysfunction in hypothyroidism on connective tissue. Tendinitis can be the first complaint in hypothyroidism and symptomatic relief can be provided with the appropriate treatment of primary thyroid deficiency. There are studies, showed softening in Achilles tendon with age, in patients with intermittent claudication, diabetes patients, and chronic kidney failure patients. To our knowledge, there are no studies in the literature on ARFI elastography findings of the Achilles tendon in hypothyroidism patients. The aim of our study was to investigate the effect of thyroid dysfunction on tendons and the contribution of Acoustic Radiation Force Impulse (ARFI) elastography to the diagnosis of tendinopathy.
Methods
Eighty Achilles tendons of 40 patients under levothyroxine treatment, who had previously known hypothyroidism but high serum TSH levels, and 80 Achilles tendons of 40 healthy individuals were evaluated with ARFI (Virtual Touch Quantification®). 19 of 40 of the patients with hypotiroidism' Achilles tendons were re-evaluated after thyroid stimulating hormone levels reached to normal limits following the adjustments in thyroid hormone replacement therapy. The middle portion of the each Achilles tendon was chosen for the examination. Every examination consisted of three to five independent measurements (shear wave velocity – meters per second). The mean shear wave velocity value was calculated for each tendon, and used for statistical analysis.
Results
The stiffness values of both left and right Achilles tendons, represented as shear wave velocity, were similar in patients with hypothyroidism and control group (Right achilles 5.07 ± 1.14 vs 5.36 ± 1.11, P = 0.245; left achilles 5.09 ± 1.16 vs 5.21 ± 1.11; P = 0.662). There was no significant difference between the Achilles tendon shear wave velocity measurements of 19 of 40 hypothyroidism patients who were re-evaluated after the adjustments in thyroid hormone replacement therapy (right achilles 5.14 ± 1.45 vs 4.7 ± 1.37, P = 0.269; left achilles 5.34 ± 1.36 vs 4.7 ± 1.17, P = 0.097)
Conclusions
The lack of significant difference in Achilles tendon stiffness between non-naive hypothyroid patients and the control group may be explained as a positive clinical effect of thyroid hormone replacement therapy. This study is important in terms of being a pilot study on a subject that can be considered new for the literature. Further prospective studies with larger sample size, which also include naive hypothyroidism patients, are needed to identify the causal relationship between the sonoeleastographic changes in Achilles tendon and hypothyroidism.
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AEP689

The SARS-CoV-2 infection and thyroid disorders: review on the literature

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Introduction
Coronavirus disease (COVID-19) caused by SARS-CoV-2 infection, resulted in serious respiratory and other systemic complications, has spread worldwide since December 2019. In patients with the infection, many organ systems can be involved with potentially fatal results due to robust and disorganized systematic immune activation.
The state of the art
Since the outbreak of the SARS-CoV-2 pandemic, many reports of autoimmune diseases related to COVID-19, have been revealed. Regarding thyroid disease, the occurrence of Graves' disease, Hashimoto's and postpartum thyroiditis after the viral infection, has been reported. SARS-CoV-2 could act as a trigger of latent or new-onset autoimmunity. Moreover, the molecular mimicry of the viral and thyroid epitope relating to the presentation on HLA molecule, might be a possible mechanism for post-COVID-19 subacute thyroiditis. It has been indicated that antibodies against SARS-CoV-2 spike protein strongly react with thyroid peroxidase and may play also a role in initiating the autoimmune responses. Induction of inappropriate apoptotic reactions seems to be other common features of the virus-induced disease processes. What is more, it has been proven that thyroid gland shows higher expression of the angiotensin-converting enzyme 2 (ACE 2) cell receptors (the main receptors for SARS-CoV-2 acting) compared with the lungs. Thus, the direct cell damage in the thyroid gland may occur and the possibility of thyroiditis may arise. However, during the SARS-CoV 2002 outbreak, the absence of SARS-CoV per se in the damaged thyrocytes in autopsy patients' material, was strongly indicative of exaggerated innate and adaptive immune responses to COVID-19 (cytokine storm), as a main mechanism leading to damage of tissues and destructive thyroiditis. On the other hand, thyroid hormone abnormalities seem to be associated with an enhanced risk of severe SARS-CoV-2 infection. Thyroid hormones are important in the regulation of innate immune response so their excess or deficiency may lead to its dysregulation. What is more, increased levels of proinflammatory cytokines such as TNF-ńand IL-6, were observed in patients with thyroid diseases as well as in ones with severe COVID-19. Moreover, some patients with subacute thyroiditis use corticosteroids – the drugs which have been proven to be associated with higher mortality in COVID-19 patients.
Conclusions
SARS-CoV-2 infection may be associated with the development of thyroid diseases. The several mechanisms have been proposed of thyroid organ damage from the immune overreaction to direct cellular destruction with apoptosis. The presence of thyroid dysfunction may lead to deterioration of the course of COVID-19.
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AEP690

LOW calcium level and thyroid diseases

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Background
The thyroid gland helps regulate the calcium levels in the body. It produces the hormone calcitonin that works by decreasing the available amount calcium in the bloodstream. When the thyroid gland is disrupted, calcium

concentrations in the body can be affected as well. It is important that those with thyroid disorders be treated to prevent the effects of hipocalcemia.
Aim
The objective of this study were the measure the serum calcium level in patients with thyroid diseases.
Material and methods
The study includes 110 persons who came to our outpatient service for thyroid diseases from September 2020 to December 2020. Among them 85.4% were female and 14.6% were male. Was measured total calcium level, TSH, freeT4, freeT3, and ultrasound thyroid, total bilirubin, ALT, AST, total protein. The level of calcium was measured with the photometer method. Normal range of calcium 8.5-10.5 mg/dl.
Results
According to thyroid function in 62.7% were determined euthyroid goiter (TSH 1.77 mIU/l), in 12% hyperthyroidism (TSH 0.1 mIU/l), in 9% Hashimoto's thyroiditis (TSH 10 mIU/l and high levels of antithyroid antibodies) and 16.3% normale people. Low calcium levels were found in 12 patient with euthyroid goiter, the average value of calcium was **7.9 + 0.35** s.d.,(min = 7.1 mg/dl,max = 8.4 mg/dl), in 6 patient whith hyperthyroidism, the average value was **8.1 + 0.33** s.d.,(min = 7.4 mg/dl,max = 8.4 mg/dl), in 4 normale people, the average value was **8.22 + 0.14** s.d.,(min = 8.0 mg/dl,max = 8.4 mg/dl),in 1 patient with Hashimito's thyroiditis. The average level of calcium it was not comparable between the groups. Lower calcium levels than the norm was more in individuals with euthyroid goiter than in hyperthyroidism, and normale people. There were no significant differences in blood total bilirubin, ALT,AST and total protein.
Conclusion
There was low calcium levels in patient with thyroid diseases when compared to normale people. The number of people with low calcium level was twice high in euthyroid goiter compared to hyperthyroidism, three times higher compared to normale people.
Keywords
Total calcium level, euthyroid goiter, hyperthyroidism, Hashimoto's thyroiditis.

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AEP691

Hypocalcemia post total thyroidectomy : incidence and management
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Goals
The most common complication of thyroidectomy is hypocalcaemia. The aim of this work is to determine the epidemiological, ethiopathogenic and therapeutic characteristics of hypocalcemia after total thyroidectomy.
Material and methods
This is a retrospective study of 27 cases of patients operated on for a total thyroidectomy complicated by hypocalcemia, over a period of 9 years (2009–2017) collected by ENT Farhat Hached Sousse.
Results
27 of 320 patients operated on for total thyroidectomy presented with postoperative hypocalcaemia (8%). The average age was 40.5 years [17–78 years], with a clear predominance of women (92.6%). Systematic preoperative serum calcium was correct in all cases. Calcium assay was systematic on D3 postoperatively. Hypocalcaemia was asymptomatic in 48% of cases. The clinical manifestations were observed on D1 postoperative in 3 patients and on D2 postoperatively in 11 patients. Paresthesia of the extremities was the most common symptom (85.7%). Muscle cramps were observed in 2 patients. No patient presented with a heart rhythm disturbance or an attack of tetany. The mean serum calcium was 1.67 mmol/l [1.4–1.9 mmol/l]. A parenteral, intravenous correction was necessary in 18 patients. Oral relay in combination with Vit D was initiated in all patients. The mean duration of treatment was 3.7 months [1–9 months]. The course was marked by regression of symptoms and biological correction in all cases.
Conclusion
Hypocalcaemia is a frequent complication of total thyroidectomy, which can be feared by its cardiac and respiratory complications that can be life-threatening, hence the importance of detecting it by systematic dosing after surgery. Understanding of ethiopathogenic mechanisms is necessary for correct management.

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AEP692

Amiodarone-induced thyrotoxicosis in children: a clinical case
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Introduction
Amiodarone is a drug commonly used for the treatment of refractory atrial or ventricular arrhythmias. In 20% of patients, amiodarone may cause subclinical or clinically overt hypothyroidism or hyperthyroidism. The high iodine exposure caused by amiodarone treatment interferes with thyroid autoregulation. Two underlying mechanisms are considered to be involved in the pathogenesis of amiodarone-induced thyrotoxicosis (AIT). AIT1 is more common in patients with underlying Graves' disease or nodular goiter and results in excessive synthesis of thyroid hormones due to the high iodine intake by amiodarone. In AIT2, a destruction of thyroid follicles due to amiodarone toxicity (subacute and destructive thyroiditis) is observed leading to uncontrolled thyroid hormone release. Also mixed forms are described. We present the patient with amiodarone-induced thyrotoxicosis developed in two years after amiodarone therapy initiation.
Case description
We examined 15-year-old girl whose arrhythmia in the form of a ventricular extrasystole was first diagnosed at the age of 10 (2015) during a preventive examination. A cardioverter-defibrillator was implanted in 2018 and Amiodarone therapy was initiated. Her current Amiodarone dose is 500 mg per day. She regularly underwent examinations and only the thyroid volume increase was noted by ultrasound while hormonal examination always showed euthyroidism. In December 2020 (2.5 years after initiation of amiodarone therapy) patient began to complain of increased heart rate. Hormonal analysis identified a decrease in thyroid-stimulating hormone level (0.0001 uIU/ml; N: 0.35–5.5 uIU/ml) and a pronounced increase in free-thyroxine (fT4) (52.11 pmol/l; N: 11.5–22.7 pmol/l) and free-triiodothyronine (fT3) (7.35 pmol/l; N: 3.5–6.5 pmol/l) levels. Therapy with Prednisolone was initiated at a starting dose of 30 mg per day. Two weeks after the start of therapy, it was possible to achieve the decreasing of fT4 (18.49 pmol/l; N: 10.1–17.9 pmol/l) and fT3 levels (3.5 pmol/l; N: 2.8–6.3 pmol/l). Also, according to the results of ultrasound of the thyroid gland, a decrease in the volume to 14.2 ml was noted (from 21 ml initially). The girl was consulted by cardiologists, the cancellation of therapy was started. We continue to monitor her condition.
Conclusion
Amiodarone-induced thyroid dysfunction is usually atypical; therefore, monitoring of thyroid status before, during, and after Amiodarone treatment is demanded. AIT could significantly deteriorate the clinical status of children with complex cardiac diseases. Early and proper diagnose of AIT allows the introduction of immediate and appropriate treatment considering the cardiac condition of the young patient.

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AEP693

The value of serum thyroglobuline alteration after ultrasonography-guided fine-needle biopsy of suspicous cervical lymph nodes in the diagnosis of metastasis in patients with differentiated thyroid cancer
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Aim
It is known that serum thyroglobulin (TG) can increase after fine-needle biopsy of thyroid nodules. We aimed to determine whether TG is increased after ultrasonography guided fine needle capillary biopsy (FNC) of suspicious cervical LNs in thyroidectomized patients and investigate the possible association between change in TG and cytology results.
Material and methods
Data of 188 patients who underwent FNC of suspicious cervical LNs were retrospectively evaluated. Demographical features, radioactive iodine (RAI) treatment status, thyroid-stimulating hormone (TSH), TG, anti-TG antibody and ultrasonography features of LNs were noted. TG levels before FNC ($TG_{b\text{-}FNC}$), after FNC ($TG_{a\text{-}FNC}$), $TG_{a\text{-}FNC}/TG_{b\text{-}FNC}$ ratio and the number of patients with increased TG were determined. Patients were grouped as

benign, nondiagnostic, suspicious for malignancy and malignant according to the cytological results.
Results
The age, gender, clinical diagnosis, history of RAI treatment and TSH levels were similar in different cytological groups. $TG_{a\text{-}FNC}$, $TG_{b\text{-}FNC}/TG_{a\text{-}FNC}$, and rate of patients with increased TG were significantly higher in malignant cytology group than other groups (P<0.001)(Table). The optimal cut-off level of TG increase that was predictive for malignancy was 7.6% with a sensitivity of 73.7% and specificity of 85.2%. TG increase was not associated with age, sex, TSH level, antiTG positivity and US features of LNs while signficantly lower in patients who received RAI treatment. Among 31 patients with positive anti-TG, $TG_{b\text{-}FNC}/TG_{a\text{-}FNC}$, and rate of patients with increased TG were higher in malignant compared to benign and nondiagnostic cytology groups.
Conclusions
Serum TG increment and rate of patients with increased TG after FNC of suspicious cervical LNs were higher in patients with malignant cytology than with all other cytology results both in all study group and in sub-group of anti-TG positive patients. Increase in TG after FNC might be an additional tool for determining LN metastasis.

Table. Demographical, clinical and ultrasonography features and thyroglobulin levels in patients with respect to the cytological results of lymph nodes

Characteristics	Benign (n = 124, 66.0%)	Malignant (n = 19, 10.1%)	Nondiagnostic (n = 38, 20.2%)	Suspicious for malignancy (n = 7, 3.7%)	P-value
$TG_{a\text{-}FNC}$ (mcg/l)	0.076 (0.012–0.471)[1]	1.283 (0.207–7.931)[1,2]	0.224 (0.036–1.385)[2]	0.161 (0.026–0.998)	<0.001
$TG_{b\text{-}FNC}$ (mcg/l)	0.072 (0.014–0.382)[1]	2.313 (0.437–12.247)[1,2,3]	0.196 (0.037–1.037)[2]	0.071 (0.013–0.375)[3]	<0.001
$TG_{b\text{-}FNC}/TG_{a\text{-}FNC}$	1.000 (1.000–1.000)[1]	1.408 (1.068–1.839)[1,2,3]	1.000 (0.824–1.000)[2]	0.821 (0.531–1.000)[3]	<0.001
Increased TG	18 (14.5)[1]	14 (73.7)[1,2,3]	7 (18.4)[2]	0 (0.0)[3]	<0.001

Quantitative and categorical variables are summarized by median (IQR: 25th–75th percentiles) and frequency (%), respectively.
[1,2,3]The same numbers indicates that the corresponding groups are significantly different from each other.

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AEP694

Predictive factors of thyroid differentiated cancers

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Introduction
Thyroid nodules are common. They are mostly benign nodules. Thyroid cancer is rare: 1 % of all cancer sites. Thyroid differentiated cancers are the most common histologic types. There are several factors that can predict the malignancy in patients with thyroid nodule. The purpose of this study is to identify the predictive factors of thyroid differentiated cancers.
Material and methods
This retrospective study included 333 patients who underwent surgical treatment for thyroid nodule(s), from 2010 to 2020 at our institution. The diagnosis of thyroid cancer was determined according to the histological results. We chose $P < 0.05$ for statistical significance.
Results
The study included 294 women and 39 men. The mean age was 44 years [10 years – 92 years]. Histologic exam revealed a thyroid cancer in 43 cases (13 %) and a benign nodule in 290 cases (87 %). Histologic types of thyroid cancer were: papillary thyroid carcinoma in 37 cases (83 %) and vesicular thyroid carcinoma in 6 cases (14 %).Predictive factors of thyroid differentiated cancers were: male sex ($P = 0.04$), unique nodule ($P = 0.01$), the presence of lymph node ($P = 0.017$), size > 4 cm ($P < 0.001$), solid nodule (ultrasound) ($P < 0.001$), hypoechoic nodule ($P = 0.004$), central ($P < 0.001$) and mixed ($P = 0.006$) vascularization and the presence of microcalcifications ($P < 0.001$).
Conclusion
Many epidemiological, clinical and ultrasonographic factors of thyroid differentiated cancers, have been reported in the literature. Knowing these factors allows for an adequate selection of patients needing fine needle aspiration and surgery.

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AEP695

Systemic erdheim-chester disease associated with braf-positive papillary thyroid carcinoma

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Erdheim-Chester disease (ECD) is a rare histiocytic neoplasm with distinctive clinical and immunophenotypic features, involving somatic mutations of *BRAF* and activation of *MAPK* pathway. Other *BRAF* mutated neoplasms such as papillary thyroid carcinoma (PTC), may also occur synchronous with EDC. There are several reports in the literature of concurrent Langerhans Cell Histiocytosis (LCH) and PTC which suggests that the association is not random, however ECD with systemic involvement and PTC has only been reported in one case only. We report a second case of EDC and concurrent PCT in a 30 years old young man, who first presented in our service with two years history of bilateral exophthalmos and progressive asthenia. Thyroid function was normal, excluding Graves disease. He had no polyuria and no other signs of hypopituitarism. The MRI of the orbit showed bilateral retroorbital pseudonodular masses of 3 cm. PET-CT scan was performed to reveal additional retroperitoneal pararenal masses with partial ureteral obstruction, bilateral and symmetric osteosclerosis of the meta – and diaphysis of femur and humerus, cardiac involvement with pericardial effusion and a right thyroid nodule with high metabolic activity. Bone scintigraphy unveiled typical lesions for ECD. Left retroorbital biopsy was performed and histiocytes with frothy cytoplasm were observed. Genetic and IHC testing of retroorbital tissue revealed BRAF V600E mutation. IHC of the histiocytes was positive for CD163 and for Phospho-ERK. EDC with central nervous system, bone, retroperitoneum and cardiac involvement was diagnosed and treatment with BRAF inhibitor vemurafenib was commenced, with rapid improvement of both exophthalmos and retroperitoneal masses at 3 and 6 months of treatment. FNAB for the thyroid nodule was performed that was suspicious of malignancy and followed by total thyroidectomy. Pathology report revealed a right papillary thyroid carcinoma T2N1b, with the presence of high cell component expressing BRAF V600E mutation. Radioiodine therapy was also performed and patient is currently under surveillance with levothyroxine substitution. This case outlines the systemic involvement of EDC and its association with *BRAF*-positive PTC with a view of considering an EDC diagnosis workup in a non-LCH histiocytic lesion with A BRAF(V600E) mutation.

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AEP696

Multiple etiology pericardial effusion in a young woman

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Context
Severe hypothyroidism and Systemic Lupus Erythematosus can both be causes for the development of pericarditis with concomitant pericardial effusion.
Case illustration
We report the case of a 23 year-old woman admitted in the ER for progressive dyspnoea, increasing fatigue and peripheral edema, associated with hepatosplenomegaly and polyadenopathy. Transthoracic echocardiogram confirmed severe pericardial effusion and an urgent pericardiocentesis and left evacuatory toracocentesis were performed. Pericardial fluid analysis was negative for any malignancy and infection. The patient was referred to an Endocrinology Unit, where she was diagnosed with primary autoimmune myxoedema (TSH = 56 UI/ml N:0.5–4.5; FT4 = < 5.15 pmol/l N:9–19; thyroperoxidase antibody titre = 949.87 mUI/ml N:0–35) and started on oral thyroxine replacement of 75 mg/day, following by a gradual improvement with this treatment. However, two weeks later, she was readmitted to the hospital where the recurrence of pericardial effusion was confirmed. New investigations showed an active systemic lupus erythematosus serology: low complement levels with C3 61 mg/dl (normal range 90–180 mg/dl) and C4 3.43 mg/dl (normal range 10–40 mg/dl), positive anti-nucleosome

antibodies,raised C reactive protein (CRP) 5.9 mg/l (normal range 0–5 mg/l, elevated erythrocyte sedimentation rate (ESR) of 62 mm/h (normal range – 2–12 mm/h. The patient was started on methylprednisolone pulse therapy, then prednisone at 1 mg/kg/day and hydroxychloroquine 200 mg/day for active lupus, with favorable evolution.
Discussion
Autoimmune thyroid diseases can be frequently be associated with SLE. In this case, there is the possibility that both conditions might contributed to the development of pericardial effusion.
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AEP697

Pembrolizumab as definitive treatment for persistence of Graves's disease: a case report
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Background
The usage of Immune checkpoint inhibitors such as pembrolizumab grows over time due to their positive effect on survival and quality of life in patients with advanced cancer. The frequency of immune-related adverse events (IRAEs) associated with this drugs grows over time accordingly. Several endocrine-IRAEs of pembrolizumab are described in the literature and the thyroid disfunction is the most common.
Case description
A 55 year old man was referred to endocrinologist due to progressive fatique, memory troubles and 15 kg weight gain over past 3 months. His past medical history included a persistence of Graves disease for last 5 years after course of antithyroid drug treatment. Patient refused to undergo surgery or radioiodine treatment, so low dose methimazole was continued. One year ago patient was coincidentally found to have an advanced lung cancer: T4N3M1c, stage IVb. At the time of diagnosis patient was euthyroid on 5 mg of methimazole: TSH, free T4 and free T3 levels were 2.9 mIU/l, 12.8 (9.0–19.1) pmol/l and 5.6 (2.6–5.7) pmol/l respectively. The patient was given pembrolizumab (200 mg every 3 weeks) and was referred to endocrinologist with upper mention complaints when he had just received 11th cycle of pembrolizumab treatment. Thyroid function tests done after referral showed a TSH level of 112 mIU/l, free T4 level of 5.15 (9.0–19.1) pmol/l and free T3 level of 1.64 (2.6–5.7) pmol/l. The methimazole was stopped and replacement therapy with levothyroxine started. Six weeks later the patient reported a significant improvement in well-being. Three months later TSH level was 2.1 and fT4 level was 14.4 (9.0–19.1) pmol/l and current dose of 100 µg levothyroxine was continued.
Conclusion
Pembrolizumab treatment is associated with wide range of thyroid dysfunction which can shift from one form to another. This can misguide diagnosis and treatment process unless there is a high index of suspicion.
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AEP698

Central hypothyroidism under Bexarotene: a significant side effect.
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Introduction
Retinoids are a class of molecules, structurally related to Vitamin A, used in various disorders of keratinization (acne, psoriasis, ichthyosis, etc.). these molecules bind two families of Retinoid Nuclear Receptors (RNR): the RA receptors (RAR), which natural ligand is retinoic acid, and the Retinoid X Receptors (RXR), which natural ligand is 9-*cis*-retinoic acid. Among synthetic retinoids, isotretinoin, acitretin, tazarotene and adapalene are ligands of the RAR, bexarotene is the first 3rd generation retinoid (ligand of the RXR), known for the treatment of cutaneous T cell lymphomas. It is the only medication that cause central hypothyroidism in 30% of patients.
Case report
A 61-year-old man, with a history of mycosis fungoides cutaneous T-cell lymphoma (T2 N1 M0) treated with different chemotherapy drugs (methotrexate, puvatherapy, INF alpha, Gemcitabine) without any improvement. Due to the several treatments failures, the Bexarotene 75 mg was introduced: 4 capsules per day the first month associated with fenofibrate 200 mg per day after a pre-therapeutic thyroid assessment: TSH = 0.981 u/ml, T3 = 3.28 pg/ml, T4 = 0.98 ng/dl, with a normal level of HDL, LDL, and TG.1 month later the dose of bexarotene was increased to 6 capsules per day. 25 days later we noticed an elevation of lipid parameters with a disruption of the thyroid function HDL = 0.20 g/l, LDL = 1.71 g/l, TG = 1.69 g/l, cholesterol = 2.25 g/l, T3 = 1.79 pg/ml, T4 = 0.70 ng/dl, TSH = 0.023 iu /ml), we decided to stop bexarotene, introduce L-thyroxine 50 µg for 4 days and increase the doses up to 75 µg for 4 days. After one week, the thyroid function was normal.
Discussion
Bexarotene is a 3rd generation synthetic selective retinoid X receptor (RXRc) agonist. Once activated, these receptors regulate cell differentiation and proliferation. Central hypothyroidism and elevated blood lipid levels are the main side effects. The exploration of the pituitary axis by MRI and hormonal assay confirms the integrity of the anterior pituitary gland, concluding in a specific impairment of the Thyrotropic axis by Bexarotene (only thyrotropic cells of the antehypohysis express RXRc). This hypothyroidism is a transient and reversible condition when the treatment is stopped or when L-thyroxine is added. Euthyroidism is usually achieved with an average dose of L thyroxine 1.6 µg/kg/day.
Conclusion
Retinoid-induced central hypothyroidism is a condition that should be known by endocrinologists and dermatologists. Monitoring the thyroid function is essential in patients with substituted central hypothyroidism in order to adjust the dosage of L-thyroxine, once a week the first month, then monthly.
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AEP699

Pembrolizumab induced Thyrotoxicosis in patient with bladder cancer
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Background
Pembolizumab is a highly specific, monoclonal antibody directed against the programmed cell death receptor, PD-1 and its ligand PD-L1. It is licenced as an immunotherapy for use in locally advanced or metastatic urothelial cell carcinoma, amongst other malignancies. Whilst rare, endocrinopathies, including thyroid dysfunction, are recognised side effects of immunotherapy such as Pembroluzimab. However, hyperthyroidism is much less common than hypothyroidism. When hyperthyroidism is present, it usually precedes a hypothyroid phase, which was not evident in this case.
Case Presentation
A 68-year old female who had recently received her first cycle of Pembrolizumab for locally advanced transitional cell carcinoma of the bladder presented with diarrhoea, vomiting and weight loss. The patient was clinically hyperthyroid, with tachycardia and goitre present. This was confirmed biochemically with a laboratory thyroid panel: Thyroid Stimulating Hormone (TSH) was 0.04 mU/l (reference range 0.27–4.5 mU/l), free T4 35.3 pmol/l (reference range 11–23 pmol/l) and free T3 6.42 mol/l (reference range 3.1–6.8 pmol/l). Thyroid ultrasound revealed benign nodules within both right and left lobes. The patient's diarrhoea progressed to grade 3 and was managed with steroids. Radiologically there was no evidence of colitis. A euthyroid state was achieved with carbimazole. She made a full recovery and was able to continue with the second cycle of Pembrolizumab as planned.
Conclusion
This case demonstrates an unusual presentation of immunotherapy related thyrotoxicosis in a patient on Pembrolizumab, requiring anti-thyroid therapy. It is important for physicians to be aware of immunotherapy-related endocrinopathies as they can present similarly to other oncological emergencies – in this patient, sepsis or colitis were also suspected. European Society of Medical Oncology (ESMO) recommends regular monitoring of thyroid function tests during immunotherapy. Steroids can be used to relieve symptoms.
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AEP700

Factitious thyrotoxicosis, a diagnostic challenge

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Introduction
The term factitious thyrotoxicosis is defined as an excess of thyroid hormone in the body caused by the ingestion of exogenous thyroid hormone. It can be intentional, usually in patients with psychiatric disorders, or accidentally. Another possible cause is the inappropriate use of thyroid hormone for the treatment of obesity, depression or infertility.
Case report
We present the case of a 32-year-old woman, with gestational hypothyroidism during her second pregnancy on treatment with Levothyroxine 50 µg and withdrawal of the treatment. She came to the clinic 2 years later, referring tachycardia, loss of 30 kg in the last 3 months, no fever or compressive symptoms. In laboratory tests she presented TSH 0.01 µIU/ml, FT4 57.67 pmol/l, T3L 14.1 pmol/l. Treatment with antithyroid drugs (Carbimazol 5 mg, 5 tablets a day) was started and a thyroid scintigraphy was requested. At the review appointment these were the blood test results: TSH <0.01 µIU/ml, FT4 97.39 pmol/l, FT3 18.1 pmol/l, TPO antibodies (TPOAb) 525.1 IU/ml, TSH receptor antibodies (TRAb) <0.8 IU/l. Thyroid scintigraphy showed absence of uptake. Due to the absence of improvement and the clinical repercussion of the patient, she was admitted to hospital for study and treatment. During admission, the patient remained in sinus rhythm with a heart rate between 60 and 100 bpm. Laboratory tests showed Thyroglobulin 1.68 ng/ml, Thyroglobulin antibodies (TgAb) <20 IU/ml. Whole body scintigraphy showed absence of thyroid uptake (ruling out struma ovarii), thyroid ultrasound with normal glandular size with heterogeneous echogenicity and no nodules. Serial analyzes were performed throughout one morning showing significant fluctuations in FT4 levels: 57.67 pmol/l – 76.98 pmol/l – 79.39 pmol/l – 80.55 pmol/l. The main suspicion was factitious thyrotoxicosis due to the coexistence of a high concentration of FT4 without thyroglobulin increase and the absence of uptake on scintigraphy. The patient did not admit the surreptitious taking of Levothyroxine and requested voluntary discharge. At discharge she was indicated treatment with cholestyramine and she was referred to a Mental Health consultation. The patient has not returned to our consultations.
Conclusion
In order to diagnose factitious thyrotoxicosis, a differential diagnosis must be made between several diseases that present with low iodine uptake on scintigraphy, such as subacute thyroiditis, iodine-induced hyperthyroidism, struma ovarii, and differentiated thyroid cancer metastases.

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AEP701

Grave's disease in a patient with thyroid hemiagenesis

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Introduction
We present the case of a 50-year-old lady who was referred to the endocrine clinic with a clinical and biochemical picture suggestive of severe thyrotoxicosis. CT scan of thorax, abdomen and pelvis (CT TAP) was performed to rule out malignancy, which showed left lobe agenesis.
Case
50-year-old lady presented to the GP with hyperhidrosis and unintentional weight loss. She also reported symptoms of lethargy, increased bowel frequency, tinnitus, periorbital oedema, cold insensitivity, oligomenorrhoea, palpitations, essential tremor and irritability. She had a background of asthma and depression with a maternal history of hypothyroidism. Initial TFTs showed severe thyrotoxicosis which was sustained when repeated 6 weeks later in the endocrine clinic. Thyroid peroxidase antibodies and TSH receptor antibodies were positive which confirmed the diagnosis of Grave's disease. CT TAP was arranged through primary care to rule out malignancy and incidentally showed a missing left lobe of the thyroid but intact isthmus and right lobe. There was no previous history of thyroidectomy so a diagnosis of thyroid hemiagenesis (THA) was made. The patient was treated with carbimazole with a good response and this is being titrated based on her 6 weekly TFTs.
Discussion
THA is a rare, congenital developmental disorder of the thyroid gland, characterised by the absence of one thyroid lobe. The exact aetiology is unknown but there are several theories based on embryological descent and lobulation, development of blood vessels, and genetic factors. The majority of cases have an absent left lobe. Absence of one lobe of the thyroid usually has no clinical significance and patients are usually biochemically euthyroid and asymptomatic. However, reports have shown that patients with THA are more likely to develop thyroid disorders with hyperthyroidism being the most common clinical presentation. Patients with THA are generally asymptomatic and diagnosis is often incidentally made on routine clinical examinations or imaging modalities. There is also a 7:1 female to male ratio of THA which indicates a possible gender association. Our case is a typical presentation of THA as we had a female patient with a missing left lobe with features of thyrotoxicosis. The aim of treatment in THA is to correct any thyroid hormone imbalance; medically or surgically, manage symptoms and prevent recurrence.

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AEP702

Management of Graves's disease during pregnancy in Covid-19 pandemic conditions - case presentation

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Introduction
The global pandemic caused by the SarsCov2 virus has brought great challenges to the medical system, the management of some cases, especially for those belonging to risk categories, such as pregnant women, being often difficult in this context. Telemedicine has been used frequently during this period, facilitating reducing patient's risk for exposure to COVID-19, providing continuous support, and coordinating the necessary services to prevent acute care necessity, or in our case mother/child short-term/long-term complications.
Objective
Presenting the management during the pandemic, of a case with Graves' disease in pregnancy, using telemedicine.
Case-presentation
A 27-year-old female patient, known with Graves' disease, previously treated with Methimazole (MMI), discontinued on her own decision, addresses to our clinic on 31.03.2020, following an obstetrical consultation (on 26.03.2020) which confirmed that she was 7 weeks pregnant. The hospital to which our clinic belongs, treats patients with Covid19, so we preferred to avoid the patient's exposure, thus management was assessed through telemedicine. We recommended her to perform thyroid functional and immunological tests (FT4, FT3, TRAb) complete blood count and liver function tests, the results confirming Graves' hyperthyroidism. Antithyroid drugs (ATD) therapy was restarted (Propylthiouracil 50 mg, 3 × 1/day), subsequently periodically monitoring the biological parameters, as well as clinical parameters, weight as well as blood pressure and heart rate. She did not require ß-blockers therapy. Entering the second trimester, PTU was replaced with MMI, starting with a dose of 7.5 mg/day, followed by dose adjustment as the pregnancy progressed.
Results:
It was possible to obtain a favorable evolution of the thyroid functional parameters and the decrease of the necessary ATD dose to a minimum required level. Pregnancy ended successfully. At 39 weeks of gestation, she gave birth, by caesarean section, to a healthy female newborn, weighing 3290 grams, Apgar score 9; with favourable postpartum evolution for both mother and newborn. The newborn was screened for thyroid dysfunction after birth and both, functional and immunological thyroid tests, were normal. The patient continued postpartum, after breastfeeding, with MMI therapy 2.5 mg daily, thyroid functional parameters being within normal range.
Conclusions
The SarsCov2 pandemic imposed the consultation and management of several patients by using telemedicine, to avoid the risk of viral exposure. Once established the diagnosis, the adjustment of ATD for Graves' disease during pregnancy was possible using telemedicine. In this case we succeed to manage it even during these difficult conditions, with favorable results so far, both for mother and child.

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AEP703

Collision tumor of the thyroid: follicular thyroid carcinoma plus metastatic renal cell carcinoma

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Introduction
The term collision tumor refers to the coexistence of two histologically distinct malignant neoplasms. The two malignancies can originate from the same organ or occur as metastases from other regions. This type of tumors involving the thyroid gland are especially rare. Reported cases are usually involving papillary thyroid carcinomas in coexistence with other types of tumors like medullary carcinoma, follicular carcinoma or metastasic disease. Metastasic disease to the thyroid is uncommon but can develop after long-disease free intervals. Among the carcinomas metastasizing to the thyroid, renal cell carcinoma is one of the most frequent.
Case report
A 68-year-old man was referred to endocrinology due to a hyper metabolic focus in the upper pole of the thyroid lobe (Suv 3.7). He has a history of 6,5 cm clear cell renal carcinoma with sarcomatous pattern. Right laparoscopic radical nephrectomy was performed six years ago. On physical examination, a soft multinodular goiter was palpable at the expense of the right thyroid lobe, and nodules were not delimited. The thyroid profile was in the normal range. A thyroid ultrasonography showed a 14 mm hypoechoic nodular image in the right thyroid lobe, not well defined, without increased vascularity. In addition a solid, hypoechoic nodule with irregular borders and an anteroposterior diameter of 11 mm was observed in the left thyroid lobe. USG-guided fine needle aspiration of the right thyroid lobe nodule was requested, which corresponded to the uptake observed on PET-CT. A pathology compatible with Bethesda II was obtained. Follow-up was carried out with laboratory tests and ultrasonography. In the control thyroid ultrasonography, a suspicious nodule with a greater craniocaudal diameter than anteroposterior and central and peripheral vascularization of 11 × 11 × 9 mm was observed in the upper pole of the right thyroid lobe. USG-guided fine needle aspiration was performed on said nodule, which was compatible with Bethesda III. Therefore, a total thyroidectomy was performed. Histologically, the thyroidectomy specimen revealed a 1.2 × 0.9 × 0.5 cm follicular thyroid carcinoma in the left thyroid lobe, as well as metastasis due to clear cell renal carcinoma in the right thyroid lobe.
Conclusion
This case report emphasizes that for any patient with a known history of malignant carcinoma, metastatic disease should be considered if new suspicious thyroid nodules appear. The role of pathological anatomy is important in the identification of collision tumors.

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AEP704

Anxiety is more common than depression in indian subjects with recently diagnosed mild subclinical hypothyroidism

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Background
With the availability of sensitive and accurate TSH assays, the entity of Mild Subclinical hypothyroidism (SCH) is being diagnosed more frequently in clinical practice. A variety of neuropsychiatric and cognitive complications have been noted in hypothyroid patients but there is a dearth of literature on the psychopathology associated with mild SCH.
Objective-
This study was undertaken to determine the prevalence of depression, anxiety in Indian subjects with recently diagnosed mild SCH.
Methods
Participants were 112 subjects recently diagnosed with mild SCH and a similar number of age matched euthyroid controls. Mild SCH was defined as serum TSH level more than 4.0 mIU/l but less than 10 mIU/l with normal FT3 and FT4. All participants underwent clinical and anthropometric evaluation along with relevant investigations. The patients were administered the Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale (HAM-A) for Anxiety. The data was analysed statistically using SPSS software.
Results
Females constituted 65% of the sample. The mean age of patient group was 47.4 ± 8.9 years and BMI 26.7± 5.6 kg/m^2 which were comparable to controls. Mean TSH value was 7.1 ± 2.7 mIU/l in patients and 2.4 ± 1.3 mIU/l in controls (*P*–0.001). Among all the participants, based on HAM-D, some degree of depression was present in 17.8% of patients (males- 15.6% and females- 19.2%) and 8.9% of controls (*P*–0.03), whereas based on HAM-A, some degree of anxiety was present in 43.7% of patients (males-35.6% and females-49.7%) and 11.6% of controls (*P*–0.012). Prevalence of anxiety or depression was not affected by age, BMI and TPO antibody level.
Discussion-
Mild SCH is a unique entity often considered separate from hypothyroidism and higher degrees of SCH in respect to clinical implications and treatment criteria. In this study we found anxiety and depression to be more prevalent in subjects with mild SCH compared to the euthyroid subjects. Among the subjects with mild SCH, anxiety was more common than depression (*P*–0.001). These findings suggest that the cognitive aspects in mild SCH subjects are different from the patients with frank hypothyroidism and higher degree of SCH, who are reported to be having higher prevalence of depression along with a spectrum of other emotional and cognitive problems. Mood changes especially anxiety in mild SCH may have an important impact on the patient's quality of life. Further studies in larger populations are needed to validate these findings.

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AEP705

Graves' disease and isolated langerhans cell histiocytosis, a rare case presentation

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Introduction
Langerhans cell histiocytosis (LCH) is a rare monoclonal disease characterized by abnormal proliferation and accumulation of bone marrow-derived Langerhans cells in various tissues. Heterogeneous collections of Langerhans cells with neutrophils, lymphocytes, eosinophils, histiocytes and Birbeck granules are observed in biopsy materials. Endocrinologic features of LCH are usually due to posterior pituitary involvement. Thyroid infiltration is rare and LCH confined only to thyroid gland is even a rarer condition. Here in we present a care with isolated thyroid LCH presenting with Graves' disease. (GD)
Case Presentation
A 41-year-old, 21 weeks pregnant, patient was referred to the endocrinology clinic because of hyperthyroidism. She had been followed up with the diagnosis of GD for 3 years and received methimazole treatment. With pregnancy her treatment was switched to PTU in the first trimestr Her test results were as follows TRAb 2.55 (<1.75 U/l), TSH 0.017 (0.27–4.20 mIU/l); FT3: 5.23 (2–4.4 pg/ml); FT4: 1.96 (0.93–1.70 ng/dl). Ultrasound showed diffused hypoechogenicity and enlargement in both sides of thyroid. A 12×11 mm hypoechoic nodule on the right and a 11*7.6 mm hypoechoic nodule on the left were detected. Upon completion of her pregnancy total thyroidectomy was performed due to on going GD. Pathologic examination revealed langerhans cell histiocytes which were positive for Langerin, S-100, CD1a in immunohistochemical staining. There was concomitant diffuse hyperplasia of the thyroid gland. With all these result was consisted with LCH and GD of the thyroid gland. Bone marrow aspiration biopsy, contrasted cranial MRI and PET-CT ruled out multisystemic involvement of LCH. After thyroidectomy she is followed with LT4 treatment. No additional systemic treatment was required due to local involvement of LCH. Her medical condition is stable under thyroid hormone replacement therapy.
Discussion
Thyroid involvement of LCH is a rare condition and of those with thyroid involvement only 1.5% present with subclinical hyperthyroidism.(1). Number of cases with LCH related with GD has been rarely reported in literature. Here in we report a case with isolated thyroid LCH who first presented with GD. We speculate that immunologic changes due to LCH may trigger autoimmunity which subsequently may cause GD.

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AEP706

Awareness of EUGOGO guidelines and attitudes regarding smoking in Graves' orbithopathy in Croatia

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Background
In 2008 EUGOGO (European group on Graves' orbitopathy) published consensus statement on the management of Graves' orbitopathy (GO) that was widespread ever since. Having in mind unknown general perception and practical usage of the statement amongst Croatian clinicians, we conducted a survey evaluating the awareness and practical usage of the EUGOGO guidelines among physicians treating Graves' disease in daily practice. Also, the idea was to explore their attitude towards importance of smoking as a risk factor for GO.
Participants and methods
An internet based, anonymous online survey was conducted among 40 ophthalmologist, 36 endocrinologists and 24 nuclear medicine specialists, members of Croatian national societies. Median age of participants was 51.15 yrs., 68% were females. From 100 participants 46% worked at Clinical Hospitals, 28% at County Hospitals and 27% at Outpatient Clinics. Two questions we concentrated on were: "Do you use EUGOGO guidelines in daily practice for diagnosis and treatment of GO?" and "Do you know which factors according to EUGOGO guidelines are associated with progression and outcome of the treatment in GO?"
Results
Results of the survey showed that 26% of the participants are not using EUGOGO guidelines; 22.5% of all ophthalmologist (9 of 40 participants), 27.8% of all endocrinologists (10 of 36 participants) and 29.2% nuclear medicine specialists (7 of 24 participants). Even 30% of all participants did not recognize smoking as risk factors determining the outcome of the disease; 37.5% of all ophthalmologist (15 of 40 participants), 16.7% of all endocrinologists (6 of 36 participants) and 37.5% nuclear medicine specialists (9 of 24 participants).
conclusion
EUGOGO guidelines were made with the aim to provide proper diagnosis and treatment for patients with GO; a third of Croatian clinicians involved in treatment of the disease still do not use it. Similar percentage of them were not aware of the clear causal association between smoking and development of GO. There is unambiguous recommendation in the EUGOGO statement for the physicians to urge all patients with Graves' disease, irrespective of the presence or absence of the GO, to refrain from smoking. Following the guidelines represents best clinical practice for the physicians treating GO. Smoking, the strongest risk factor of the progression of the GO, is easy to modify.

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AEP707

Genetic investigation of thyroid dyshormonogenesis in a Tunisian consanguineous family

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We aimed to identify causal mutation(s) in 2 patients (P1 and P2) with thyroid dyshormonogenesis (TD) from a consanguineous Tunisian family. Patient P1 developed TD at age 10; while P2 developed it at a late age (30 years) with no goiter. Scintigraphy showed homogeneous uptake of ^{131}I in P1 patient. Genetic analysis was performed using candidate gene approach. Thus, sequencing of the 17 exons of the *TPO* gene revealed only presence of rs4927611 polymorphism (Ala257Ser) at the homozygous state in P1 and P2. Structural modeling of the rs4927611 polymorphism showed that it is rather lying in the entrance of the active site of TPO enzyme. The presence of a hydrophilic residue (Ser) instead of a hydrophobic one (Ala) might influence the substrate selection. Segregation analysis of this polymorphism showed that it was also present in unaffected family members, excluding involvement of *TPO* gene in TD in this family. In a second step, and in order to target responsible gene, we have performed perchlorate test in patient P1. The test result ruled out any form of defect in iodine organization, and rather suggested a possible defect in iodine transport. We then moved to sequencing of coding region (15exons) and the 5ŕand 3ŕUTR of *NIS* gene. No causal mutation was reported in P1 patient. However, we have identified rs7250061 polymorphism (c.699–75C> T) in intron 5 (MAF = the frequency of the minor allele T = 0.1113). ESEfinder program showed that this substitution creates a new splicing enhancer sequence "CAGAAGT" which is recognized by the splicing factor SRSF1 / SRSF1 (IgM-BRCA1) with a score of 3.46589 and 2.87763 respectively therefore significantly higher than the threshold values of 1.956 and 1.867 respectively. MFOLD program showed that the c.699–75C> T substitution has no marked effect on the RNA structure, excluding thus NIS gene in this family.
Search for causing TD gene will be performed using exhaustive approach (genome scan, exome analysis...) since informativeness of the studied family. Such gene identification may help to develop a genetic screening protocol for congenital hypothyroidism in Tunisia.

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AEP708

Surgical treatment of Graves' disease in children and adolescents

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Introduction
Graves' disease is the most common cause of hyperthyroidism in children and adolescents. Treatment strategy includes antithyroid drugs, radioactive iodine and thyroidectomy. The optimal treatment of Graves´ disease is still controversial. Our aim is to describe the surgical treatment of Graves's disease in children and adolescents.
Material and methods
We report the clinical, therapeutic aspects and long-term results of 9 patients (< = 18 years old) operated for Graves' disease, from 2000 to 2016.
Results
We identified 9 patients with mean age at diagnosis of 15.8 years [9 years – 18 years]. Our study included 3 boys and 6 girls. One patient had coeliac disease. Indications for surgery were: failed medical therapy after 2 years of treatment (5 cases) and presence of a compressive goiter (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 manifestations with biological euthyroidism.
Conclusion
Total thyroidectomy for Graves' disease offers rapid and durable control of hyperthyroidism. Surgery seems to be the appropriate treatment for children and adolescents.

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AEP709

Antithyroid drugs as treatment of neutropenia in hyperthyroidism

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Introduction
Hematological abnormalities are frequently observed in hyperthyroidism and are part of complex, multifactorial pathogenetic mechanisms that are still poorly understood, which can affect the three hematopoietic lineages in isolation or in combination. For the endocrinologist, they raise the issue of the risk of their aggravation under the hamatotoxic effect of antithyroid drugs (ATDs).
Case presentation
A 28-year-old man, with no particular past medical history, presented palpitations with irritability and weight loss. Hormonal tests revealed hyperthyroidism: free thyroxine (FT4) =38 pmol/l (reference: 8.6–25

pmol/l) and thyroid stimulating-hormone (TSH) < 0.005 μUI/ml (reference: 0.4–4 μUI/ml). The physical examination didn't find a goiter or eye signs. TSH receptor autoantibodies were positive at 12,6 UI/l (reference: <1 UI/l). Therefore, the diagnosis of Graves 'disease was made. The complete blood count (CBC) showed a neutropenia with polynuclear neutrophils (PNN) = 800/mm^3 controlled at 850/mm^3. After obtaining the consent of the patient, a treatment with ATDs was started and the CBC after five days of treatment showed PNN at 1080/mm^3 and 1200/mm^3 after 12 days. The ATDs were maintained and the PNN were 2300/mm^3 after euthyroidism.

Conclusion

The threshold of neutropenia contraindicating the prescription of ATDs could well be lowered with vigilance and warning of the patient. Some authors speak of the physiological phenomenon of margination of white blood cells falsely underestimating the count of the lineage, a situation worsened by hyperthyroidism but bot contraindicating the introduction of ATD.

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AEP710

Thyroglobulin and thyroglobulin antibody measurements in the follow-up of differentiated thyroid cancer: practical implications for laboratories illustrated by means of a new highly sensitive thyroglobulin assay

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Introduction

Measurements of thyroglobulin (Tg) and Tg antibodies play a crucial role in the follow-up of treated differentiated thyroid cancer (DTC) patients, for instance to determine the response to therapy and the use of additional investigations and therapies. The aim of this study was to explore, from a laboratory perspective, the practical implications of the substantial clinical role of these measurements being imposed by national and international guidelines.[1–3]

Methods

The newly released DiaSorin LIAISON Tg II assay and the corresponding Tg antibody assay, as well as the established BRAHMS Kryptor hTg and anti-Tgn assays, BRAHMS DYNOtest Tg-pluS IRMA assay, Roche Cobas Elecsys Tg II and anti-Tg assays and Phadia EliA anti-Tg assay, were evaluated and compared in the light of the recommended cut-off values indicated in the relevant guidelines. Additionally, storage stability of the markers was evaluated using different assays, as this is an underexposed aspect in the evaluation of Tg and Tg antibody assays that may have a significant impact on both the daily clinical use of the assays and the use of the assays in clinical studies.

Results

The Tg assays showed a maximum difference of a factor two. Between the different types of Tg antibody assays, a bad correlation was generally observed. In almost all method comparisons, disconcordant results were found looking at the appropriate cut-off values. Additionally, unique data was obtained regarding the storage stability of Tg and Tg antibodies using the assays described in this study.

Conclusion

Tg and Tg antibody assay differences could potentially have a significant clinical impact on the follow-up of DTC patients. Both clinicians and laboratory professionals should be aware of this and should use these measurements accordingly. This study is an example of how unavoidable, inherent assay differences of endocrinological markers complicate use of fixed cut-offs in the guidelines.

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AEP711

Follicular epithelial dysplasia of the thyroid gland on the background of Hashimoto Thyroiditis

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Morphologically, the follicular cells of the thyroid gland on the background of chronic lymphocytic (Hashimoto) thyroiditis may exhibit atypical changes in the nucleus, expansion of the nucleus, crowding, irregularities of nuclear membranes, intranuclear grooves and purification of chromatin. Also be observed proliferative foci of thyroid follicular cells with follicular epithelial dysplasia (FED) were as presumed premalignant conditions in chronic lymphocytic thyroiditis. These foci with Hashimoto Thyroiditis (HT), which differ from the surrounding parenchyma, are less than 0.1 cm in size, do not have invasive growth, the structure of the papillary thyroid gland or intranuclear pseudo inclusions were considered as presumed premalignant conditions in chronic lymphocytic thyroiditis. Also, FED foci exhibit an immunohistochemical (IHC) profile similar to papillary thyroid carcinoma (PTC). Observation was carried out on operative materials. A total 59 cases (37 patients with HT and 22 patients with PTC in HT background). Paraffin embeded and Hematoxylin and Eosin stained samples were used for histopathological examination. IHC staining was performed on Formalin-fixed paraffin embedded tissue sections with antibodies against the following markers: 1. Thyroid transcription factor 1 (TTF1); 2. CD56; 3. p63. As control - histochemical panel: 1. CK19, 2. Cyclin-D1, 3. Galectin-3. With the results obtained, the main histopathological discovery in HT was the atrophy of the thyroid parenchyma, accompanied by lymphoid infiltration, lymphoid follicular hyperplasia, the formation of a secondary germinal center and an abundance of macrophages and plasma cells. Foci of thyroid follicular cells with atypical nuclear features (dysplastic foci) were also seen. In cases of HT without associated PTC, immunoreactivity from moderate to severe p63 was found throughout the thyroid parenchyma, including thyroid follicles, as well as squamoid regions, which is consistent with solid nest cells. In our study, Similar pattern of CD56 and p63 immunoreactivities was observed in foci of PTC arising in the background of HT - strong diffuse staining of Galectin-3 (40%), Cyclin-D1 (70%). Particularly noteworthy is the negative response to CD56 immunostaining in the HT regions of the dysplastic epithelium (FED): Thyroid nuclei showed atypical signs, but versus lymphocytic thyroiditis (40%), they did not have a set of PTC nuclear markers (26%). We can conclude, that the panel of these immunomarkers can potentially be used as a diagnostic tool to differentiate these two forms of thyroiditis, as well as to predict the risk of developing PTC, especially during preoperative evaluation in small diagnostic tissue samples.

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AEP712

Covid 19 associated with diabetes mellitus tip 2 and hyperthyroidism in one doctor patient

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SARS-CoV2 can induce multiple immunological and endocrinological changes. Diabetes and thyroid disorders tend to coexist in patients. Both conditions involve a dysfunction of the endocrine system. Thyroid disorders can have a major impact on glucose control. On one hand, thyroid hormones contribute to the regulation of carbohydrate metabolism and pancreatic function, and on the other hand, diabetes affects thyroid function tests to variable extents. SARS-CoV-2 uses ACE2 receptor combined with the TMPRSS2 as the key molecular complex to infect the host cells. Interestingly, ACE2 and TMPRSS2 expression levels are high in the thyroid gland and more than in the lungs. Physiological concentrations T4 and T3 stimulate the production and release of cytokines, which are also components of "cytokine storm" potentially characterizing systemic viral infections. COVID-19 might also predispose infected individuals to hyperglycemia. In November 2020, a 55 years old chirurg doctor presented the symptoms headache and tachycardia, dyspena, polyuria and polydisia,temperature of 39.0.He had 3 days with this symptoms.Before, he has no history of diabetis mellitus tip 2 or hyperthyrosis. The initial ECG showed a sinus tachycardia with a frequency of up to 120 beats per minute. Laboratory results revealed elevated thyroid hormone levels fT3 6.9 pg/ml; [2.0–4.4]; fT4 26 pg/ml; [9–17) as well as a supressed TSH (0.01 μU/ml; [0.27–4.20]). As thyroid autoantibodies (antithyroid peroxidase (TPO) antibody, anti-thyroglobulin (Tg) antibody and thyroid-stimulating

hormone receptor (TSHR) antibody) were negative and thyroid ultrasound was normal. Glycemia 400 mg/dl.HbA1C 5.0%,PCR 10,eritrosedimention rate 30,lymphopenia 1.06G/l.Ct scan of chest pozitiv for COVID 19.The patients was treated with anticovid treatment,no oxygen therapy, amaryl 2 mg 1 tb in the morning and vitagliptin 50 mg 1 tb in dark,unimazol 5 mg 2 tb in morning 2 tb in the dark.After 5 days we had a good improvement of glycemia,tachycardia and dyspnea.The patient was clinically better.After 1 month the patients was stabilized of Covid 19 and had good profile of glycemic control but he had supressed TSH 0.07.The antidiabetic oral and antithyroidien therapy is continued.We assume SARS-CoV-2 infection can induce a destruction of thyroid issue. All patients with COVID-19 should be monitored regarding endocrinological changes, especially diabetes, but also TSH, fT3, fT4 should be assessed. Hyperthyroidism may mimic clinical features of COVID-19 like fever, tachycardia, and diarrhoea. Thyroid dysfunction may be due to coincident primary thyroid disease, but also viral affection of the thyroid should be taken into account.

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AEP713

A male patient with subacute thyroiditis after COVID-19 infection

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Introduction
Subacute thyroiditis is a rare cause of thyrotoxicosis arising in the context or following viral infections. This disorder is more frequent in women than in men (male/female ratio of 1:4). In addition to respiratory symptoms, the SARS-CoV-2 infection (COVID-19) has been associated with extrapulmonary manifestations. Herein we report a male patient with hyperthyroid symptoms starting four-week after a positive test for COVID-19.
Case presentation
We present the clinical case of a 63-years-old caucasian man, with a past medical history of obesity, hypertension, and a recent COVID19 infection. He started complaining of neck discomfort together with anorexia, fatigue, palpitations and, heat intolerance, four weeks after a positive RT-PCR nasopharyngeal swab for SARS-CoV-2. He remained asymptomatic the 2 weeks after the positive test and was discharged from the COVID19 surveillance program. When first seen by one of us, he was anxious, tachycardic (108 beats/min), presenting a fine tremor of both hands and a discrete bilateral eyelid retraction. He had lost 8 Kg during the previous two weeks. His thyroid was slightly tender. The patient denied a past medical history of thyroid disorders. Blood tests revealed a high C-Reactive Protein (CRP) 5.65 mg/dl (<0.5); TSH 0.007 mIU/l (0.7–4.20); FT4 2.81 ng/dl (0.70–1.48); FT3 7.41 pg/ml (1.58–3.91); TPO ab 137.7UI/ml (0–60); Thyroglobulin of 127 ng/ml (<10). TRAB <1.10. Hemoglobin was 11.2 g/dl and white blood cells count of $10.2x10^6$ (59.4% neutrophils). Serum titers of IgG anti SARS-CoV-2 was 100.0 U/ml (<12) and IgM 2.74 U/ml (<1.1). Thyroid ultrasounds showed a heterogeneous gland of normal size with areas of low echogenicity and decreased tissue vascularity in Color Doppler evaluation. He was started on prednisone 40 mg/day PO. One week later blood test revealed FT4 2.03 ng/dl; FT3 3.95 pg/ml and TSH 0.01. Prednisone was reduced to 20 mg/day. One more week and CRP was 0.750, TSH 0.01 mIU/l with normal FT4 and FT3. Prednisone was taper. Two weeks later, he reported complete resolution of the symptoms. At this time, blood tests showed an increase in TSH indicating a clear biphasic evolution of thyroid function.
Conclusion
Subacute thyroiditis can be triggered by the new coronavirus (SARS-CoV-2) in a similar way to other viral infections. Therefore, clinicians must be aware of the possibility of thyroid dysfunction after COVID-19 infection. Early recognition and timely steroid treatment may successfully improve the outcome of the disorder, preventing permanent hypothyroidism.

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AEP714

Thyroid disease in insulin- treated type 2 diabetes mellitus

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Background and aim
Abundant evidence suggests an association between thyroid disease and type 2 diabetes mellitus (T2DM). To determine the interaction between these co-existing pathologies, we analyzed insulin-treated type 2 diabetes patients with diagnosed thyroid disease.
Patients and methods
This retrospective study was performed in 54 type 2 diabetes patients who had been admitted for insulin-treatment and diagnosed thyroid disease. Patients were divided into two groups: Group 1(G1) thyroid disease diagnosed after diabetes onset and group 2 (G2) thyroid disease diagnosed prior to diabetes onset.
Results
Among the 54 patients studied, 75.92% of participants were females and 25.92% had family history of thyroid disease. Sub-clinical hypothyroidism constituted 44.44% of the thyroid dysfunction in the T2DM patients, clinical hypothyroidism was 25.94% and hyperthyroidism was 29.62%. Thyroid disease was predominantly diagnosed after diabetes onset (G1: n = 42, 77.77%): Hypothyroidism was predominantly diagnosed after T2DM onset while hyperthyroidism was predominantly diagnosed prior to diabetes onset. BMI and HbA1c did not statistically differ among the two groups (30.47 kg/m^2 vs 29.22 kg/m^2, 11.21% vs 11.16% respectively). G2 patients were older at diabetes onset (53.33 years vs 44.21 years, $P = 0.01$) and were younger at thyroid disease onset than G1 patients (48.91 years vs 52 years, $P = 0.38$). Patients with type 2 diabetes and prior appearance of thyroid disease(G2) required insulin therapy significantly earlier with median insulin-free period of 4 years compared to patients who had thyroid dysfunction after diabetes onset(G1) with median insulin-free period of 8.07 years, P =0.01 Group 1 patients (thyroid after diabetes) developed thyroid disease on average only after the initiation of insulin treatment. However, a clear negative correlation was observed between age at diabetes onset and insulin-free period ($r = -0.3$, $P = 0.05$). The older the patient the sooner insulin treatment was started.
Conclusion
Patients with thyroid disease prior to T2DM required significantly earlier insulin therapy compared to patients without thyroid diseases at the time of diabetes onset. Further studies are needed to elucidate mechanisms of interaction of thyroid disease in type 2 diabetes patients.

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AEP715

Voluminous primary mediastinal multinodular goiter as a rare cause of hyperthyroidism.

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Introduction
Primary mediastinal goiter is an extremely uncommon entity. The majority of primary mediastinal goiters were reported as incidental findings on chest imaging of asymptomatic patients. Symptoms related to compression of adjacent structures and hyperthyroidism were rarely described. Herein we report a case of subclinical hyperthyroidism secondary to a primary mediastinal goiter.
Observation
A 50 year-old woman was referred to our department for hyperthyroidism. She presented with palpitations and hand tremors for 4 months. No history of dysphagia, dyspnea or hoarseness was reported. Physical examination found homogeneous thyroid gland and no superior vena cava syndrome. Thyroid function tests revealed subclinical hyperthyroidism. Thyroid peroxydase antibodies and thyrotropin receptor antibodies were negative. Thyroid ultrasound showed a normal-sized thyroid gland with a 7.5 mm nodule classified TIRADS II and a voluminous anterior mediastinal mass of 75 mm, hyperechoic, heterogeneous and containing multiple calcifications. Cervico-thoracic CT scan revealed a 120 × 70 × 128 mm anterior mediastinal mass independent from the thyroid gland, containing multiple calcifications, with a large tight contact with the aortic arch, the supra aortic trunks and the superior vena cava. A complete resection of the mediastinal tumor was performed through a total median sternotomy. There were no vascular or tissular connections between the mass and the thyroid gland. The feeding artery was dependent on intrathoracic vessels. The histopathological findings revealed a multinodular colloid hyperplasia with no signs of malignancy. The postoperative outcome was marked by a spontaneous euthyroidism.

Conclusion
Our case highlights necessity to keep in mind that ectopic mediastinal goiter, although uncommon, can induce hyperthyroidism. The final diagnosis of primary mediastinal goiter is made by histopathological examination.

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AEP716

Pattern of autoimmune thyroid disease among patients with goitre at a tertiary hospital, lagos nigeria

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Introduction
Thyroid disorders are second largest endocrine condition seen in clinics. The most common manifestation of thyroid dysfunction is the appearance of goitre. The elimination of iodine deficiency as a cause of goitres decades ago has demanded a closer look into autoimmune aetiology of thyroid disease in our population. The characteristic features of these autoimmune goitres: Graves' Disease (GD) were also explored in this study. The finding of a higher than reported prevalence of Marine Lenhart syndrome in this study raises the concern for possible induction of autonomous nodules in the presence of iodine sufficiency.
Methods
One hundred and thirty-four participants with goitres were recruited for the study. Seventy-seven of these participants with goitre had features of toxic goitre confirmed with low TSH and elevated free Thyroxine and Triiodothyronine had Thyrotropin Receptor Antibody (TRAb) assayed to determine autoimmune hyperthyroidism. Thyroid ultrasonography was carried out on all participants.
Results
The TRAb is a confirmatory test for Graves' disease, of the 77 with clinical, radiological and /or biochemical diagnosis of Toxic goitre tested, 60 were positive with a Prevalence rate of 77.9%, of which males were 20 and females 40. The prevalence of autoimmune thyroid disease among the general population using Anti-Thyroid Peroxidase was 38.7% while among those with goitre; 53.7%. Out of 77 with toxic goitres tested, 72 had positive Anti-TPO with a prevalence of thyroid autoimmunity at 93.5%. 18 males and 54 females. Both Antibodies were positive in 48 of the 77 tested giving a prevalence of 62.3%. Among those with toxic goitre tested using TRAb, 7.6% had other clinical diagnosis other than GD as clinical /provisional diagnosis. Fifty percent of the subjects with clinically indeterminate diagnosis between Toxic Multinodular Goitre (TMG) and GD had positive TRAb result while 66.7% of those who had clinical and radiological diagnosis of TMG had positive TRAb. There is an increased prevalence of Marine Lenhart Syndrome in this study of 10% compared to previous reports of 0.8–4.1 percent
Conclusion
Diagnosis of GD (Autoimmune Hyperthyroidism) is most certain with TRAb. The use of clinical features alone is prone to misdiagnosis while isolated use of Anti-TPO for diagnosis of GD could lead to inappropriate diagnosis. The high prevalence of TRAb-positive nodular goitres raises the concern of possible association between autoimmune thyroid disease and possible iodine sufficiency in which autonomous thyroid nodules are spontaneously developed.

Keywords: autoimmune, hyperthyroidism, anti-thyroid peroxidase, thyrotropin receptor antibody, Graves' disease

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AEP717

Thyroid carcinoma in cowden syndrome

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Cowden's syndrome (CS), also called multiple hamartoma syndrome is an orphan pathology which associates pathognomonic cutaneous-mucosal manifestations with multiple and disseminated hamartomas (skin, mucous membranes, gastrointestinal tract, thyroid, breasts and genitourinary system) and an increased risk of the development of certain malignant tumors, in particular breast, thyroid and endometrial tumors, which are very serious.

Observation
Case 1
A 41-year-old woman followed from a young age in dermatology for skin lesions associated with macrocephaly. She also has a history of multinodular goiter operated on 4 times, the micro-invasive follicular carcinoma is diagnosed, it was extended to the 3rd and 4th tracheal rings and cervical lymph node. The treatment is completed by two iratherapy (cumulative activity: 448 mCi). The diagnosis of Cowden syndrome is confirmed and other explorations are made, they have resulted in the discovery of 3 gastric polyps of 6 to 8 mm, multiple colonic polyps of 10 mm, and more recently, left breast cancer currently undergoing chemotherapy.
Case 2
A 20-year-old women with a history of a 20 mm granulosis tumor of the right ovary, operated on at the age of 14. A left nodular goiter is discovered accidentally, a thyroidectomy is performed and the diagnosis of trabeculo-follicular carcinoma is made. The treatment is completed by iratherapy (105 mCi). During follow-up, a bilateral breast biopsy is performed. The histological study confirms benign adenofibroma. The association of ovarian tumor, thyroid carcinoma, adenofibromas of the breasts with skin lesions such as papillomatous papules of the nose, of the neck, of the gums and nasal mucosa suggests the diagnosis of Cowden syndrome. The digestive tract could not be explored because the patient's refusal, the ultrasounds made during the follow-up did not find any lesion of the urinary or the genital system.
Discussion
CS is a tumor predisposition syndrome related to a mutation in the tumor suppressor gene PTEN located on the long arm of chromosome 10 (10q 22–23) whose loss of function leads to activation of the PI3K/Akt/ pathway. mTOR involved in cell growth, migration and proliferation. The hamartomatous lesions characteristic of CS concern organs from 3 embryological outlines: ectoderm, mesoderm and endoderm, its diagnosis is purely clinical based on the association of major and minor criteria established by the international Cowden consortium. a rare but potentially serious pathology due to the frequency and aggressiveness of the malignant neoplastic lesions characterizing it, requiring multidisciplinary management is close monitoring.

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AEP718

Primary diffuse B-cell thyroid lymphoma: A case report

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Introduction
Primary thyroid lymphoma (PTL) is a rare affection that represents only 1% to 5% of thyroid malignancies and 1% to 2% of extranodal lymphomas. It involves by definition only the thyroid gland and adjacent neck lymph nodes, at diagnosis.
Case presentation:
A 65-year-old woman with a controlled Hashimoto's thyroiditis presented with a 12-month history of painless neck swelling, recently increasing in size and occasionally causing hoarseness. Physical examination showed a large no tender nodular goiter, anterior cervical adenopathies and a positive Pemberton's sign. Cervical ultrasound revealed a 6 cm left thyroid nodule EU-TIRADS 5. Fine needle aspiration was suggestive of a high-grade lymphoma. Thyroid and cervical lymph node biopsies later confirmed the diagnosis of diffuse large B-cell lymphoma (DLBCL). On immunohistochemical staining, the tumor cells were positive for CD20, CD10, Bc16 and Ki67 (70%). No other dissemination was found on the thoracic-Abdominal-Pelvic scan nor the bone marrow biopsy. So the lymphoma was classified IIE on the Ann Arbor classification. The chemotherapy was delayed for 2 months because of the patient's Covid-19 infection, she then was started on an 8-cycle chemotherapy regimen including cyclophosphamide, adriamycin, vincristine and prednisone in association with rituximab. Adjuvant radiotherapy is scheduled.
Discussion and conclusions
Similarly to our case report, PTL is usually observed in middle to older aged females, but it commonly has a faster progression. DLBCLs account for 50 to 80% while mucosa-associated lymphoid tissue lymphoma, presents 20–30% of all PTLs. Autoimmune chronic lymphocytic thyroiditis is a well-established risk factor with an 80-fold risk compared to individuals without Hashimoto's thyroiditis, which suggests a pathogenesis related to chronic inflammatory stimulation. Our Patient has a low intermediate International Prognostic Index (IPI). Prognostic factors include age, Size of the tumor, stage of the disease, the presence of symptoms due to B-cells, levels of

LDH. The conventional chemotherapeutic regimen for PTL includes cyclophosphamide, doxorubicin, vincristine, and prednisone. Rituximab, a monoclonal antibody anti-CD20, represented an advance in the treatment of DLBCL. Currently, most authors support combined chemo-radiation therapy since it ensures a better outcome for five-year overall survival.

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AEP719

Medullary thyroid carcinoma development five years after thyroidectomy for benign non-toxic goiter

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Total thyroidectomy is the preferred surgical procedure in patients with high-grade multinodular goiter. The necessity for long-term neck ultrasound (US) surveillance after thyroidectomy for benign diseases remains unclear as the risk of recurrence is very low. However, in a minority of patients a thyroid neoplasm could arise from very small thyroid remnants. We report a case of a 65-year-old female who underwent thyroidectomy for nontoxic multinodular goiter in 2013. Histological examination was consistent with benign nodular hyperplasia. Levothyroxine replacement therapy was started thereafter but regular US examination was not performed. Five years later the patient presented with newly developed persistent dysphonia and was diagnosed with vocal cord paralysis. The subsequent US neck imaging found a big hypoechoic nodule in the left thyroid bed with irregular shape, blurred margins infiltrating the trachea (EU-TIRADS 5). Lymph nodes with metastatic US features were detected in the left lateral compartment (level IV). Serum calcitonin was significantly elevated. Fine needle aspiration biopsy revealed cytological evidence of malignancy and the extremely elevated calcitonin in the cervical lymph nodes washout confirmed metastases from medullary thyroid cancer. The patient was referred to surgery but due to the local invasion complete tumor resection was not possible. Following surgery targeted therapy with tyrosine kinase inhibitors was initiated to prevent further disease progression. The clinical case suggests that aggressive thyroid malignancy can develop from microscopic tissue remnants several years after thyroidectomy. Ultrasound examination is a valuable tool in the long-term follow-up after thyroidectomy even for benign disorders.

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AEP720

Post covid-19 myxedema a case report

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A 65 year old female presented to ER with progressive massive lower limb oedema and dyspnea on mild exertion of insidious onset. The patient started to complain of progressive lower limb oedema shortly after her discharge from Hospital ICU in June 2020 where she was being treated for severe COVID-19. She presented then with acute kidney injury, generalized oedema and was diagnosed with COVID-19 based on clinical, laboratory criteria, PCR, and CT findings. She is a known patient with type 2 diabetes and hypertension since 20 years on premixed insulin, she was diagnosed with heart failure since 3 years for which she was receiving diuretics and she had a past history of recurrent cellulitis since 10 years. Family history was negative for thyroid illness. Following her post Covid-19 discharge she started to suffer of progressive lower limb oedema that was assumed to be exacerbation of her cardiac condition and consequently the diuretics therapy was titrated up to 500 mg Lasix daily, followed by metozolone 10 mg and spironolactone 100 mg twice with no response. Lower limb oedema extended to thighs, incapacitating the patient ability to move, skin started to be dry, scaly with oozing blisters. On examination she was obese BMI = 35 kg /m^2, orthopneic, her neck showed congested pulsating neck veins and no goiter, her Left UL and both lower limbs exhibited lymphoedema, her chest revealed moderate pleural effusion. Her laboratory profile showed renal impairment creatinine= 1.8 mg/dl on admission, normocytic normochromic anemia Hb=9 gm/dl,hypoalbuminemia = 3 gm/dl and hyperuricemia = 15 mg /dl.She underwent pleural tap that revealed exudative pleural effusion. Screening for thyroid functions showed a TSH of 33.5 mIU/l. Patient was instituted on escalating dose of levothyroxine starting with 25 mgm/dl followed by 50 mgm/dl and by the end of 10 days marked decrease of pleural effusion was noted and improvement of kidney functions creatinine = 1.3 mg/dl. To our knowledge this is the second case reporting myxedema complicating COVD-19 that hypothesized invasion of thyroid tissue via surface expressed ACE2 receptors.[1]

Conclusion

COVID-19 had a short and long term extrapulmonary effects. Thyroid state should not be overlooked in the assessment of post and long COVID states.

Reference

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AEP721

A novel DUOXA2 mutation in russian family with thyroid dysgenesis

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Background

DUOXA2 mutations in patients with congenital hypothyroidism (CH) was first described in 2008 as rare cause of CH. mRNA of *DUOXA2* is expressed predominantly in thyroid and less in salivary glands. Human *DUOXA2* gene is located on 15q21.1 and inherited in an autosomal recessive pattern. In most cases *DUOXA2* gene mutations were described in patients with thyroid dishormonogenesis. Last investigations conferred *DUOXA2* susceptibility to thyroid dysgenesis (TD).

Methods

Twenty one genes related to CH (AITD3, DUOX2, DUOXA2, DUOX1, FOXE1, FOXE2, GLIS3, GLIS4, GNAS, IYD, NKX2–1, NKX2–5, PAX8, SECISBP2, SLC16A2, SLC26A4, SLC5A5, THRA, THRB, TPO, AITD4) were sequenced and screened for variations by next-generation sequencing (NGS) in this family.

Case report

1 patient: adult 24 yrs. female with congenital hypothyroidism caused by thyroid dysgenesis. Neonatal TSH was 173.7 mU/l, serum TSH – 301.1 mU/l. She was followed in endocrine research center from infancy. Ultrasound imagines did not reveal thyroid tissue, thyroglobulin was low (less 0.1 ng/ml). She gave birth to a baby at 24. The pregnancy proceeded normally and the delivery was without complications. 2 patient (proband): daughter of patient 1, five weeks aged, with no signs of hypothyroidism in neonatal period. Neonatal screening conducted on the third day of life. TSH was slightly increased to 9.5 mU/l and 22 mU/l on 3d and 14th day, respectively. Before onset of therapy, serum TSH was increased to 78 mU/l and fT4 decreased to 7.5 pmol/l, serum thyroglobulin level was high as 125 ng/ml (reference range 0–50). Ultrasound imaging did not show thyroid gland in typical position of the neck, during following investigation thyroid tissue was found near the hyoid bone. Heterozygous novel variant mutation c.552A > G:p.L184L in *DUOXA2* (NM 207581.4) was detected in mother and proband with thyroid dysgenesis.

Conclusions

We report a novel heterozygous *DUOXA2* mutation in the family with thyroid dysgenesis (mother and daughter). Homozygous *DUOXA2* mutations described in patients with thyroid dyshormonogenesis. However last investigations revealed heterozygous mutations in *DUOXA2* gene in TD patients. The significance of our heterozygous mutation remains unknown and require further researching.

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AEP722

A prospective study of anesthetic risk and anesthesia particularities under thyroidectomies in thytoxocosis patients

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Objectives.
A prospective study to analyze anesthetic risks and anesthesia particularities in thyrotoxicosis syndrome (TTS) patients who were undergone thyroidectomy.
Materials.
It was analyzed 880 operated the TTS patients. Surgical interventions were performed under general anesthesia with mechanical ventilation by using the inhalation anesthesia (IA) with sevoflurane in 698 (79.3%) patients, by the total intravenous anesthesia (TIVA) with propofol in 182 (20.7%) cases. We assessed the physical status on the American Association of Anaesthesiologists (ASA) classification, the frequency of concomitant pathology, the anesthesia particularities of the according to anesthesiologist's recording reports.
Results
Among TTS patients, the 596 (68%) patients had diffuse toxic goiter (DTG), 208 (23%) patients had a multinodular goiter (MNG) with TTS, the rest of patient were with toxic adenoma - 44 (5%), 24 (3%) patients were with relapse of previously operated DTG or MNG. In 8 (1%) cases there was a combined pathology - papillary cancer in the background of MNG with TTS. The average age had a significant difference ($p < 0.01$) by Wilcoxon test between the groups DTG and MNG and was 42.1 ± 1.6 and 52.8 ± 1.7 years, respectively. According to ASA only 210 patients (23.9%) had - ASA I. 76.1% out of 880 TTS patients had ASA II–IV class. 21.1% of patients were at high risk ASA III and IV. It was analyzed that the anesthesiologists performed systemic haemodynamic and cardiac rhythm correction by administering antihypertensive, antiarrhythmic, sympathomimetic drugs in 404 (45.9%) cases, of which 320 (45.8%) – IA with sevoflurane, 84 (46.2%) – with TIVA with propofol ($P = 0.551$, no statistically significant difference). Bradycardia appeared in 9.5% and 2.2% of cases of IA and TIVA respectively ($P < 0.05$). Perioperative hypertension, which required medication, arose in 26.1% of cases and 25.3% with IA and TIVA respectively ($P > 0.05$). The most commonly observed concomitant diseases in patients with DTG were dismetabolic cardiomyopathy – 55.0%, and the patients with MNG with thyrotoxicosis had arterial – 64.3%. No fatal case was observed.
Conclusions
TTS impairs the ASA physical status. There was 76.1% of patients with thyrotoxicosis, who had one or more concomitant pathologies - ASA II-IV class. 21.1% of the patients had ASA III and IV. Abnormal anesthesia were noted in 404 (45.9%) cases, that means than the personified approach to the choice of type of anesthesia is needed.

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AEP723

Thyroid morphologic characteristics assessment in a cohort of patients with different glucose tolerance status

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Background
Thyroid diseases and diabetes are the two most common endocrinopathies. A relationship between these two conditions is suggested by many studies, as diabetic population seems to present increased thyroid impairment. However, clinical data are still very sparse.
Aim
To evaluate thyroid morphologic characteristics among patients with different glucose tolerance status.
Material and methods
This retrospective study was conducted on 227 patients who underwent both an oral glucose tolerance test (OGTT) and an thyroid ultrasound (US) exam at our center. The following data were collected: thyroid US characteristics, thyroid nodules cytology, glucose tolerance defined as normal (N), impaired (I) and type 2 diabetes (D). HOMA index was also calculated.
Results
The cohort included 44 males and 183 females. After OGTT, 58%, 34% and 7% of patients were identified as (N), (I) and (D), respectively. (D) were significantly older (67.4 ± 6.8 yr) as compared to (I) (56.9 ± 13.5 yr) and (N) (52.3 ± 16.5 yr), without differences concerning thyroid function and gender distribution. (D) presented higher mean thyroid volume than others, but this difference did not reach statistical significance. Thyroid volume was significantly higher in euthyroid patients as compared to hypothyroid patients on L-thyroxine replacement therapy. Mean insulin peak levels after glucose load was consistently higher in (D). The incremental area under the curve (AUCins) increased from (N) to (I) to (D). Simple linear regression did not show any correlation between thyroid volume and insulin level nor HOMA index. Thyroid nodules were diagnosed in 68% of (N), 64% of (I) and 82% of (N). Thyroid nodules presented US characteristics suspicious for malignancy in (D) more often than other groups. 174 out of 203 nodules underwent to cytology investigation. Benign cytology was prevalent in all three groups.
Conclusion
Our data suggest a correlation between impaired glucose tolerance and increased thyroid volume, in agreement with literature evidence. More prospective studies with larger samples are needed in order to confirm this association. Finally, impaired glucose tolerance was not found to be predictive of malignancy at US and cytology.

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AEP724

Post-operative resistant hypothyroidism of Graves' disease patient resistant to anti-thyroid treatment

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Introduction
Graves' Disease resistance to anti-thyroid treatment and poor treatment compliance with levothyroxine treatment (pseudomalabsorption) are not common conditions. We presented this case because of the inability to provide euthyroidism with anti-thyroid treatment before the surgery and with levothyroxine after the surgery in the same patient.
Case Report
A 24-year-old female patient was admitted with complaints of hair loss, tremors in the hands, weight loss, and palpitations. Methimazole was initiated in the patient, whose biochemical results (Table 1) supported Graves' disease as a result of ultrasonography and scintigraphy. In the patient whose hyperthyroidism did not improve despite high dose methimazole (80 mg/day) treatment, lithium 600 mg, Lugol 3 × 5 drops, methylprednisolone 40 mg, and plasmapheresis were administered to the patient, and underwent total thyroidectomy. After the surgery, levothyroxine replacement was started for the patient as 1.8 mg (microgram)/kg/day. Upon the arrival of fT4 (free T4) < 0.15 ng/dl and TSH (thyroid-stimulating hormone) > 47.900 mIU/l at the control admission, the patient was hospitalized. She was taking medication regularly and there was no history of drug use that could affect levothyroxine absorption. The Celiac antibodies (Anti-gliadin Ig A, Anti-endomysium Ig A, Anti-transglutaminase Ig A) and helicobacter pylori test (pathological diagnosis), which were done for malabsorption, were negative. Despite the LT4 (levothyroxine) replacement treatment under observation, she had no increase in sT4 levels, and a challenge test with supervised intake of 1,000 µg of levothyroxine was performed. Based on the 2–3 times increase in sT4 levels and decrease of approximately 40% in TSH levels, the patient was diagnosed with pseudomalabsorption. The patient was discharged with a daily dose of 2.2 mg/kg/day levothyroxine. The laboratory results of the patient after the discharge are given in the table (Table 1). The patient is followed by us.

Table 1. Biochemical results

	Before surgery	Hospitalization	2nd Week after discharge	Referance range
TSH	<0.005	>47.900	0.21	0.270–4.2 mIU/l
sT3	15.68	1.55	4.51	2–4.4 ng/l
sT4	6.9	<0.15	1.83	0.93–1.7 ng/dl
Anti-thyroid peroxidaz	397			0–9 IU/ml
Anti-thyroglobulin	10.2			0–4 IU/ml
TSH reseptor antibody	5.4			<1 U/l

Conclusion
Drug compliance, malabsorption, and the presence of antibodies against drugs and intrathyroidal drug concentration measurements are recommended in patients resistant to anti-thyroid treatment. In case of failure to provide euthyroidism despite high-dose hypothyroidism treatment, malabsorption syndromes must be eliminated, and the patient must be evaluated for pseudomalabsorption. In these patients it is recommended that higher doses be given than normally needed.

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AEP725

Vitamin D deficiency and Hashimoto's thyroiditis

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Introduction
The main role of vitamin D is regulating bone metabolism, but over the past years, the importance of vitamin D in non-skeletal actions has been studied. Vitamin D deficiency is very common in our environment. This deficit has been associated with higher risk of many chronic diseases, such as osteoporosis, hypertension, diabetes and even obesity. Recent evidence has demonstrated an association between low vitamin D status and autoimmune thyroid diseases such as Hashimoto's thyroiditis. Moreover, vitamin D plays a significant role in modulation of the immune system, enhancing the innate immune response while exerting an inhibitory action on the adaptive immune system.
Objectives
To evaluate whether there is a higher prevalence of vitamin D deficiency among patients with Hashimoto's hypothyroidism and whether it is correlated with laboratory parameters such as TSH, free T4 or the levels of anti-peroxidase (TPO) and anti-thyroglobulin antibodies.
Methods
The medical history and laboratory tests of 200 patients with autoimmune hypothyroidism treated in our hospital (Hospital Clínico Lozano Blesa, in Zaragoza; Spain) were collected for this study. Vitamin D levels under 30 ng/ml were considered to be vitamin D deficiency. Student's T test was used for statistical analysis.
Results
Vitamin D deficiency was frequent among hypothyroid patients (42.6%). In addition, higher mean values of anti-tiroglobulin antibodies have been obtained in patients with low vitamin D (235.14 IU/ml versus 102.32 IU/ml, $P = 0.011$), as well as higher mean values of TSH (20.45 mU/l vs 8.45 mU/l $P = 0.028$). There were no differences between the FT4 values or anti-TPO antibodies of both groups.
Discussion and conclusion
A high prevalence of vitamin D deficiency was found among patients with Hashimoto's thyroiditis. Moreover, those with higher TSH and/or higher anti-thyroglobulin antibody levels had lower vitamin D levels. Various studies have recognized the pleiotropic roles of vitamin D, which have suggested a beneficial role of this vitamin in the management of thyroid disease. However, only an ambiguous causal relationship has been reported to date, so the potential of vitamin D as a treatment in thyroid diseases remains debated. Long-term, randomized controlled trials are required to determine whether patients with low vitamin D levels are at increased risk of developing autoimmune thyroiditis, and to provide insight into the efficacy of vitamin D as a therapeutic agent for this disease.

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AEP726

Proposal of a predictive scoring system for the accurate diagnosis of Hashimoto's thyroiditis

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Background
The protean and non-specific nature of diagnostic criteria of Hashimoto's thyroiditis leads either to overdiagnosis or underdiagnosis. The aim of this study is to propose a comprehensive diagnostic scoring system based on objective clinic-investigative criteria.
Methods
A case-control study of patients who underwent surgical thyroidectomy, were compared a with a set of clinical, biochemical, pathological parameters in patients with Hashimoto's thyroiditis ($n = 75$) and controls ($n = 75$), in order to design a comprehensive multi-parametric scoring system. We analysed twelve criteria - Age, Sex, goiter grade, associated pathology, duration of disease, euthyroid/ hypothyroid status; family history, presence of auto-immune features, anti-thyroid peroxidase titer, anti thyroglobulin antibody titer, thyroid cytopathological diagnosis of HT, extent of thyroidectomy. All these features were analysed and scored in comparision with histopathology as gold standard. A different validation cohort of 56 patients were reviewed and classified according to the score. Linear correlation and descriptive statistics were performed with SPSS 20.0 version.
Results
The study parameters were dichotomized in to major criteria (euthyroid/ hypothyroid status; family history, presence of auto-immune features, anti-thyroid peroxidase titer, anti thyroglobulin antibody titer, thyroid cytopathological diagnosis of HT) and minor (Age, Sex, goiter grade, associated pathology, duration of disease, extent of thyroidectomy) criteria. Diagnostic accuracy of various combinations of major criteria was – with 6 = 100%; 5 = 100%; 4 = 100%; 3 = 100%, 95%, 85%; 2 = 90%; 1 = 82%. Finally, score of atleast ≥ 3/6 major criteria, with mandatory elevated anti Tg and anti TPO Ab titer was diagnostic of HT. This diagnostic accuracy was statistically significant compared to controls.
Conclusions
This multi-parametric scoring system appears to be a comprehensive, accurate and simplistic in the diagnosis of Hashimoto's thyroiditis and resultant optimal management.
Keywords: Hashimoto's thyroiditis; goiter; histopathology; thyroidectomy; thyroglobulin.

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AEP727

The impact of treatment adherence on the control of the thyroid function in Hashimoto's thyroiditis patients

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Hashimoto's thyroiditis (HT) is a chronic disease that needs a daily substitution by thyroid hormones. The purpose of this study was to assess the level of therapeutic adherence to the hormonal treatment in HT patients and its impact on the thyroid function control.
Methods
It is a cross sectional study including 43 patients treated for hypothyroid Hashimoto's thyroiditis by levothyroxine (LT4). The patient adherence to treatment was evaluated by using the Girerd questionnaire in its Tunisian version. The level of adherence was considered good if the score was equal to 0, medium if it was equal to 1 or 2, and poor if it was equal to 3 or more.
Results
The mean age of the study population was 50.0 ± 12.9 years (41 women and two men). The mean duration of the disease was 7.9 ± 6.3 years. The TSH level was above the therapeutic target in 19% of the patients. The adherence was good in 9% of the patients, medium in 44% of the patients and poor

in 47% of the patients. A TSH level higher than the therapeutic target was found in 0% of subjects with a good therapeutic adherence level, 21% of subjects with a medium therapeutic adherence level and 20% of subjects with a poor therapeutic adherence level ($P = 0.6$).
Conclusion
Poor adherence to hormonal treatment is frequent in HT patients. However, its impact on the control of the thyroid function is uncertain. This, may be explained by the extended half-life of the levothyroxine which is between 6 and 7 days, allowing occasional forgetfulness.

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AEP728

A case of Graves' disease (GD) associated with HIV disease and late immune reconstitution inflammatory syndrome (IRIS) following initiation of antiretroviral therapy (ART)

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GD following ART occurs rarely, in 3% of HIV-infected women[1]. It is suggested that CD4 cells increase in a biphasic pattern following ART initiation, with the expansion of naïve CD4 cells following months after the initial redistribution of memory CD4 cells from lymphoid tissue[2]. A 40-year-old Brazilian lady was diagnosed with HIV in late 2016 following admission with cryptococcal meningitis and salmonellosis, requiring treatment with anti-fungal agents and high dose steroids. Initial CD4 count was 17 cells/μl (540–1660), CD4% 4% (32–60) and HIV viral load was 1804502 copies/ml. Primary adrenal insufficiency was confirmed and treated following presentation with persistent hypotension and fatigue (peak Cortisol post Synacthen of 407 nmol/l, ACTH 111 ng/l (7–63), adrenal and TPO antibodies negative, CT adrenal showed no infiltrative process). ART (emtricitabine/tenofovir, alafenadmide and darunavir/ritonavir) was deferred until five weeks post admission. She developed fevers, vomiting and headaches five days after the initiation of ART, which was attributed to IRIS. 19 months post original diagnosis, she presented with cervical lymphadenopathy (CD4 count 585 cells/μl, undetectable HIV viral load). Following extensive work up, including biopsy, a late IRIS to cryptococcus was diagnosed. High dose steroids resulted in complete resolution of lymphadenopathy. 45 months after ART initiation, she developed symptomatic Graves' hyperthyroidism with weight loss, tremor and hair thinning. Free T4 (FT4) was 28.9 pmol/l (9–20), thyroid stimulating hormone (TSH) <0.01 mIU/l (0.35–4.94) and TSH receptor antibody 3.7 IU/l (< 1.8)). Prior TFTs and thyroid imaging were normal. Family history was negative for thyroid and autoimmune disease. FT4 reduced to 12 pmol/l on carbimazole 10 mg daily. The onset of GD post ART in this case is outside of the reported 12–36 months heretofore documented[2]. We cannot be definitive if the GD was of new onset independent of HIV status or if it occurred as part of an IRIS. However, the diagnosis of documented late IRIS to cryptococcus may suggest that the GD is a consequence of ART immune reconstitution. This case highlights the importance of remaining vigilant for potential endocrine effects that can occur during clinical follow-up in patients following ART initiation.
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AEP729

A case report of ectopic thyroid gland with Hashimoto's thyroiditis

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Introduction
Ectopic thyroid gland (ETG) is a rare developmental disorder, and when occurs in the midline of the neck, it mimics the clinical presentation of thyroglossal duct cyst (TGDC). inadvertent surgical removal of ETG simulating TGDC has been reported in the literature in spite of the modern diagnostic methods for this pathology.[1,2]. We report a case of a 27-year-old female with Hashimoto's thyroiditis of ectopic thyroid in whom a preliminary clinical diagnosis of thyroglossal duct cyst was made clinically and planned for surgery.
Case Report
A 27-year-old female was referred to for evaluation of an anterior upper neck mass that had been present since the age of 6 years without significant change in size. There was no complaint of pain, dyspnea, dysphagia, or voice change and no history of radiation exposure or familial thyroid disease. Patient was evaluated earlier and provisionally diagnosed to have thyroglossal duct cyst and planned for surgery. Preoperative investigation revealed hypothyroidism, so she was referred to our department for the management of hypothyroidism prior to excision. Physical examination showed a palpable rounded smooth mass (3 × 3 cm in size) of rubber-like consistency, that moved upwards on swallowing. It was non-tender, mobile, not attached to overlying skin and skin over the mass was normal. Serologic testing revealed normal FT4 and FT3 of 4.81 pmoL/l, and elevated TSH level of 9.56 mIU/l. Thyroid peroxidase antibodies was strongly positive of 1299 IU/ml. Ultrasonography of the neck revealed a solid soft-tissue mass with diffuse heterogeneous echotexture corresponding to the palpable lesion. The thyroid gland was not visualized in the normal thyroid position. A 99mTc Pertechnetate SPECT/CT Scan showed a single focus of radiotracer uptake anteriorly n the submental region at the site of the palpable mass (Fig 2). There was no evidence of other functioning thyroid tissue in the lower neck region or in other ectopic position. The diagnosis of midline neck ectopic thyroid with subclinical hypothyroidism and Hashimoto's thyroiditis was made. Replacement with L-thyroxine 50 mcg/day was started and no surgery was performed. On follow-up, patient is doing well, her TSH was 4.3 miU/ml with slight reduction in the size of the ectopic thyroid.

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AEP730

Intravenous thyroxine administration in hospitalized patients, a common but unreported practice: A single institution recent experience

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Background
Intravenous levothyroxine (IVT4) is FDA-approved for the treatment of myxedema coma (ME). We noticed that at our hospital, IVT4 is administered more frequently than expected.
Aim of study
To assess the extent of IVT4 administration, the indications for such a treatment, and its outcome at a tertiary facility.
Methods
A retrospective study of IVT4 administered to adult inpatients at Tel Aviv-Sourasky Medical Center between 01/2017 and 07/2020. Patients' charts were searched for relevant clinical and laboratory data.
Results
107 patients (62 W/45 M), age 62.5±17.3 y (range 20–97) received IV T4, in the course of 113 hospitalizations. 94 subjects had primary hypothyroidism (PH), 10 had central hypothyroidism, while 3 subjects had no documented evidence of hypothyroidism. ME was likely *in only 4 cases* (3.5%). The leading stated indication for IVT4 was profound hypothyroidism in 57 instances (50.4%), jeopardized enteral route in 11 (9.7%), while no obvious indication was found in 39 cases (34.5%). In subjects with PH, median serum TSH prior to treatment was 36.4 mIU/l (IQR 8–42), while free T4 was 0.4 ng/dl (IRQ 0.22–0.61, normal 0.8–1.7). In subjects with no ME, altered consciousness was present in 19%, bradycardia in 6.3% and 4.5% were hypothermic. The median initial dose of IV-T4 was 150 mg (range 20−500). Repeated administrations ranged from 1 to 29 times, with a median cumulative dose of 250 mg (IQR 150−400, range 20−3300). We could not identify adverse events directly attributable to IV-T4. Of the 113 admissions, 61 ended in patient's recovery and discharge (54%), 22 (19.5%) in transfer to a rehab or nursing facility, while there were 30 cases of death (26.5%). Only one of the 4 patients with presumed ME died. In a logistic regression model, that also included age, gender, and ICU admission, the only variable that significantly predicted death was a need for artificial ventilation (OR:27.8, CI 3.5−189). In contrast, free T4, TSH, hospitalization

length, altered consciousness, and other potential variables, were excluded from the equation.
Conclusions
IVT4 administration is a common practice at our hospital. In a small minority of cases (13.2%), it is given for approved clinical conditions, while in all the others it appears to be unjustified. Reports on this practice are all but absent from the literature. Studies from other institutions are needed to determine its global extent, safety, and efficacy. Until it is proven safe and cost-effective, greater caution should be exercised before allowing it.

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AEP731

Hypothyroidism in the elderly: clinical and therapeutic aspects

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Introduction
Hypothyroidism (HT) is widespread in all age groups particularly within the increasing elderly population while its diagnosis is challenging owing to extremely varied and atypical symptoms. The objective of this study is to outline the clinical and biochemical features of HT and determine its main etiologies in a geriatric population.
Methods
We reviewed the medical charts of 53 patients aged 65 years and over, who had been diagnosed with HT and hospitalized between 2009 and 2019 at the endocrinology department of Hedi Chaker university hospital, Sfax, Tunisia.
Results
The mean age of our sample was 72.7±5.5 years with a female predominance (sex ratio=1.94). A medical history of ischemic cardiopathy or arrhythmia was found in 18.86%. HT was diagnosed based on the worsening of some "usual" aging-related symptoms such as asthenia (81%), cognitive and psychomotor limitations (77%), constipation (50%), dry skin (47%), hearing loss (19%), and myalgia (17%). A goiter was encountered in 23%. Complicated forms seem to be more frequent in seniors than in younger patients for insistence: myxomatous coma (1.88%), pericarditis (7.55%), and hypothyroid myopathy (5.66%). At diagnosis, the mean TSH and T4 levels were 68.13±55.24 mUI/l and 6.11±1.2 pmol/l, respectively. Subclinical hypothyroidism (SCH) was detected in 9.43% with a mean TSH level of 6.9 mUI/l. Lipid metabolism was troubled in 39.62% of cases with a mean total-cholesterol and triglycerides levels of 5.06±1.49 and 1.83±1.24 mmol/l, respectively. Rhabdomyolysis and hyperuricemia were observed consecutively in 23% and 13% with mean uric acid and Creatine phosphokinase levels of 1060±112.1 UI/l and 326.4±95 µmol/l, successively. Anemia was underlined in 60% and the normocytic form in 43% with a mean hemoglobin rate of 10.75±2 g/dl. Leading etiologies of HT were: autoimmune thyroiditis (81%), amiodarone use (9%), total thyroidectomy (6%), and radioactive iodine therapy (2%). Considering the severity of HT, a hormone replacement therapy (HRT) by stepwise approach was adopted by increasing the dosage by 12.5 µg every three days reaching a mean thyroxine dose of 109.57 µg/day. The evolution was favorable in all patients excepting one senior who developed atrial fibrillation during HRT. We opted for HRT in patients having SCH associated with goiter and/or positive thyroid autoantibodies.
Conclusion
Hypothyroidism should be screened for in the elderly in front of cognitive and functional changes even those usually attributable to aging. HRT must be conducted gradually and carefully considering the frailty and cardiovascular comorbidities to target an age-appropriate TSH range (age/10 mUI/l).

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AEP732

Pulmonary embolism and pulmonary arterial hypertension: Atypical complication of hyperthyroidism

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Introduction
Basedow disease is the most common etiology of hyperthyroidism; the cardiac manifestations seen in hyperthyroidism often affect people over 60 years of age, manifested mainly by sinus tachycardia, atrial rhythm disturbances or increased cardiac output. Pulmonary arterial hypertension and pulmonary embolism are atypical manifestations.
Observation
39-year-old patient, followed for basedow disease for 14 years on carbimazole 20 mg/day, Basedowian orbitopathy for 2 years having received corticosteroid boluses. Clinically, the patient presented with bilateral exophthalmos, sinus tachycardia, tremors, and pretibial myxedema. Palpation found a homogeneous goiter. TSH was collapsed with T4L at 0.7 µg/ml and positive TSH receptor antibodies 40 IU/l. During hospitalization, the patient developed dyspnea. The cardiac ultrasound revealed significant pulmonary hypertension at 73 mmHg, and increased cardiac output. A pulmonary CT angiogram revealed a bilateral basal sub-segmental pulmonary embolism with the presence of a submerging thyroid goiter. The patient was put on LMWH curative dose with good clinical outcome. The dose of carbimazole was reduced to 10 mg/day.
Conclusion
Basedow disease, a potentially serious endocrinopathy, leads to a prothrombotic and hypofibrinolytic state. This observation underlines the importance of determining the place of this risk factor within the various risk factors of thrombotic disease already known and the need to put in place preventive strategies for thrombosis.

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AEP733

Endocrinologists' choice of levothyroxine formulation in hypothyroid and euthyroid patients in the republic of belarus

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Background and aims
In the Republic of Belarus treatment of hypothyroidism in the adult population is regulated by the order of the Ministry of Health dated 2013. Levothyroxine is available in tablet form (dosage in increments of 25 µg). Liothyronine are not registered in the Republic of Belarus, but patients can purchase them on their own abroad. Thus, the aim was to study of possible endocrinologists' preferences of choosing the levothyroxine formulation.
Materials and methods
From 01.10.2020 to 26.12.2020 there was survey using THESIS questionnaire: Treatment of Hypothyroidism in Europe by Specialists: International Survey (Russian version). 210 members of Belarusian Public Medical Association 'Endocrinology and Metabolism' received the mailing with questionnaire in Word and Excel formats, agreed to participate and filled out the questionnaire. Taking into account the duration of medical practice for more than 5 years, the experience of working with patients with hypothyroidism and the mandatory specialization as an endocrinologist, 146 doctors were included in the study.
Results
132 (90.4) women and 14 (9.6%) men responded. LT4 as the first choice of the hypothyroidism therapy indicated 99.3% (145) respondents, and 0.7% (1) LT4 and LT3 combination. there was Clinical experience in prescribing LT3 was identified in 3.4% (5 persons), desiccated thyroid – 0.7% (1 person), LT4 and LT3 combination – 6.2% (9 persons). The LT4 and LT3 combined may be used in following cases: for a short period, in patients recovering from protracted hypothyroidism – 41.8% (61 responses), in patients with normal serum TSH and hypothyroidism symptoms – 10.3% (15 responses), in hypothyroid patients with normal serum TSH and unexplained weight gain – 1.4% (2 responses); never be used – 46.5% (68 responses). General clinical experience shows next form of LT4 is better absorbed: tablets 64.4%

(94 responses), soft-gel capsules 4.1% (6 responses), liquid solution 4.1% (6 responses), no major changes with different formulations 27.4% (40 responses). Choice of levothyroxine formulation in patient who self-reports intolerance to various foods raising: tablets – 55.5% (81 responses), soft-gel capsules – 14.4% (21 responses), liquid solution – 14.4% (21 responses), no major changes –21.2% (31 responses). Choice of levothyroxine formulation for patient who has unexplained poor biochemical control of hypothyroidism: – tablets 78.8% (115 responses), soft-gel capsules –7.5% (11 responses), liquid solution 4.8% (7 responses), no major changes 17.1% (25 responses).

Conclusions

Based on general clinical experience, it is possible to use combination therapy with the introduction of both LT4 and LT3. The preference for alternative forms varies with clinical situations.

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AEP734

Possible causes of hypothyroidism symptoms in euthyroid patients - an endocrinologist opinion study in the republic of belarus

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Background and aims

It has been reported that some patients with hypothyroidism treated with levothyroxine continue to experience persistent symptoms despite normal serum TSH. Thus, the aim was to study of causes of hypothyroidism symptoms in euthyroid patients.

Materials and methods

From 01.10.2020 to 26.12.2020 there was survey using THESIS questionnaire: Treatment of Hypothyroidism in Europe by Specialists: International Survey (Russian version). 210 members of Belarusian Public Medical Association 'Endocrinology and Metabolism' received the mailing with questionnaire and agreed to participate. 146 endocrinologists with the medical practice for more than 5 years, the hypothyroidism working experience were included in the study.

Results

Persistent hypothyroidism symptoms despite normal serum TSH and levothyroxine treatment has been reported by 88.4% (129 persons) respondents. 52.1% (76 persons) respondents notice the symptoms in less than 5% of patients, and 32.9% (48 respondents) in 6–10% patients. Possible clinical conditions for thyroid hormone treatment in euthyroid subjects were admitted: unexplained fatigue – 7.5% (11 responses), obesity resistant to life-style interventions – 7.5% (11 responses), as a complementary treatment in severe hypercholesterolemia – 8.2% (12 responses), depression resistant to anti-depressant medications – 8.2% (12 responses), female infertility with high level of thyroid antibodies – 34.2% (50 responses), simple goiter growing over time – 24.7% (36 responses), treatment is never indicated for euthyroid patients – 57.5% (84 responses). Doctors who did not prescribe levothyroxine for normal TSH were comparable in gender (8 (5.5%) men vs 76 (52.0%) women, χ^2= 0.00001, p=0.975), age (under 40 years 23.3% (34) vs over 40 years 34.3% (50), χ^2= 0.046, P = 0.829) and medical experience (< 10 years in medical practice – 16.4% (24) vs > 10 years – 41.1% (60), χ^2= 1.090, p=0.296). Using score range of likely causes from 1 (most likely) to 8 (least likely) explanations for persistent symptoms in patients with normal TSH were identified: psychosocial factors – 2 (1–4) score, comorbidities 2 (1–4) score, chronic fatigue syndrome – 2 (1–4) score, the burden of chronic disease– 2 (1–4) score. The least likely explanations were inability of levothyroxine to restore normal physiology – 8 (7–8) score and the burden of having to take medication – 8 (6–8) score. As neutral factors were assessed patient unrealistic expectations (4 (2–6) score) and presence of underlying inflammation due to autoimmunity (6 (4–8) score).

Conclusions

Despite the appointment of levothyroxine, symptoms of hypothyroidism in such patients are noted by 88.4% of endocrinologists, that is probably due to psychosocial factors, comorbidities, chronic fatigue syndrome and the burden of chronic disease.

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AEP735

Block-replace therapy in the management of Graves' disease

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Introduction

Anti-thyroid drugs (ATDs) are the first line treatment in Europe for hyperthyroidism due to Graves' disease (GD). Adding levothyroxine to ATDs, so called block and replace therapy (BRT) is still controversial.

Aim

To follow up the outcomes after treating patients with Graves' disease in a block and replace regimen.

Patients & methods

A prospective study which enrolled 33 patients with Graves's disease, from 1st January 2020 until 28th January 2021. Inclusion criteria were: age > 18 years, new diagnosis of hyperthyroidism due to GD, patients with GD following block and replace therapy. Exclusion criteria were: age<18 years, pregnancy, GD treated with radiotherapy or surgical. Recorded data at diagnosis and each visit in the hospital were regarding to thyroid function tests (TSH (N:0.5–4.5 mUI/l), fT4 (N:9–19 pmol/l), T3 (N:80–200 ng/ml)) and specific thyroid antibodies (TRAb (N:<1.75 IU/l)), thyroid ultrasonography, level of 25OH-vitamin D. Data were recorded in Microsoft Excel and analyzed in Minitab v19.

Results

28 women, aged 44.32±12.54 years and 5 men, aged 54.6±18.6 years were included. New diagnosis of GD was made for 16 women and 4 men, the rest of them were already in a BRT. The group was characterized by insufficient levels of vitamin D (mean: 20.35±9.19 ng/ml, range 7.1–35 ng/ml). At diagnosis: TSH=0.0076 ±0.0107 mUI/l; TRAb=16.2±11.8 UI/l. BRT had a mean dose of 18±17.85 mg per day of Methymazole and 38.24±23.58 mg/day of Levothyroxine. From diagnosis to first visit in a BRT, fT4 decreases from a mean of 38.6±23.2 pmol/l to 14.59±8.31 pmol/l (P < 0.05), but it was in normal range. During BRT, TRAb titer decreased from 11±13.3 UI/l at first visit to 8.6±13.3 UI/l at the second visit in the Institute. One patient had adverse reaction to Methymazole so she was switch to Propylthyouracil. The volume of thyroid gland measured by ultrasound was 25.35±13.03 cm^3. Twelve patients associated Graves' ophthalmopathy, but only two of them needed steroids.

Limitations

Small number of patients, limited time for observation, heterogeneous group (patients newly diagnosed with GD, patients in BRT for more than 6 months).

Conclusion

BRT can maintain normal levels of TSH and fT4 and can decrease TRAb levels using combined Methymazole and Levothyroxine.

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AEP736

Nutritional status of iodine in the basque country

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Background

Iodine is an essential nutrient necessary for the synthesis of thyroid hormones. Humans need a daily intake of 90–250 μg per day. The WHO criteria on the adequate iodine intake in the general population is: median iodine 100–199 μg/l, levels <100 μg/l in <50% of the population; <50 μg/l in <20% of the population and iodized salt consumption in >90% of households.

Objectives
The aim of this study was to establish the nutritional status of iodine in the adult population of the Basque Country, measured by the excretion of iodine in the urine.
Methods
Randomly selected participants from the study of the incidence of diabetes in the adult population (18–90 years old) in the Basque Country (2017–2018) were invited to take part in this observational study. Of the 847 selected participants, 409 provided a urine sample for the study. Ioduria was determined by chromatography. Clinical, sociodemographic and laboratory data were obtained, including thyroid hormones. All participants completed a lifestyle and eating habits survey.
Results
The mean age was 58 years old and 57.5% of the participants were women (235/409). The mean ioduria was 159 μg/l (SD 106) and the median 133 μg/l (P25-P75: 90–204 μg/l). Based on the WHO criteria, 40% of the population had an adequate iodine intake, 32% a deficit of iodine and 28% excessive levels. There were no significant differences in ioduria regardinggender, age or geographic location. Only 41% of the study population confirmed they take iodized salt.
Conclusion
According to our study, the population of the Basque Country has an adequate intake of iodine; however, the intake of iodized salt is well below the 90% recommended by the WHO. We therefore believe that public health campaigns are necessary to promote the consumption of iodized salt in our population, as well as periodic evaluations of the nutritional status of iodine.

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AEP737

Thyrotoxic crisis induced by amiodarone therapy

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Background
Thyrotoxic crisis (TxC) is a medical emergency status needed rapid diagnostic a urgent treatment, presented by failure or multiorgan dysfunction. Amiodarone induced thyrotoxicosis (AIT) is one of the severe complications caused by amiodarone therapy.
Aim
Analysis of patients suffered from thyrotoxic crisis induced by Amiodarone therapy, with focus on clinical picture, laboratory findings and therapeutic options.
Methods and results
A total of 35 consecutive patients with AIT during the period 2005–2019 were included. We performed retrospective analysis of 4 consecutive patients with thyrotoxic crisis, who were hospitalized on department of Internal Medicine University Hospital Banska Bystrica. All of patients were men (mean age 55 ± 4.7 years), All of analysed patients (n = 4) have been treated for arterial hypertension, 25% (n = 1) ischaemic heart disease, 50% (n = 2) suffered from heart failure and 50% (n = 2) had implantable cardioverter defibrillator. Indication for Amiodarone therapy was atrial fibrillation (n = 2) and ventricular tachyarrhythmias (n = 2). The average time of use of amiodarone until development TxC was 937 ± 241 days, median 883 days. Mean TSH in the time of diagnosis was 0.007 ± 0.06 mIU/l and mean free T4 was 55.0 ± 16.1 pmol/l (median 59 pmol/l). Mean volume of thyroid gland was 22.21 ml. Three pacients have been diagnosed as mixed type AIT, and the one of threm as AIT type 2. All of patients (n = 4) have been treated with antithyroid drugs and corticosteroids at the maximum recommended doses. 75% (n = 3) underwent urgent thyroidectomy and one was threated conservatively. The thyroid papillary microadenocarcinoma was histologically confirmed in 1 of observed patients. When comparing the two cohorts with and withoud TxC, we found that patients with TxC are 8 years younger, have higher fT4, larger volume of thyroid. The dose and duration of Amiodarone use did not differ in both groups.
Conclusion
Thyrotoxic crisis induced by Amiodarone is an endocrine emergency which is charecterized by multiple organ failure due to sever thyrotoxicosis. Risk factors of thyrotoxic crisis development in patient with AIT are: younger age, higher fT4, larger volume of thyroid, atrial fibrillation and heart failure.

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AEP738

Hyperparathyroidie primary & pregnancy : A case report

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Introduction
Parathyroid diseases are infrequent during pregnancy, but produce significant perinatal morbidity and maternal mortality if not diagnosed and properly managed. Primary hyperparathyroidism (PHP) is a rare disease in women of childbearing age. The incidence of the disease is unknown, but it is certainly rare, and most of the reported cases have been simple supplemented by a review of the literature.
Case presentation
We report the case of a 34 year old woman, G4P0 (03 caesarean section), pregnant at 19 weeks of amenorrhea, presents to the consultation for asthenia and a polyuro-polydipsic syndrome accompanied by muscle weakness. Biological data show hypercalcemia at 112 mg/l (81–104), hypophosphoremia at 22 mg/l (25–48), PTH 163 pg/ml (15–65) compared to a normal vitamin D with hypercalciuria at 922 mg/kg/24 h (100–300). Cervical ultrasound reveals a homogeneous highly hypoenogenic left lobar formation of irregular contours measuring 10.2 × 9.7 × 12.5 mm consistent with a parathyroid adenoma, with thyroid gland and left parathyroid lodge without abnormality. These data are therefore in favour of primary hyperparathyroidism on parathyroid adenoma. Abdomino-pelvic ultrasound: no visible lithiase, unpasceded excretory cavities. The patient benefits at 20 weeks of amenorrhea from the surgical exenosia of the left parathyroid adenoma under complicated local anesthesia of a left recurrent paralysis, anatomopathological analysis in favor of a parathyroid adenoma. Calcemia normalizes rapidly after surgery, and the patient gives birth without complication at 39 weeks of amenorrhea.
Discussion
The prevalence of primary hyperparathyroidism during pregnancy is unknown. Etiology is in 85% of reported cases, a unique parathyroid adenoma. Diagnosis is difficult due to physiological changes in pregnancy that can mask the clinical and biological symptoms of hypercalcemia (digestive disorders, hemodlution, hypoememia). Surgical exeresis is usually proposed in the second trimester of pregnancy when calcemia is greater than 2.75 mmol/l despite medical treatment, and represents an acceptable therapeutic solution as evidenced by favourable clinical-biological evolution of the mother and fetus without major complications due to surgery.
Conclusion
Primary hyperparathyroidism during pregnancy is rare, but needs to be researched in the face of a clinical presentation associated with hypercalcemia, in order to rapidly establish appropriate treatment, and reduce the risk of maternal and fetal complications

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AEP739

Thyroid cancer detection in routine clinical setting-pilot study

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Background
Most thyroid nodules are benign, but therefore it is crucial to correctly stratify the malignancy risk of nodules to avoid unnecessary invasive procedures and/or surgery, but and still identify aggressive tumors. The aim of our study was to address the potential for improvement of malignancy detection in routine clinical setting using clinical examination, risk stratification of thyroid nodules on ultrasound using the American College of Radiology Thyroid Imaging Reporting and Database System (ACR TI-RADS) and fine-needle aspiration cytology (FNAC) concurrently with molecular diagnostics.
Methods
A prospective study in 105 patients was performed. DNA from FNA samples was used for next generation sequencing to identify mutations in genes: BRAF, HRAS, KRAS, NRAS and TERT. RNA was used for Real Time

PCR to detect RET/PTC1, RET/PTC3 and ETV6/NTR3 rearrangements. All specimens were histologically confirmed. Multivariate regression (a method of orthogonal projections to latent structure, OPLS) was used for data evaluation.
Results
FNA samples were cytologically evaluated as Bethesda II (n = 16; 15.2%), III (n = 23; 21.9%), IV (n = 18; 17.1%), V (n = 24; 22.9%) and VI (n = 24; 22.9%). Histologically, 48 findings were malignant (45.7%); especially papillary thyroid carcinoma (93.8%); 54 were benign and 4 were borderline tumors (MB). Total detection rate of mutations was 4/54 in benign tissues, 41/48 in malignant and 1/4 in MB. Total detection rate of mutations was 4/16 in Bethesda II; 6/23 III; 3/18 IV; 14/24 V and 20/24 VI. The strongest relevant positive predictors for malignancy were the presence of genetic mutation (t-statistic = 14.10; $P < 0.01$), FNAC (10.39; $P < 0.01$), ACR TI-RADS (4.02; $P < 0.01$), positivity of anti-thyroglobulin antibodies (4.09; $P < 0.01$), TSH (3.6; $P < 0.01$), presence of neck resistance (2.86; $P < 0.05$) and lymphadenopathy (2.33; $P < 0.05$). In common, FNAC, ACR TI-RADS and genetic testing reached sensitivity 86.3% (95% CI 74.3–93.2), specificity 88.9% (95% CI 77.8–94.8) and diagnostic odds ratio 50.3 (15.7–161.2).
Conclusion
FNA molecular testing has seemed to have substantial potential for thyroid malignancy detection. Clinical examination, FNAC and risk stratification of thyroid nodules on ultrasound have been other relevant factors. However, a broader spectrum of molecular markers must be involved to make correct diagnosis in all patients in a routine clinical setting.

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AEP740

Medullar thyroid carcinoma in a patient with Hashimoto's thyroiditis – A case report

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Introduction
Hashimoto's thyroiditis (HT) has been linked to papillary carcinoma of the thyroid, Hurthle cell cancer or even lymphoma. In contrast, there are only a few reports of co-existence of HT with medullary thyroid carcinoma. The link between them is unknown. An overall prevalence of medullary carcinoma of only 0.35% has been reported in HT patients. This prevalence is higher in female rather than male. We present the case of a female patient treated for Hashimoto's Disease that was diagnosed with medullary thyroid carcinoma during her routine medical appointment with the endocrinologist.
Case description
The patient, female of 45 years first came with headache, hair loss and extreme fatigue. She was diagnosed previously with chronic thyroiditis and was under treatment with Levothyroxine. Her physical examination did not reveal anything in particular. Her blood tests were as followed: CEA 126 ng/ml (<6.3), Calcitonin > 2000 pg/ml (<10), TG 64, TSH 14.58 (0.3–4.5), fT4 14.04 (9–20), TPO antibody 874.6 (0–30) and TG antibody 2229 (<115). Other laboratory tests were within normal range. Neck ultrasound revealed: the thyroid gland had heterogeneous hypoechoic structure, aspect HT. In the right lobe, it was evident a nodule, isoechoic, taller than wide, with dimensions 2.44 × 2.16 × 1.9 cm, with diffuse micro calcifications inside. Schinti scan with TC99 revealed a cold nodule in the right thyroid lobe. Patient's past medical history: was unremarkable, without neck irradiation. Family history: without thyroid diseases. The patient underwent total thyroidectomy and lymph nodes dissection. Histopathological examination of total thyroidectomy specimen revealed Hashimoto's thyroiditis along with medullary thyroid carcinoma, oncocytic variant inside the nodule. She was discharged from the hospital under thyroid hormone replacement treatment. A month after surgery, Calcitonin and CEA levels dropped sharply. Their measurements were repeated after 3, 6, 9, 12 months and resulted normal. The patient continues to be under endocrinologist's follow up, euthyroid and cancer-free.
Conclusion
The prevalence of the co-existence of Hashimoto's thyroiditis and medullary thyroid carcinoma is low and rarely described. It is important to know this, in order to be diagnosed and treated in time.

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AEP741

Cardiovascular outcome in thyroid cancer patients with thyroidectomy: a systematic review and meta-analysis

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Thyroid dysfunction is associated with increased risk of cardiovascular disease (CVD) in general population, but it remains controversial whether the treatment of differentiated thyroid cancer (DTC) including thyroidectomy and thyroid stimulating hormone suppression add any risk of CVD compared to general population. We performed a systematic review of observational studies reporting associations between DTC and CVD in MEDLINE, EMBASE, Web of Science and other source (PROSPERO: CRD42020223057). We excluded studies with CVD evaluated as a comorbidity prior to thyroid cancer diagnosis or those with active surveillance without thyroidectomy. Risk of bias was assessed by ROBANS version 2.0. Risk estimates were pooled using random-effects and fixed-effects models when ≥ 3 studies reported data for each outcome. Eighteen studies were included. Compared to general population, DTC was associated with higher risks of atrial fibrillation (pooled risk ratio (RR) 1.55 [95% confidential interval (CI) 1.41–1.71]), coronary artery disease (RR 1.09 [1.01–1.17]), and cerebrovascular accident (RR 1.14 [1.09–1.20]), but not heart failure (RR 0.96 [0.78–1.18]) nor all-cause mortality (RR 1.31 [0.81–2.11]). To elucidate the direct effect of treated DTC on cardiovascular disturbance, clinical, echocardiographic, and hemodynamic parameters were also analyzed. DTC was associated with the higher heart rate (standardized mean difference [SMD], 0.34; 95% CI, 0.15–0.56; P = 0.002) and left ventricular mass index (SMD, 0.66; 95% CI, 0.43–0.90; $P < 0.00001$) and lower E/A ratio (SMD, −0.42; 95% CI, −0.79–0.05; P = 0.03), but not with ejection fraction nor blood pressure. In conclusion, results suggested possible association between DTC and the higher risk of CVD and atrial fibrillation as well as increased heart rate and left ventricular mass. A large prospective study with long term follow-up is required to confirm the association of two disease entities.

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AEP742

Anomalous uptake of 131-iodine in an endometriosis cyst

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Introduction
Radioiodine whole-body scintigraphy plays an important role in the follow-up of patients with differentiated thyroid carcinoma (DTC), as it is highly accurate in detecting thyroid residues and recurrent disease. Unusual 131-iodine uptake outside the thyroid bed and areas of physiological uptake is strongly suggestive of distant metastasis. However, uncommon uptake may occur and lead to diagnostic errors.
Case report
A 45-year-old woman with a history of DTC underwent total thyroidectomy and dissection of the involved lateral neck compartment in 2005. The anatomopathological examination revealed papillary thyroid right lobe carcinoma with 25 mm - pT1b N1a Mx (8th Edition AJCC TNM Staging). She received two 131-iodine treatments in 2005 and 2006. The second post treatment whole-body scan showed a focal uptake in the left pelvic cavity. A CT scan and transvaginal ultrasound were performed, that showed a 5.6 cm cystic lesion in the left ovary. She underwent total hysterectomy and bilateral adnexectomy in 2007. The histological examination revealed an endometriosis cyst. A radioiodine whole-body scan was performed a year later and there were no areas of abnormal uptake. The patient is being kept under surveillance with no evidence of recurrent disease.
Discussion
We present a case of unusual 131-iodine uptake in the pelvic region, originated by an endometriosis cyst in the left ovary. This entity is a rare cause of incidental uptake of iodine-131, whose mechanism is not yet

completely understood. Anomalous uptake in the pelvic region requires a gynaecological evaluation and complementary tests.

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AEP743

Is there a role of measuring preoperative serum thyroglobulin?

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Introduction
The measurement of serum thyroglobulin (Tg), a glycoprotein produced exclusively by follicular thyroid cells, is an important tumour marker used in the follow-up of patients with differentiated thyroid carcinoma (DTC) and residual or recurrent disease. However, its role as a screening tool before thyroid surgery is not yet defined, as benign conditions can result in its increase.
Objective
The aim of this study was to retrospectively assess whether there is a relationship between high preoperative serum Tg levels and thyroid carcinoma patients undergoing thyroid surgery.
Material and methods
Retrospective review of the medical records of patients who underwent thyroid surgery in our Institution for nodular goitre, whose serum Tg levels were assessed preoperatively.
Results and conclusions
Thirty-three patients (22 female/11 male) were identified, with a mean age of 51.7 ± 15 years. Twenty-seven (81.8%) underwent total thyroidectomy and six (18.2%), lobectomy alone. High levels of serum Tg were identified in 23 patients: 13 patients (56.5%) among 23 with malignant histopathological features and in 10 patients (43.5%) among 13 with benign histology (P = 0.143). Among four patients with higher Tg levels (Tg > 1000 ng/ml), only one had a malignant histology. Preoperative elevated levels of serum Tg showed a 56.5% sensitivity, 15.4% specificity, a positive predictive value of 54.2% and a negative predictive value of 16.7% in detecting DTC. In conclusion, there was no statistically significant association between preoperative serum Tg levels and the diagnosis of thyroid carcinoma. These results confirm the current recommendations in the management of patients with nodular thyroid disease.

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AEP744

Coexistence of primary hypothyroidism and hypopituitarism due to pituitary adenoma – pitfalls during levothyroxine supplementation

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95% of all cases of overt hypothyroidism are primary. It is defined as low levels of blood thyroid hormone due to disorder of the thyroid gland causing decreased synthesis and secretion of thyroid hormones. Levothyroxine is recommended as the preparation of choice for the treatment of this disease. The therapy should eliminate the symptoms of hypothyreosis, lead to the normalization of thyroid axis hormones and the avoidance of iatrogenic thyrotoxicosis. Serum TSH is the parameter recommended to monitoring the treatment. The target serum TSH depends on patient age and underlying comorbidities.[1,2]. Sometimes, such monitoring may be insufficient. We report the coexistence of primary hypothyroidism and pituitary insufficiency due to pituitary adenoma.
Case report
The patient underwent total thyroidectomy due to giant goiter (histopathological examination excluded neoplasm of thyroid gland) in 2008 year. Postoperative hypothyroidism was treated successfully. The TSH level was stable within limits (1–3 uIU/ml) on levothyroxine dose 150 and 125 μg alternately. In 2018, the TSH level was decreased (TSH <0.05 uIU/ml).The patient was asymptomatic. His weight was unchanged. There were no new medications, supplements or mistakes in levothyroxine treatment. The dose of the drug was reduced to 125 mg. The control results reveled the level of TSH,ft3 and ft4 below the normal range. The patient was admitted to the hospital. The diagnostic test revealed low levels of cortisol, ft4, ft3, testosterone,LH,GH. An MRI scan showed a 34x39x39 mm pituitary adenoma. Unfortunately, ischemic stroke complicated hospitalization, so surgery was delayed. In 2019, the patient underwent transsphenoidal tumor resection. Hydrocortisone and levothyroxine 150 μg were used as replacement therapy. Ft4 levels normalised, TSH level was 0.3 uIU/ml and ft3 remained low due to NTIS.
Conclusions
We should measure ft3 and ft4 during the monitoring of primary hypothyroidism treatment, especially when TSH level declines. TSH levels lowering during the monitoring of primary hypothyroidism treatment may be the marker of concomitant hypopituitarism.
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AEP745

Secondary intrathyroid localization of bronchial micro- papillary carcinoma

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Objective
To highlight the diagnostic difficulties that a pathologist may encounter in identifying intra-thyroid metastasis when the primary cancer is not known.
Case report
A 73-year-old woman with no specific pathological history, admitted for the management of a right mean spinal swelling that had appeared two months earlier and is gradually increasing in size. The evolution was marked by the association of dyspnea and discomfort to swallowing but without signs of thyroid dysfunction. On physical examination, the thyroid lodge was free. No neck nodes are palpable. Ultrasonography of the neck showed multiple jugular-carotid and sub-digastric right glands and thyroid nodule isthmic 8 mm. A lymph node biopsy concluded to a lymph node metastasis of partly papillary carcinoma compatible with thyroid origin. The Patient had a total thyroidectomy with a bilateral recurring and straight functional neck dissection with simple operating suites. The anatomopathological examination with immunohistochemistry concluded to a thyroid metastasis of a pulmonary-induced micropapillary carcinoma. Thoracic CT showed multiple parenchymal nodules and two focal areas of right basal pulmonary parenchymal condensation.A bronchial endoscopy with biopsy showed bronchial adenocarcinoma in its micropapillary variant. The patient received 3 chemotherapy cures based on cysplatyl and Vepeside with good evolution.
Conclusion
The frequency of intrathyroidal metastases are probably underestimated. The examination of the thyroid and a fine needle aspiration cytology at the slightest doubt represents a logical course of action. Thyroidectomy, when possible, improves patient survival. The prognosis depends on the primary lesion and the uni- or multi-visceral character of the metastasis.

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AEP746

Case report: Inaugural diabetic ketosis revealing hyperthyroidism

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Introduction
Secondary diabetes mellitus is seen in 10 to 70% of cases depending on the endocrinopathy involved; it can be indicative of the disease and often associated with other metabolic disorders. We report the case of a patient with inaugural diabetic ketosis revealing hyperthyroidism.

Case report
It's a 42-year-old patient with a history of gestational diabetes not followed 5 years ago, with diabetic inheritance in the brother and sister profile T2DM. Accepted for inaugural ketosis. On examination: the symptoms go back to 4 months with the onset of polyuropolydipsic syndrome with 3 nocturnal awakenings associated with urination burns and vaginal pruritus. The clinical examination revealed a goiter at the expense of the right lobe. The patient was in ketosis with normal renal and hepatic function, the infective workup is negative and the thyroid workup demonstrated hyperthyroidism with TSH at 0.01 mIU/l, T4 at 19.8 pmol/l and T3 at 7 pmol/l. Cervical ultrasound showed multiple nodules in the goiter classified as EU-TIRADS 4.3 and 2. Management of diabetes consisted of correcting ketosis and putting on premix insulin. As well as a treatment of the etiology, synthetic antithyroid drugs dose of 20 mg/day. A fine needle aspiration of the nodules is planned.
Conclusion
Diabetes mellitus secondary to endocrinopathy is not that rare. The physiopathological mechanisms are diverse. In the presence of clinical manifestations giving rise to strong suspicion of an underlying endocrinopathy, the latter should be actively sought so as not to intensify the antidiabetic treatment without treating the primary disease.

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AEP747

Agranulocytosis due to antithyroid drugs : A case report

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Introduction
Hyperthyroidism is a very common disease due to an overactive thyroid gland. Antithyroid drugs (ATD) represent the first line treatement. Their side effects can be severe and even potentially fatal. Among them, agranulocytosis, defined as an absolute neutrophils count less than 500/µl is the most feared one.
Observation
We report the case of 57 year-old woman with no medical history, recently diagnosed with hyperthyroidism due to Grave's disease (Anti R-TSH antibodies 19.2 UI/l). She was put under thiamazol and beta-blockers treatement. One month later, she consulted for fever (40°C), a poor state of health, labial herpes, buccal aphthous and a sore throat. The blood count revealed a leucopenia at 1660 /µl, an agranulocytosis at 0/µl and an anemia at 8.4 g/dl. The CRP level was high at 77 mg/dl. Four blood cultures were performed with a normal result, and the cytobacteriological examination of the urine as well as the chest x-ray and the abdominopelvic ultrasound did not show any abnormalities. The bone marrow biopsy concluded to a toxic agranulocytosis due to the antithyroid treatement. The thiamazol was immediately interrupted and the patient received antibiotherapy and granulocyte colony-stimulating factor (G-CSF). After 10 days of treatement, the blood count improved significantly with a white blood cell level at 13290/µl and a polynuclear neutrophils level at 10170/µl. Thus, all antithyroid drugs are contraindicated in this case and the patient benefited from a radioactive iodine therapy and she is currently with hypothyroidism.
Conclusion
Even though agranulocytosis is a rare complication that occurs in around 0.2–0.5% of patients under ATD, it can be life threatening. There for blood count surveillance before and after the initiation of the ATD is the key to an early diagnosis and an effective treatement.

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AEP748

Paraneoplastic hyperthyroidism in hCG-secreting metastatic testicular cancer

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Introduction
We report a case of severe thyrotoxicosis due to a metastatic testicular tumor secreting human chorionic gonadotropin (hCG), known to have a TSH-mimicking effect due to alpha-subunits' structural similarity.
Case report
In November 2020 a 38-year-old man was referred to our Department for thyrotoxicosis of unknown etiology. He had no family history of thyroid disease and his medical history had been unremarkable until August 2020, with normal thyroid function. He denied alcohol or substance abuse, was a nonsmoker and was taking no medication. One month before, a lumbosacral MRI performed because of recurrent back pain incidentally discovered multiple lesions in the aortocaval region. A CT scan showed fourty-seven bilateral solid lung lesions and extensive retroperitoneal and iliac chain lymphadenopathy. Tumor markers panel showed 180-fold increase of alpha 1-fetoprotein levels and a subsequent testicular US revealed multiple nodules with calcifications in the left testis. Pulmonary and pelvic lesions biopsies and left orchifunicolectomy were performed, with histological diagnosis of metastatic nonseminomatous germ-cell tumor (AJCC stage IIIC; 75% Embryonal carcinoma, 15% Teratoma, 10% Yolk sac carcinoma, <1% Choriocarcinoma). Clinical examination revealed tachycardia (HR 104 bpm), but no neck pain or ocular signs. The patient complained of agitation and weight loss. Laboratory tests showed suppressed TSH levels, a marked rise in free-thyroxine (FT4 36.1 pg/ml, normal range 9.3–17) and free-triiodothyronine (FT3 10.9 pg/ml, range 2–4.4) levels, with no serological evidence of thyroid autoimmunity (AbTg, AbTPO, TRAb); dramatically increased hCG levels (745.506 mU/ml, range 0–2) were detected. Thyroid US revealed normal volume, homogeneous isoechogenic echotexture (vascular pattern not available), without solid nodules. A diagnosis *per exclusionem* of HCG-induced hyperthyroidism was established and treatment with Methimazole 20 mg/day and Propranolol 40 mg/day was initiated. One week later, FT4 levels improved (FT4 26 pg/ml) and FT3 levels normalized (FT3 3.33 pg/ml). Concurrently, chemotherapy with cisplatin, etoposide and bleomycin (PEB) was started, then shifted to cisplatin, etoposide and ifosfamide (VIP) because of respiratory failure. After a sharp rise (>1.000.000 mU/ml), HCG levels progressively decreased to almost physiological levels and the thyroid function normalized as well; Methimazole treatment was tapered to 5 mg/day.
Conclusions
HCG overproduction by germ cell tumor represents a rare cause to consider in differential diagnosis of hyperthyroidism; the presence of misdiagnosed paraneoplastic thyrotoxicosis could negatively impact on clinical and pharmacological management and on patient's QoL.
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AEP749

Warthin-like variant of papillary thyroid carcinoma

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Introduction
A rarely reported histologic subtype of the papillary thyroid cancer is the Warthin-like variant (WLPTC). This carcinoma resembles the *Warthin tumour* of the *salivary gland* by virtue of a papillary pattern of *eosinophilic* tumour cells associated with a rich lymphoplasmacytic infiltrate in the cores of the papillae. Due to the its rarity, the pathological characteristics and clinical behavior of WLPTC are not well documented.
Case report
We report a case of a 51 year old female patient, with no relevant personal history and no familial history of thyroid disease. Due to the presence of palpable thyroid nodules the patient underwent a thyroid ultrasound scan. The exam documented the presence of an heterogeneous thyroid, hypoechogenic in nature, with multiple millimetric hypoechogenic nodules, favoring the diagnosis of thyroiditis. Of particular interest a 28 mm hypoechogenic solid nodule was identified on the left thyroid lobe, and two strongly hypoechogenic nodules on the right thyroid gland (13 mm and 15 mm), surrounded by multiple punctiform hyperechogenic foci. The fine-needle aspiration cytology of the largest right lobe nodule was compatible with papillary carcinoma while the left lobe largest nodule was benign. Thyroid function exams were normal and anti-thyroid antibodies were positives. The patient underwent complete thyroidectomy. The histology revealed the diagnosis of WLPTC, two foci on the right lobe, 25 mm and 5 mm in size, with no angioinvasion nor extrathyroidal extension, associated to Hashimoto thyroiditis, with large lymphoid follicles and normofollicular nodular hyperplasia. After a follow-up of six months, there is no evidence of disease.

Discussion
The Warthin-like variant of *papillary carcinoma thyroid* is a rare and relatively unknown variant of papillary thyroid carcinoma. This variant is frequently associated with *Hashimoto's thyroiditis* and it is classically diagnosed in females over the age of 50 years. The prognosis is expected to be similar to that of classic papillary thyroid carcinoma.

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AEP750

Increasing levothyroxine requirements in a patient with previously stable hypothyroidism

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A 44 year old woman presented with leg swelling. Past history included hypothyroidism and ulcerative colitis treated with eltroxin (100 mg/day) and azathioprine (100 mg/day) respectively. Clinical examination revealed pitting oedema to knees and a 'puffy face'. Free T4 was 5.8 pmol/l (12–22 pmol/l), TSH 84.61 mU/l (0.27–4.20), serum albumin 24 g/l (40–49 g/l). She reported good compliance with L-thyroxine and no recent gastrointestinal symptoms. L-thyroxine dose was increased to 150 μg daily. Further investigations revealed 4+ proteinuria on urine dipstick with normal creatinine. 24 hr urine collection showed 12 g proteinuria. Renal biopsy was performed. Light microscopy was normal but electron microscopy showed diffuse podocyte effacement. A diagnosis of minimal change disease likely secondary to NSAID exposure was made. She was commenced on prednisolone 60 mg/day, with remission of her nephrotic syndrome. Her thyroid function normalized and she reverted to 100 mg of eltroxin daily. Our patient presented with gross hypothyroidism and oedema which could have been mistaken for myxoedema. Her hypothyroidism had previously been stable on replacement, however, and she was compliant with her medication. Nephrotic syndrome results in urinary loss of free and protein-bound thyroid hormones and can result in increased thyroxine requirements[1]. When evaluating patients with increasing thyroxine requirements, nephrotic-range proteinuria should be considered in addition to causes such as poor compliance with treatment or malabsorption of thyroxine.
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AEP751

Topiramate Induced Hyperthyroidism –? New emerging evidence.

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Case Presentation
A 25-year-old lady presented with symptomatic hyperthyroidism. She had a 4–6-week history of unexplained weight loss, pain in her neck and difficulty swallowing. Bloods confirmed mild hyperthyroidism with TSH 0.19 mU/l (reference range 0.27–4.2) with free T4 24.4 pmol/l (reference range 12.0–22.0), and she was commenced on carbimazole. There was no evidence of inflammation with CRP < 1 mg/l. Her mother had a thyroidectomy for thyroid cancer. Ultrasound of the thyroid showed multiple nodules with U2 features with no evidence of thyroiditis. She had positive TPO antibodies 415 IU/ml (reference range 0–5.5). Carbimazole was rapidly tapered to the lowest dose, and thyroid function stabilised. She has been under the sleep disorder clinic for severe sleepwalking and sleep-related eating disorder (SRED), which was treated with Topiramate with modest effect. Topiramate was considered a possible cause of thyroiditis, on a background of elevated TPO antibodies, and this medication was therefore discontinued.
Discussion
Topiramate was initially approved in 1995 in the UK as adjunctive treatment of partial-onset seizures. It blocks voltage-dependent sodium and calcium channels, inhibits the excitatory glutamate pathway while enhancing the inhibitory effect of GABA and inhibits carbonic anhydrase activity. In an open-label retrospective trial, Topiramate was found to be highly effective in reducing nocturnal eating in patients with chronic SRED. There have been no peer-reviewed studies of Topiramate induced hyperthyroidism; however, there are a few cases reports in the literature with no exact mechanism postulated. It is unclear whether Topiramate interacts with the immune system as postulated in non-thyroidal side effects. In our case, as the thyroid peroxidase antibodies were elevated this may have contributed to the possible effect of Topiramate on thyroid function.
Learning Points
Drug-related hyperthyroidism and thyroiditis need to be considered in biochemical thyrotoxicosis. Thorough drug history and clinical evaluation with correlating biochemistry are vital; however, there is often no definitive cause. In addition to the previous case reports of thyroid derangement observed with Topiramate, we also wanted to highlight our patient's possible link. Further research is required into the exact mechanisms however thyroid autoimmunity may be an indicator of individuals who require thyroid function monitoring during treatment with Topiramate.
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AEP752

Characteristics of differentiated metastatic thyroid cancers: experience at the endocrinology service of chu ibn rochd of casablanca, morocco

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Introduction
Differentiated thyroid cancers DTC are metastatic in 10% of cases. The most frequent sites are the lungs, the bones, the brain and the liver. The presence of a metastasis reduces the life expectancy of patients by 60%. The objective of this work is to describe the characteristics of metastatic DTC in our service.
Methodology
Descriptive retrospective study of 740 patient files monitored at the endocrinology department of the CHU IBN ROCHD for DTC from January 1986 to April 2019. All cases of DTC with regional or distant metastases were included. The variables studied: age, histological variant, capsular intrusion, TNM stage and multifocality. Statistical analysis performed by IBM SPSS Statistics 25 software.
Results
75 patients had presented regional or distant metastases, a prevalence of 9.7%. The mean age at diagnosis was 46.4 years ± 14.2 years. The sex ratio M/F: 0.1. All patients had undergone a total thyroidectomy, 49% of them with lymph node dissection. 78% of patients underwent ira therapy with an average delay of 19 months after surgery. Metastasis were revealed in 14 cases. 56 patients had lymph node metastasis, 17 patients had bone metastasis and 13 patients had lung metastasis. The most frequent histological types were classical papillary carcinoma (53%), papillary carcinoma with vesicular differentiation (24%), followed by vesicular carcinoma (11%). Regarding the histological characteristics, capsular effraction was found in 34% of cases, vascular emboli in 16% and multifocality in 23% of cases. Analysis of the variables studied showed that patients aged over 55 had more vascular emboli with no statistically significant difference $P = 0.06$, capsular effraction was statistically more common in women $P = 0.02$. The presence of bone metastases was statistically correlated with the presence of vascular emboli $P = 0.006$.
Conclusion
The regional or long-term recurrence rate of differentiated thyroid cancers in our series is relatively similar to that found in the literature

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AEP753

Predictive factors of central lymph node involvement in differentiated thyroid cancers

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Introduction
Papillary and follicular thyroid carcinomas are the most common forms of endocrine carcinomas. Lymph node involvement seems to be a low risk factor for death, but it increases the risk for loco-regional recurrences and distant metastasis. Lymph node involvement is more seen in case of papillary thyroid carcinoma, less reported in vesicular carcinoma. The aim of this work is to determine the clinicopathologic predictive factors of central lymph node involvement.
Material and methods
A retrospective study of 75 patients treated for a differentiated thyroid cancer, between 2000 and 2016.
Results
Our population consisted of 75 patients (66 women and 9 men). The mean age was 44 years [15 years - 78 years]. The mean consultation delay was 19 months. Histologic types were: papillary thyroid carcinoma (92%) and vesicular thyroid carcinoma (8%). Total thyroidectomy was performed in 74 cases, associated with a central lymph node dissection in 69 cases: unilateral in 23% of cases and bilateral in 77% of cases. Lateral lymph node dissection was performed in 25 cases: unilateral in 16% of cases and bilateral in 84% of cases. Multifocal involvement was noted in 31% of cases. Extrathyroidal extension was detected in 19% of cases. We noted a lymph node involvement in 50.6% of patients: central in all cases and lateral in 16 cases. After statistical analysis, 2 factors were identified as predictive of central lymph node involvement: multifocality ($P = 0.000$) and extrathyroidal extension ($P = 0.023$). Sex, age, histological type, tumour size and presence of vascular emboli were not correlated with central node involvement. Involvement of the central area was not significantly predictive of the involvement of the lateral area ($P = 0.105$).
Conclusion
Prophylactic central neck dissection in differentiated thyroid cancer is controversial and should only be performed selectively in high-risk patients. Our study, as well as other studies, clearly shows the possibility to estimate pre and intraoperatively, the risk of lymph node involvement in differentiated thyroid carcinomas and thus avoid unnecessary prophylactic central lymph node removal with all its morbidity.

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AEP754

Follicular thyroid carcinoma with lymphatic and macroscopic vascular extension

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Introduction and aims
Macroscopic angioinvasion associated to lymph node metastasis from follicular thyroid carcinoma (FTC) is scarce and leads usually to a poor outcome.
Subjects and methods
We report a case of FTC with extensive vascular invasion into the right jugular vein and numerous lymph nodes. We reviewed clinical records of our patient and analysed clinical outcomes and thyroglobulin rate as well as imaging findings after radio-iodine therapy.
Results
Our patient was 60 years old female, who underwent total thyroidectomy. Histopathology exam revealed a FTC infiltrating the thyroid parenchyma and the thyroid capsule minimally with no search for malignant thyroid nodules which are supposed to be exceptional in this pattern. The patient was referred for RAI therapy. The initial post therapeutic whole body scan showed cervical uptake with high thyroglobulin levels (500 ng/ml). The second iodine scan revealed a left thoracic uptake corresponding to a costal metastasis, with persistent cervical uptake and elevated thyroglobulin. A hard dyspnea with facial and neck edema have marked the evolution of the disease, requiring a curative subcutaneous treatment with heparin and morphological exams. Cervical Tomography (CT) scan revealed a neoplasic thrombus infiltrating intraluminally the right jugular vein and numerous metastatic lymph nodes confirmed by magnetic resonance imaging (MRI). Highly challenging cooperative operation for thrombus and lymph nodes ablation has been practiced to avoid worsening clinical symptoms and mortality. Histological examination has confirmed the metastatic origin of the lesions.
Conclusion
Lymph node metastasis occur in less than 10% of patients with FTC but do not impact disease specific mortality.Vascular malignant infiltration from FTC is more frequent, and may uncommonly turn to potential life threatening clinical entity like for our patient. It requires specific management strategies with anticoagulation regimens and mostly targets the prevention of thrombus expansion as well as embolic phenomena. When feasible, thrombectomy should be seen as the best surgical procedure when an intraluminal extension of the disease is evident.

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AEP755

Is there a link between the levels of vitamin D and differentiated thyroid cancer risk in multinodular goiter patients?

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Introduction
Both vitamin D insufficiency and multinodular goiter (MNG) are widespread throughout the world, with Romanian population being no exception. However, at this point in time there is insufficient data whether there is a connection between the two or is it just a coincidence. The aim of this study is to evaluate whether there is a relationship between serum level of 25-hydroxyvitamin D (25OHD) and the risk of differentiated thyroid cancer (DTC) in patients with multinodular goiter.
Materials and methods
we performed a retrospective study which included 129 patients evaluated for euthyroid nodular goiter in a tertiary Endocrinology Department. Patients ages ranged between 18-79 years, with exclusion criteria as follows: hypo/hypercalcemia, associated endocrinopathies (excepting: diabetes, obesity, primary osteoporosis, hyperparathyroidism due to vitamin D deficiency, adrenal incidentalomas, non-functioning pituitary adenomas without pituitary disfunction), active cancer, drugs (glucocorticoids, vitamin D supplements). Laboratory evaluations included a CBC, ESR, biochemistry, TSH, fT4, 25OHD levels and a FNA, if indicated. We investigated the differences between replete and non-replete vitamin D groups, Bethesda risk groups, and correlations using SPSS 26.0.
Results
Out of the 129 patients with euthyroid MNG, 95 (73.6%) had their vitamin D levels tested with a median value of 22.30 (13.19) ng/ml. Seventy five% of the patients presented vitamin D insufficiency (10–30 ng/ml), whereas 6.25% of patients had vitamin D deficiency (<10 ng/dl). Chi-square tests showed no differences regarding the Bethesda risk among the groups defined as vitamin D replete (>30 ng/ml) ($n = 18$) and non-replete ($n = 78$) ($P = 0.445$). Patients were divided in two groups: group 1 ($n = 111$) with Bethesda I-III, including those without a FNA indication, and group 2 ($n = 18$) with Bethesda classification ranging from IV to VI. Patients in group 2 were younger (p 0.043) and had a higher TSH level (p 0.028) than patients in group 1. The two groups were similar in terms of serum level of 25OHD (p 0.445). TSH levels correlate with a Bethesda risk above IV in MNG patients in Kendall's tau correlation (p 0.028).
Conclusions
our study did not find a relationship between serum level of 25OHD and an increased risk for DTC evaluated by Bethesda classification system. Higher TSH levels were associated with a higher risk for DTC. We recommend further research to this matter.

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AEP756

Papillary thyroid cancer presenting with splenic infarction

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Introduction
The close relationship between cancer and thrombotic phenomena has been widely recognized and paraneoplastic organ infarctions may occur. Reports of papillary thyroid cancer associated to paraneoplastic phenomena are particularly scarce.
Case report
A 39-year-old man with no prior relevant medical history was evaluated for acute onset of fever, malaise and mild pain referred to his left hypochondrium.

He had no clinical suspicion of infection or alterations on the complete blood count, but had an elevation of serum C-reactive protein (75.4 mg/l). His abdominal ultrasound was suggestive of splenic infarction. Despite reporting no history of intravenous drug use nor having any other obvious entrance point, the main initial diagnostic suspicion was infective endocarditis. Blood culture sets were sterile. Transthoracic echocardiogram and transesophageal echocardiogram were both negative for infective endocarditis. The patient underwent a further pro-thrombotic study which also revealed no abnormal results. Thoraco-abdominopelvic CT scan confirmed the splenic infarction with no other abnormal findings except for a contrast-enhanced nodular lesion on the right lobe of the thyroid gland. Ultrasound thyroid evaluation revealed an EU-TIRADS category 5 thyroid nodule measuring 19 × 21 × 28 mm. Fine needle aspiration cytology revealed a Bethesda category VI pattern. His thyroid function tests and calcitonin levels were within normal range. A total thyroidectomy was performed and confirmed the presence of a classical variant of papillary carcinoma. Lymph node metastasis in the central compartment were documented (T2N1Mx). The patient then underwent radioiodine ablation with 100 mCi. At last follow-up evaluation (about 6 months after radioiodine ablation) he met criteria for an *indeterminate* biochemical response (thyroglobulin 0.7 ng/ml).

Discussion

Splenic infarctions with no obvious cause are frequently attributed to endocarditis but a paraneoplastic etiology must always be discarted. In our case, a papillary thyroid carcinoma with nodal metastasis was found and assumed to be linked to this rare paraneoplastic feature. To our knowledge, this case represents the first report of organ infarction associated with a differentiated thyroid cancer. When evaluating patients with thrombotic events with no other recognizable cause, our case reinforces the need for searching occult tumors that should include the thyroid gland.

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AEP757

Fetal and neonatal thyrotoxicosis after 12 years from thyroid surgical ablation for Graves disease

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Clinical fetal thyrotoxicosis is a rare disease occurring in 1-5% of pregnancies with Graves disease. Although transplacental passage of maternal TSH receptor stimulating autoantibodies (TRab) to the fetus does occur early in gestation, the fetal concentration is low until the end of second trimester, but reaches maternal levels in the last period of pregnancy. The mortality of fetal thyrotoxicosis is 12–20% mainly due to heart failure. We present a case of fetal and neonatal thyrotoxicosis with favorable development and evolution in a 37-year-old woman, known with Graves disease with ophthalmopathy and thyroidectomy performed 12 years ago, with hypothyroidism and post-surgical hypoparathyroidism, in substitution treatment, which has in history a complicated pregnancy with fetal anasarca, premature birth and neonatal death. Pregnancy begins with euthyroid status and persistently increased TRAb (40 IU/l), whose value reaches 101 IU/l at 20 weeks gestational age, decreases rapidly within 1 month to 7.5 IU/l at the same time with the installation of fetal tachycardia in the absence of any other signs of fetal thyrotoxicosis, rapidly remitted under methymazole 20 mg/day. The patient gives birth by cesarean section at 37 weeks gestational age to a live, male fetus, 2530 g with mild congenital hyperthyroidism (fT4 = 3.46 ng/dl. fT3 = 7 pg/ml), TRAb titer 18.6 UI/l, which gradually disappears under methymazole (0.5 to 2 mg/kg body weight/day) and propranolol within 8 weeks postpartum. In conclusion, monitoring for signs of fetal thyrotoxicosis by periodically assessing fetal growth, heart rate, and constant monitoring of maternal anti-TSH antibody titer to detect massive decline through massive transplacental passage may successfully guide the progression of pregnancy associated with Graves disease.

AEP758

Prevalence of autoimmune thyroid diseases in patients with prolactinomas and non-functioning pituitary adenomas

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Aim

Prolactinoma, which is the most important cause of hyperprolactinemia, is an adenoma that originates from lactotropic cells of the pituitary and causes excessive prolactin release. Besides various physiological effects, the immunoregulatory effect of prolactin and its role in the development of autoimmune diseases are well known. The thyroid gland is one of the organs most frequently affected by autoimmunity. However, in our country, there are few studies examining the relationship between autoimmune thyroid disease (AITD) and prolactinoma. With this study, we aimed to investigate the prevalence of AITD in patients diagnosed with prolactinoma and non-functional pituitary adenoma and to determine the necessity of investigating prolactinoma patients in terms of AITD after diagnosis.

Material and methods

A total of 231 patients were included in the study. 93 patients (66 women/27 men) were included in the prolactinoma group, 68 patients (47 women/21 men) in the NFPA group, and 70 patients (45 women/25 men) in the control group. Pituitary size in patients with prolactinoma and NFPA, serum prolactin level in patients with prolactinoma, thyroid function tests, thyroid autoantibody (anti-Tg and / or anti-TPO, TRAB), thyroid US findings, thyroid fine needle aspiration biopsy and thyroidectomy results of all patients were recorded.

Results

AITD was found in 38.7% (n: 36) of patients in the prolactinoma group, 27.9% (n: 19) of patients in the NFPA group, 37.1% (n: 26) of patients in the control group, and total it was detected in 35% (n: 81) of the patients. There was no significant difference between the groups in terms of the presence of AITD (p: 0.334). Autoantibody positivity and AITD were more common in individuals with microadenomas in the prolactinoma group (p: 0.039, p: 0.019, respectively).

Conclusion

Although there was no statistically significant difference in the prevalence of AITD between the groups, the frequency of AITD in the prolactinoma group was higher than the frequency of AITD reported in previous studies. Another result was that AITD was detected more in patients with microadenoma in patients with prolactinoma than in patients with NFHA. For this reason, it would be beneficial to investigate all newly diagnosed prolactinoma patients in terms of AITD in case of clinical necessity.

Keywords: prolactinoma, hyperprolactinemia, non-functioning pituitary adenoma, autoimmune thyroid disease, hashimoto.

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AEP759

The fluctuation the oxygen delivery during thyroidectomy in the thyrotoxicosis syndrome patients

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Objectives

Impact of inhalation anaesthesia (IA) during thyroidectomy in the thyrotoxicosis syndrome (TTS) patients on the fluctuation the oxygen delivery (DO2).

Materials

90 TTS patients undergoing thyroidectomy. Depending on the type of anaesthesia, patients were divided into the «balanced analgesia-sevoflurane» group (BA-S) – 44 patients (where bilateral superficial cervical plexus blockade (BSCPB) was added to IA and was used IA in minimal flow scheme with FGF = 400 ml/min) and «control-sevoflurane» group(C-S) – 46 patients (monoanaetsthesia with FGF = 1000 ml/min). The anaesthetic depth control was performed by monitoring the bispectral index. The perioperative period was divided into the following stages: Stage 1 – primary examination by the anaesthesiologist; Stage 2 – the patient arrived at the operating room and connected to the monitoring; Stage 3 – immediately after anaesthesia induction and trachea intubation; Stage 4 – surgery start; Stage 5 – thyroid removal; Stage 6 – after wound suturing (end of surgery); Stage 7 – 24 hours after surgery. At all stages were assessed the hemodynamic parameters with measuring cardiac output (CO) by the estimated continuous cardiac output (esCCO) monitoring and oxygen delivery (DO2).

Results

The results indicate that IA with sevoflurane has an effect on hemodynamic parameters. The highest depression of DO2 has been noted at the stage 3 – after the IA induction and its initiation. Decreasing DO2 values was noted in

both groups vs initial stages nr.1-2 (see Table.). It was found that in the next stages 4–6, the highest DO2 values were significantly noted in BA-S vs C-S, where use less aggressive scheme of IA due to better nociceptive control with BSCPB. The use of FGF = 2000 ml/min for IA induction and 400 ml/min for basic IA in BA-S reduces DO2 to a lesser extent compared to FGF = 4000 ml/min and 1000 ml/min in C-S respectively.

Table. Oxygen delivery (ml/min × m^2) in groups (M ± m)

Groups	BA-S	C-S
Stage 1	544.4 ± 12.2	542.3 ± 17.1
Stage 2	545.9 ± 11.8	546.3 ± 14.1
Stage 3	498.7 ± 13.1	478.1 ± 14.2
Stage 4	505.8 ± 12.0	483.8 ± 11.1
Stage 5	521.5 ± 10.5	513.7 ± 10.4
Stage 6	498.9 ± 10.7	481.2 ± 10.0
Stage 7	495.6 ± 13.9	480.2 ± 9.9

Conclusions.
The study highlights the negative impact of both scheme general IA with sevoflurane on oxygen delivery in TTS patients, however use BSCPB affords reduced negative impact on oxygen delivery due to less doses IA.

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AEP760

Graves' Disease after COVID-19

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Introduction
Graves' Disease is an autoimmune syndrome that include hyperthyroidism, goiter, thyroid eye disease, and occasionally, a dermopathy called pretibial or localized myxedema. As each autoinmune ailment to develop in sufferers with genetic susceptibility after a certain environmental exposure (infection, stress…). COVID-19 can cause both pulmonary and systemic inflammation, potentially determining multi-organ dysfunction. Since the outbreak of the SARS-CoV-2 pandemic, there have been many reviews of autoimmune illnesses brought about with the aid or associated with COVID-19. Our objective is to report a case of Graves' Disease ocurring after recuperation from moderate coronavirus disease 2019 (COVID-19).
Case report
We describe a case of autoinmune hyperthyroidism (Graves' Disease) ocurring after SARS-CoV 2 infection. A 24-yeas-old woman was admitted to hospital emergency department on October 29, 2020 reporting fever, myalgia, cough and general malaise for three days. Naso-pharyngeal swab test for SARS-CoV-2 was positive and chest X-ray turned into normal. She did not require hospitalisation and was discharged symptomatically. A week later she returned to the emergency room beacause of a sense of dizziness, tremor and palpitations. The EKG confirmed sinus rhythm at one hundred thiry beats per minute without others alterations. Thyroid function was assessed, showing suppressed serum TSH with increased free thyroxine. Also this analysis showed IgM and IgG against SARS-CoV-2 were positive. The female pronounced having lost 3-5 kgs in the last month, sweating and distant tremor. No goiter was found and she referred no cervical pain. She denied Family history of thyroid diseases. We requested thyroid antibodies and treatment with a combination of methimazole and beta blocker was started on Nov 13th, 2020. The patient started follow-up. On Dec 15th, 2020 and refered clinical improvement. The laboratory testing results included suppressed TSH, normal free T4 and free triiodothyronine, TSH receptor antibodies were positive. Clinical presentation, ultrasound and positive TSH receptor antibodies are well matched with a diagnosis of Graves' disease.
Conclusions
We file the development of Graves' Disease in a patient 1 week after the medical onset of SARS-CoV-2 infection. Previous chencking out of thyroid function was normal, and she had no medical signs or symptoms of hyperthyroidism previous to her contamination with COVID-19. Whether COVID-19 contributes to the development of Graves' Disease, or the occurrence is coincidental, calls for definitive studies. This presentation may also align with the idea of a viral link in the development of autoimmune thyroid disease in people with genetic predisposition.

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AEP761

Management and outcome of Graves orbitopathy

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Introduction
Graves orbitopathy is the main extra thyroidal manifestation of Graves' disease, though severe forms are rare (< 5%). Management of Graves orbitopathy is often suboptimal, largely because available treatments do not target pathogenic mechanisms of the disease. The aim of our study was to evaluate different treatment modalities and assess their impact on the outcome of Graves orbitopathy.
Patients and methods
We conducted a retrospective study including 50 patients with Graves orbitopathy. Clinical and therapeutic data were collected.
Results
Participants had a mean age of 41.1 ± 16.6 years and a sex-ratio (M/F) of 0.38. Eighteen patients were smokers. Proptosis was bilateral in 96% of cases and asymmetric in 57%. Referring to EUGOGO criteria, 32 patients had a mild form, 15 patients did not receive any treatment and 17 had local topical eye care. The outcome was marked by stabilization in 20 patients, remission in 2 patients and regression of manifestations in 7 patients. Thirteen patients had a moderate to severe form and were put on oral glucocorticoids (Prednisone 0.5−1 mg/kg/d) in 5 cases and on intravenous glucocorticoids (Methylprednisolone 1 g/d for 3 consecutive days) followed by oral glucocorticoids in 8 cases. The outcome in this group was marked by worsening in one case. Five patients had a very severe orbitopathy and were treated with intravenous glucocorticoids (Methylprednisolone 1 g/d for 3 consecutive days followed by 500 mg repeated every week for 6 weeks). Two of them got their ocular manifestations regressed and two patients got their orbitopathy stabilized. Absence of response was noticed in one case.
Conclusion
Our study illustrated the difficulty of management of Graves orbitopathy which remains a therapeutic challenge and dilemma. Novel pharmacological treatments are on the horizon and might target pathogenetic mechanisms of the disease better than glucocorticoids.

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AEP762

clinical aspects of cardiothyreosis in adult population of southern tunisia

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Introduction
Cardiothyreosis is the most dreadful complication of hyperthyroidism. In Tunisia, cardiothyreosis has rarely been analyzed. The aim of our study was to describe the clinical aspects of this disease in an adult population of southern Tunisia.
Methods
Retrospective study (January 1999 to December 2018) including all cases of hyperthyroidism with cardiothyreosis followed in our department.
Results
100 cases of cardiothyreosis were collected with a prevalence of 16, 3%. Mean age was 49, 3 ± 13 years and sex ratio was 0, 75. The most common causes of hyperthyroidism were Grave's disease (61%), Hashimoto thyroiditis (21%) and toxic multi-nodular goiter (11%). The delay of cardiothyreosis appearance was 18, 94 months and cardiothyreosis was inaugural in 54%. The most common symptoms of hyperthyroidism were weight loss (91%) and flushing (86%). The mean concentration of TSH and free T4 (FT4) were 0,042 µUI/ml and 59, 6 pmol/l, respectively. Subclinical hyperthyroidism was found in 11% of patients. Hypocholesterolemia (85%) and hepatic cholestasis (80%) were the most frequent biological abnormalities. Echocardiographic findings showed low left ventricular

ejection fraction in 44,6%, pulmonary hypertension in 43% and right ventricular dilatation in 33.8% patients. Atrial fibrillation (AF) and cardiac heart failure (CHF) were the most noted manifestations of cardiothyreosis (75% and 56% patients, respectively). 37% of patients had concomitant AF and CHF. Those patients were significantly younger, have more anemia, hepatic cholestasis and pulmonary hypertension ($P > 0.05$).
Conclusion
The prevalence of cardiothyreosis is relatively frequent in our country. Cardiac complications are dominated by atrial fibrillation and CHF. Cardiothyreosis may occur in young patients and during subclinical hyperthyroidism.

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AEP763

Immune-related adverse effects as predictors of the response to ANTI-PD-1 immunotherapy: a clinical and diagnostic challenge

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Introduction
Current rise in use of monoclonal antibodies to Immune Check Point inhibitors (ICPIs) has led to the appearance of a great variety of immune-related adverse effects (irAEs), mainly affecting gastrointestinal tract, skin, liver and endocrinological system. With a variable prevalence (4–21%), thyroid dysfunction (TD) is the most common immune-mediated endocrinopathy. However, in the literature, it occurs in different patterns and levels of severity and its etiology is still unknown. Nivolumab is a monoclonal antibody, ICPI, indicated in advanced melanoma which acts by binding to the PD-1 receptor (programmed cell death protein 1), enhancing the immune response against tumor cells. We report a case of Nivolumab-induced thyroiditis in a woman with non-mutated BRAF cutaneous melanoma.
Case
An 82-year-old woman with non-mutated BRAF cutaneous melanoma (T3N0M1c) begins treatment with Nivolumab. The patient has no history of thyroid disease. After first cycle of Nivolumab, it is observed: TSH 0.008 uU/ml (0.50–4.00), FT4 1.80 ng/dl (0.80–2.00) and FT3 2.290 pg/ml (1.70–4.00). In following cycles, laboratory analysis revealed hypothyroidism: TSH 62.229 uU/ml, FT4 <0.400 ng/dl and FT3 <1.070 pg/ml. Due to sudden elevation of thyrotropin, antithyroid antibodies are requested: anti-peroxidase IgG (TPO) 27.56 IU/ml (0.00–5.61) and anti-thyroglobulin IgG (ATG) 518.59 IU/ml (0.00-4.11). At this time, replacement therapy with levothyroxine 50 micrograms is prescribed. Hypothyroidism continues in next cycle (TSH 66.638 uU/ml) and it is decided to increase the dose of Levothyroxine to 175 micrograms. Subsequently, TSH decreases to 3.143 uU/ml and the patient is currently continuing her anticancer treatment (Nivolumab) and thyroid replacement, remaining euthyroid.
Conclusion
Thyroiditis induced by amiodarone, lithium or interferon-alpha are well known. However, ICPI immune-mediated thyroiditis constitute a pathology whose characteristics, patterns and prevalence have yet to be determined. We present a case of thyroiditis with a sudden suppression of TSH, prior to its extraordinary elevation, which later normalizes with administration of levothyroxine, which reflects the importance of early diagnosis to avoid suspending antitumor treatment. Thyroid function monitoring is crucial to allow optimization of causal treatment since it may be necessary to modify anti-PD-1 dose or proceed to withdrawal in severe thyroid disfunction. Recent studies associate ICPI immune-mediated thyroiditis and increase of antithyroid antibodies with an improved overall survival and progression-free survival. So, in the future these irAEs could be considered a new prognostic marker in cancer patients with Anti-PD-1 immunotherapy and should be diagnosed correctly.

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AEP764

Amiodarone-induced hyperthyroidism

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Background
Amiodarone is a widely-used anti arrhythmic medication. Amiodarone-induced hyperthyroidism (AIH) develops in 3% of amiodarone-treated patients. AIH is classified as type 1 or type 2. Type1 AIH occurs in patients with underlying thyroid condition while Type2 AIH is a result of amiodarone causing a subacute thyroiditis. Appropriate therapy for amiodarone-induced hyperthyroidism requires a careful diagnosis that may be difficult to achieve.
Aim
The aim of this study is to describe epidemiological, clinical and biological features of AIH, study the followed therapeutic strategies and report their clinical and biological outcomes.
Methods
We retrospectively analyzed the data of Tunisian patients affected with AIH from 1996 to 2020.
Findings
We reported data of 15 patients affected with AIH (5 men, 10 women), aged 54 years old on average, all from the Tunisian south. Type1 AIH was reported in 10 patients and type2 AIH in 5 patients, none of them was known to have a prior thyroid condition. Amiodarone was prescribed to treat atrial fibrillation in all patients with a dose of 200 mg daily, 5 days per week. Average symptoms onset term was 5.4 months for type1 AIH (0–24) and 16 months for type2 AIH (2-30). All patients exhibited clinical signs related to thyrotoxicosis. Most common symptoms were tremor, nervousness, palpitation, and sweating. No sign has shown to be statistically related to a AIH subtype except for exophthalmia which was seen only in patients with type1 AIH. Goiter was identified in all patients with type1 AIH but only in 2 patients with type2 AIH. Biologically, all patients had high FT4 and low TSH serum level except for one who had high TSH and FT4 serum level. Only 3 patients, all from type 1 AIH group, had serum antithyroid auto-antibodies. Scintigraphic imaging showed mild iodine fixation in type1 AIH group and absence of iodine fixation in type2 AIH group. While all patients were ordered to interrupt Amiodarone protocols, different antithyroid treatments were used for type1 AIH patients, 50% of them evolved to hypothyroidism. Patients with type2 AIH were followed up until euthyroidism was obtained (8 months on average).
Conclusion
Amiodarone-induced hyperthyroidism is a major adverse effect of Amiodarone. Careful history, physical examination, immunological tests and thyroid imaging are key to distinguish between AIH subtypes which is an important step for determining further management. Finally, we argue for the assessment of thyroid function before and while using Amiodarone.

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AEP765

Graves' disease and myasthenia gravis: About a rare association

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Introduction
Graves' disease is found in 5% of patients with myasthenia gravis. It's a described but rare association that addresses pathophysiological, diagnostic and management challenges. We report a case of Graves' disease revealed by an orbitopathy in a patient with coexisting mysthania gravis.
Case report
A 40-year-old woman with established myasthenia gravis presented to the emergency room with upper eye lid ptosis and bilateral eye protrusion for 3 months. It was associated with a two-week history of palpitations, tremors, irritability and moderate weight loss. Thyroid function was assessed, showing suppressed TSH (0.01 µUI/ml), elevated free thyroxine (46 pmol/l) and positive autoantibody tests. Ultrasound found an enlarged hypervascular thyroid gland. The diagnosis of graves' ophtalmopathy with coexistent myasthenia gravis was retained. Treatment initially consisted of antithyroid drug by carbimazol before performing a thyroidectomy.
Discussion
The association between Graves' disease and myasthenia gravis has been described for decades, but the exact mechanism for such coexistence is not clearly understood. It seems, however, that autoimmunity and genetic factors play a role in this association. The symptoms of the two conditions may overlap. Graves' ophthalmopathy shares with myasthenia gravis the presence of extraocular muscle damage but is differentiated by the presence of a red, inflammatory eye and exophthalmos. Treatment of the two conditions can be challenging, as the treatment of an entity can worsen

the other. Propanol is contraindicated in this case and radical treatment of hyperthyroidism is recommended.
Conclusion
The association between Graves' disease and myasthenia gravis has been recognized. The distinction between the two autoimmune diseases can be difficult as symptoms may overlap. This association should be known by physicians as it implies diagnostic and therapeutic measures.

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AEP766

Thyroidian abscess (about an observation)

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Aims
Studying the clinical presentation, paraclinical explorations, and therapeutic modalities of thyroid abscess.
Materials and methods
We report the observation of a diabetic patient with multiple thyroidian abscesses, hospitalized in the ENT department.
Observation
The patient is 55 years old, diabetic, treated one month before admission for urinary tract infection. She came to us for increasing lower anterior cervical enlargement rapidly evolving volume in a febrile environment. On examination: Swelling of 3cm of large firm axis, mobile at swallowing, softening with Inflammatory signs looked on. The rest of the exam was without peculiarities. Biology: biological inflammatory syndrome (leukocytosis at 12100, accelerated VS and CRP high) blood glucose 10 mmol/l, hyperthyroidism with TSH at 0.11 µUI/l and T4 at 30 pg/ml. Cervical ultrasound: thyroid gland of altered appearance heterogeneous site of multiple formations cystic hypoechogenic. Cervical CT: multiple well-defined hypodense lesions with peripheral elevation after injection. The puncture brought back frank pus with bacteriological examination: a Klebsiella pneumoniae. Before the history of urinary tract infection, an ECBU was practiced, it allowed to isolate after culture the same germ. The patient was given antibiotic therapy adapted to the isolated germ. Evolution: collection at the end of 5 days which had needed its flattening under general anesthesia. The suites were simple.
Conclusion
Thyroid abscesses are a rare pathological entity. This may be suppurated thyroiditis complicated by an abscess, a thyroid abscess developed in contact with a contiguous infectious home, or from a secondary location to a remote infectious home. The diagnosis of thyroid abscesses is often delayed given the polymorphism of clinical pictures. The most commonly encountered germs are streptococcus and staphylococcus. Treatment is based on intravenous antibiotic therapy adapted to the antibiogram associated with a surgical procedure.

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AEP767

Thyrotoxicosis and its association with sarcopenia

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The aim of this study was to assess the physical well-being among women with thyrotoxicosis. It was important to investigate the relationship between thyrotoxicosis and muscle quantity and quality as being components of sarcopenia.
Methods
36 women over 40 years of age with thyrotoxicosis took part in this cross-sectional study. After excluding factors affecting physical performance and body composition 13 women remained (mean age 64 ± 9.38 years). Anthropometric parameters were measured. Grip strength was used to assess muscle strength. As recommended by The European Working Group on Sarcopenia in Older People 2 (EWGSOP2), appendicular skeletal muscle mass (ASM), adjusted for body size (ASM/height^2) was used to asses muscle quantity. Physical performance was measured by gait speed test. We divided women in two groups: group A- patients with newly diagnosed thyrotoxicosis prior to treatment and group B- patients who had already started treatment. Group A consisted of 46.2% of the participants (6 women) and group B- 53.8% (7 women).
Results
We found no association between thyroid hormone levels and grip strength, gait speed or ASM/height^2. Only the anti-thyroid peroxidase antibodies (TPO-Ab) correlated negatively with borderline significance with gait speed (r –0.546; p 0.054). A statistical significant positive correlation was established also between TPO-Ab and ASM/height^2 (r 0,697; p 0.008). Although insignificant, a tendency for decreasing values of muscle strength and mass in group A compared to group B was observed. Probable sarcopenia is identified by low muscle strength and while it didn't reach the cut-off point for sarcopenia, it was lower in group A (23.5 ± 10.291 kg). It tended to increase and reached normal levels in group B (31.86 ±10.107 kg). The same tendency was observed for muscle mass and gait speed - they were lower in group A and increased in group B. Only 2 of the patients in group A had grip strength less than 16 kg, and there was 1 patient with borderline value (19 kg). All the three of them were diagnosed with severe sarcopenia by additional documentation of low muscle quantity and low physical performance. Thus the frequency of sarcopenia was 50% in newly diagnosed patients with thyrotoxicosis. None of the women in group B met the criteria for sarcopenia.
Conclusions
Despite the small number of women in this study, we can conclude that untreated thyrotoxicosis is a risk factor for decreased muscle strength, muscle quantity and physical performance and thus could cause secondary sarcopenia.

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AEP768

Is it necessary to perform a thyroid evaluation on patients who will undergo parathyroidectomy for primary hyperparathyroidism?

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Introduction
The association of autoimmune, nodular or neoplastic thyroid disease and primary hyperparathyroidism (PHPT) has been reported in 17 to 84% of cases. In the surgical treatment of PHPT, simultaneous thyroidectomy may be necessary to optimize surgical access and / or when there is abnormal thyroid pathology. On the other hand, an incomplete diagnosis in the previous study of PHPT increases the risk of not removing clinically significant thyroid lesions.
Objective
To analyze the prevalence of thyroid disease (TD) associated with PHPT in patients undergoing parathyroidectomy, as well as the frequency with which simultaneous thyroidectomy had to be performed.
Methods
The medical records of 156 patients diagnosed with PHPT and operated on in our Hospital between 2005 and 2017 were retrospectively reviewed. The statistical analysis was performed with the SPSS V21 program.
Results
The mean age was 56.4 years (± 12.7), with 80.3% being women. The prevalence of TD was 52.6% (n = 82), being significantly more frequent in women (89% vs 11%; P <0.01). Thyroid nodular disease (TND) was diagnosed in 36.5% (n = 57) (34% multinodular goitre and 2.5% single nodule). Autoimmune thyroid disease (ATD) in 23.6% (n = 37) and papillary thyroid cancer (PTC) in 3.2% (n = 5). Fifty-two patients (33.3%) underwent simultaneous total or partial thyroidectomy, of which 75% (n = 39) had TND. PTC was incidentally diagnosed in one patient. TND was diagnosed preoperatively by radiological imaging techniques in 92.3% (35 by ultrasound and 1 by CT scan).
Conclusions
1. In our series of PHPT patients undergoing surgery, TD was associated in more than half of the cases. 2. Simultaneous thyroidectomy was required in 33.3% of all parathyroidectomies performed, with only 1 case of malignant lesion detected incidentally. 3. These findings highlight the need for a pre-surgical diagnosis of TD in patients with PHPT who are going to be operated on.

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AEP769

Fluctuations of thyroid autoimmunity pattern in a female patient with excessively elevated TRAb titers- a case report

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Introduction
Thyroid autoimmunity comprises a dynamic entity and may manifest with different forms over the course of time at the same patient, thus causing fluctuations in thyroid functionality. Hereby, we present the case of a patient treated for hypothyroidism of autoimmune etiology, who developed hyperthyroidism accompanied by an excess of thyrotropin receptor autoantibodies (TRAb) and was followed by multiple swings in the thyroid state over an 1.5-year period of time.
Case report
A 36-year old smoking female patient receiving supplementation therapy with levothyroxine 88 μg in terms of chronic hypothyroidism presented for endocrinological evaluation due to newly detected symptomatic hyperthyroidism. She reported no signs/symptoms of orbitopathy. The neck ultrasound revealed a pattern typical of autoimmune thyroiditis with diffuse heteroechogenicity and inhomogeneity accompanied by elevated blood flow; the adjunctive laboratory evaluation showed an excess of thyroid autoantibodies and TRAb-titers of 23 IU/l (reference range <2). As a diagnosis of thyrotoxicosis due to Graves' disease seemed to be confirmed, levothyroxine was paused and the patient was started on methimazole 15 mg daily but developed in 6 weeks overt hypothyroidism. Due to the rapid manifestation of iatrogenic hypothyroidism a switch of diagnosis to a possible rare variant of late-onset hashitoxicosis with elevated thyrotropin-receptor blocking autoantibodies was presumed. The thyrostatic therapy was paused and the patient became euthyroid in one month. The euthyroid state persisted over the next 5 months, but a relapse of subclinical hyperthyroidism with partially suppressed TSH and a new onset of hyperthyroid symptoms were manifested and a low dose of methimazole (2.5 mg daily) was prescribed. Euthyroidism was restored in one month and mild subclinical hypothyroidism developed 2 months later. A cessation of methimazole led to moderate subclinical hyperthyroidism relapse without thyroid specific symptoms. The patient underwent thyroid scintigraphy, which showed a pattern typical of Graves' disease. As euthyroidism was automatically restored after scintigraphy performance the patient remained without thyroid specific medication and is actually clinically and biochemically euthyroid.
Conclusion
Thyroid dysfunction due to autoimmunity has a potential of multiple swings and manifestations, possibly due to the switch of relative activity of thyroid related autoantibodies, thus causing unexpected fluctuations from hypo- to hyperthyroidism and vice versa. Although these swings do not represent the typical pattern of autoimmune thyroid disorders they should always be taken into account as they may trigger rapid changes in the thyrometabolic state and influence the path to diagnosis confirmation and subsequent choice of medical treatment.

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AEP770

Thyroid pathologies in acromegaly

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Introduction
Acromegaly is a rare disease, but serious in its complications. It is a multisystemic pathology also affecting the thyroid. The aim of our work is to study thyroid involvement in acromegaly.
Patients and methods
This is a retrospective study of acromegalic patients, in the endocrinology department of Sousse over a period of 20 years.
Result
These are 40 acromegaly patients, with a sex ratio (M/F) of 0.74. The mean age was 38.9 years [13–77]. The mean IGF1 level was 937 ng/ml [367–1700]. Anterior pituitary insufficiency was present in 32.5% of cases and thyrotropic insufficiency in 17.5% of cases. Thyroid ultrasound was performed in 20 patients. It was normal in 12 patients (60%). A multi-nodular goiter was found in a quarter of the cases and it was indicative of the disease in one case. Nodules on a normal-sized thyroid were found in 20% of cases. Fine needle aspiration was performed in two patients, showing a benign appearance. A thyroid scintigraphy done in three patients showed one cold and two hot nodules. There was no correlation between the level of IGF1 and the onset of goiter.
Discussion and conclusion
It is well established that acromegaly can affect pituitary function, including the thyrotropic axis. On the other hand, it is associated with an increased prevalence of goiter, as thyroid follicular cells express IGF-I receptors. Studies suggest a positive relationship between thyroid volume and elevated serum IGF-I levels. Hence the interest of a systematic exploration of the thyroid to the discovery of acromegaly and during the follow-up.

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AEP771

A case of Grave' s disease complicated with thyrotoxic hepatic failure and thyrotoxic period paralysis.

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Introduction
Grave's disease is an autoimmune thyroid disorder. It is the most frequent cause of hyperthyroidism with variable manifestations. When not recognized in time and not adequately treated, Graves' disease poses serious risks and can have severe complications.
Observation
A 63-year-old female was admitted to the endocrinology department for severe thyrotoxicosis. She was diagnosed in 2011 with Grave's disease medically treated using Benzylthioluracil. She has been in remission since 2015. She had a SARS-CoV-2 infection three months ago. Two months before her admission, the patient presented vomiting and diarrhea with a weight loss and jaundice. The physical examination revealed no signs of thyroid eye disease and no goiter with a regular pulse rate of 120 beats and a normal blood pressure. The patient had no hepatomegaly. she was alert and oriented with 1/5 strength in the lower extremities with no sensory deficits. Laboratory investigations confirmed the diagnosis of hyperthyroidism showing high serum free T4 (7.7 ng/dl) and low serum thyroid-stimulating hormone (TSH <0.001 IU/l). Sodium 140 mmol/l , potassium 2.4 mmol/l. Hepatic function tests revealed cytolysis cholestasis and hepatic failure: total bilirubin 519 μmol/l, direct bilirubin 300 μmol/l, alkaline phosphatase 84 U/l, gamma-glutamyl transferase 22U/l, aspartate aminotransferase 249 U/l, and alanine aminotransferase 174 U/l; prothrombin time 40% a normal factor V level. Viral serologies and investigations for other autoimmune disease and hepatic disease antinuclear antibodies, anti-smooth muscle antibodies, anti-liver kidney microsomal antibodies and anti-mitochondrial antibodies were negative and abdominal imaging did not show hepatic lesions. The diagnosis of thyrotoxic hepatitis associated with a thyrotoxic periodic paralysis was retained. The patient was treated with corticosteroids and a high dose of Benzylthioluracil, and a potassium correction. Ten days after treatment initiation, the thyroid function was normal with regression of cytolysis and cholestasis. The patient regained normal strength, and she received radioiodine therapy.
Discussion
In this case, we report two different complications of Grave's disease. Liver injury caused by thyrotoxicosis is relatively common and can be conveniently divided into hepatitis or cholestatic types. It represents a real problem since it can limit the use of antithyroid drugs and prolong the state of hyperthyroidism, exposing the patient to more severe complications. As for thyrotoxic period paralysis, it is a severe and rare complication of hyperthyroidism. When not recognized, it can lead to respiratory failure and possibly death.

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AEP772

Hyperthyroidism diagnosed in a patient hospitalized for COVID-19 hypoxaemic pneumonia : Diagnostic and therapeutic challenges

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Introduction
Patients who are critically ill can have alterations of thyroid function tests, known as non-thyroidal illness syndrome (NTIS). Moroever thyrotoxicosis can result from SARS-CoV-2 directly infecting the thyroid gland, as described in other viral infections. We report a case of hyperthyroidism diagnosed in a patient hospitalized for COVID-19 severe hypoxemic pneumonia.
Observation
A 78-year-old patient admitted to the COVID Unit for pneumonia related to COVID-19. On clinical examination, there was no sign of hyperthyroidism or pain on palpation of the thyroid. In biology, the TSH level was at 0.07 mU/l and the FT4 level was at 16.1 pmol/l (NR: 6–14). There were no arrhythmias on the electrocardiogram. The diagnosis of subacute thyroiditis related to COVID-19 was made and the patient was put on a low dose of methimazole.
Discussion
The most likely diagnosis was subacute thyroiditis related to COVID-19. The subacute thyroiditis is characterized by self-limiting thyrotoxicosis of variable duration, lasting a period of weeks or months, followed by hypothyroidism with final restoration of euthyroidism. However, the likelihood of pre-existing hyperthyroidism discovered incidentally is not ruled out in this case. There may be a direct effect of SARS-CoV-2 on thyroid function, potentially leading to exacerbation of preexisting autoimmune thyroid disease. The immunological investigation was postponed in our patient. A thyroid ultrasound and a thyroid scintigraphy would be scheduled after improvement of his condition. FT4 was not as high as the level of suppression of TSH, which can be explained by the coexistence of a NTIS. The decision to prescribe antithyroid drug was based on the age of the patient and the stage of hyperthyroidism. The stage II of hyperthyroidism (TSH < 0.1 mU/l) in patients older than 65 years should be treated according to the 2015 ATA Guidelines. Arrhythmias are not uncommon in COVID-19 patients related to COVID-19 myocarditis. This risk of arrhythmias may be increased by hyperthyroidism, another argument to prescribe antithyroid drug in this case.
Conclusion
This case presented both diagnostic and therapeutic challenges. The most likely diagnosis is subacute thyroiditis secondary to COVID-19. Despite the fact that hyperthyroidism is believed to be transient in this case, antithyroid drug were prescribed for several reasons.

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AEP773

The lower information...the greater risk of malignancy. A retrospective study of 50 patients underwent thyroid surgery

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Objective
The aim of the study was to evaluate the overall malignancy rate on final histopathology in nodules with Bethesda III or IV surgically excised and review the ultrasound and cytological features given
Material and methods
Is a retrospective analysis of patients referred to our outpatient clinical of endocrinology after thyroid surgery with a previous thyroid nodule FNA cytology in Bethesda III or IV category. We also reviewed the information given in the ultrasound (echogenicity, margins, presence and type of calcifications, shape if taller than wide, vascularity and the presence or absence of any suspicious cervical lymph nodes in the central or lateral compartments) and cytopathology (architectural and/or nuclear atypia) reports
Results
Of the 50 patients: 72% underwent a total thyroidectomy and 28% hemithyroidectomy. In Bethesda III nodules 77.41% total vs 22.58% hemithyroidectomy and in Bethesda IV nodules 63.15% total vs 36.48%. The overall malignancy rate was 42%; in Bethesda III 35.48% and in Bethesda IV 47.36%. Papillary thyroid cancer represents 10%, follicular thyroid cancer 8%, incidentally thyroid microcarcinoma (<5 mm) 16% and NIFTP 6%. The US report inform about echogenicity and cervical lymph nodes in 62%, size in three diameters in 50%, vascularity in 36%, calcifications in 24%, margins in 22% and no one taller than wide. Only 20% of cytopathology reports information about cytologic or architectural atypia. In those with cytologic atypia the malignancy rate was 50%. Only in 16% the FNA was repited. The medium nodule size was 2.84 cm
Conclusions
Our malignancy rate (42%) was higher than estimated risk of malignancy predicted by Bethesda system. However more than a half correspond with incidentally thyroid carcinomas <5mm and NIFTP. The high rate of thyroidectomies is possibly related to the limited information obtained in the reports. Both of them are remarkable

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AEP774

Variables related to Response to Therapy in 340 patients with thyroid follicular epithelial cell-derived carcinoma

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Introduction
Response to Therapy, according to ATA's dynamic classification, provides a description of the clinical situation in patients with thyroid cancer (TC) a year or more after treatment. It gives us more accurate information than the obtained at diagnosis by static staging systems as AJCC and ATA risk system.
Objetives
To analyse the association between some factors collected at diagnosis and the type of Response to Therapy in TC patients.
Patients and methods
Subjects included in the study underwent TC surgery in our hospital between January 2011 and December 2018 with a minimum follow-up of 18 months, except those who died from CT. Response to Therapy was evaluated a year after diagnosis and at the last visit. Two types of Response to Therapy were defined based on dynamic risk stratification: Adequate Response (AR) and Incomplete Response (IR). AR included both Excellent Response and Indeterminate Response, while IR included Biochemical and Structural Incomplete Responses. The variables evaluated at diagnosis for their potential association with IR were demographic variables, cancer presentation (clinical or incidental), maximum tumour size, and the presence or absence of: nodal and distant metastases, macro and microscopic extrathyroidal extension (EE), multifocality and incomplete resection.
Results
We describe 340 patients (5.6% men) with an average age of 54 ±15 years. A year after diagnosis, 91.2% of subjects were in the AR group, rising to 94.4% at the last visit. 12 months later, IR was significantly associated with clinical presentation of cancer, tumour size, presence of nodal and distant metastasis, presence of macro and microscopic EE and incomplete surgical resection. At the last visit, except for microscopic EE, same variables were found associated with IR in addition to male gender. Multivariate analysis showed that nodal metastasis represented independent risk factors for IR at both one year (OR: 3.2, CI 95% [1.1–9.6] and the last visit (OR: 5.3, CI 95% [1.4–20.3]. Other independent risk factors found were macroscopic EE at one year (OR : 7.6, CI 95% [1.1-51.4] and incomplete resection at the last visit (OR: 5.9, IC 95% [1.3–26.9]
Conclusions
Evidence of nodal metastases, macroscopic EE and incomplete resection are independent factors and lead to a worse Response to Therapy in patients with TC. Based on these findings, a more aggressive therapy during the initial stage should be considered**.**

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AEP775

Behind seeming sepsis. An outstanding clinical debut of medullary thyroid carcinoma

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Procalcitonin (PCT) is a sepsis diagnostic marker and mortality predictor, although its elevation can be related to other diseases such as medullary thyroid carcinoma (MTC). A 72-year-old woman was transferred to the intensive care unit of our institution from another center. One week before, she had been admitted with a clinical picture of progressive malaise, fever, and dyspnea. Weeks before her admission, she had consulted for dyspnea, anorexia, asthenia, and weight loss. Initial studies revealed bilateral lung infiltrates with leukocytosis and high C-protein reactive (CPR), starting

antibiotics after discarding SARS-COV-2 infection. Despite active treatment and support, the clinical condition worsened, with renal and respiratory failure, needing orotracheal intubation. A computerized tomography scan (CT) showed persistent lung infiltrates and a 14 mm nodule in the right lung's lower lobe. After transferring to our center, she showed leukocytosis, high CPR, and remarkably high PCT (4560 ng/ml). She was treated with meropenem, trimethoprim-sulfamethoxazole, levofloxacin, vancomycin, and caspofungin. CPR levels and leukocytosis improved, but PCT levels did not. Another CT showed persistent lung infiltrates and two nodules in the left thyroid lobe. We determined calcitonin (11.072 pg/ml) and carcinoembryonic antigen (CEA) levels (521.4 ng/ml) and performed a core needle biopsy (CNB) of the thyroid nodules, revealing an MTC. There was no ultrasonographic evidence of cervical nodal disease. The patient's clinical condition worsened, with no evidence of any infectious foci and sustained PCT levels. A whole-body magnetic resonance imaging (MRI) seven days after admission showed multiple hepatic, osseous, and cerebral metastatic foci. The patient died three days later. The present case reflects an outstanding clinical debut of a metastatic MTC. The first signs of the disease were disproportionately high levels of PCT, mimicking a septic shock. The usual presentation of MTC is the detection of a cervical mass. It can also be detected in family studies after discovering a germinal RET mutation, and exceptionally by clinical symptoms, derived from hormonal hyperproduction, either diarrhea or flush secondary to calcitonin or paraneoplastic (Cushing's syndrome secondary to ACTH production). In this case, PCT levels were exceptionally high despite intensive sepsis treatment and other sepsis markers improvement. The thyroid nodule evaluation and calcitonin and CEA evaluation reassured the MTC suspicion, confirmed by CNB. Calcitonin levels suggested metastatic spread, not confirmed by CT but established by MRI.

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AEP776

Epidemiological, clinic-pathological, evolutionary profile of papillary thyroid microcarcinomas

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Introduction
Papillary carcinoma is the most frequent histological form of malignant thyroid tumors, increasingly diagnosed at the microcarcinoma stage. Papillary microcarcinomas, often localized, are classified as very low risk.
Objective of the study
To describe the epidemiological and clinical characteristics, the evolutionary profile as well as to determine the predictive factors of recurrence of papillary microcarcinomas.
Methods
Retrospective study including 232 patients followed for papillary thyroid microcarcinomas collected at the Endocrinology and Diabetology department of Ibn Rochd Casablanca University Hospital, spread from 1986 to December 2019. The analysis was carried out by SPSS version 25 software.
Results
The mean age of our patients was 44.31 years, with a clear predominance of women (93.1% of cases). The most frequent symptomatology was cervical swelling in 88.36%, the discovery was fortuitous in 11.63%. In our series 71% patients had multinodular goiter, 1.7% followed for dysthyroidism, 26.7% had no personal history and 1 patient (0.6%) followed for Basedow's disease. All patients had clinical and biological euthyroidism except 4 patients who had hyperthyroidism. All patients underwent total thyroidectomy with pathologic papillary thyroid microcarcinoma, the most frequent histological variant is the classic papillary with an average size of 4.5 mm. Multifocality was objectified in 70 patients. Lymph node dissection was performed in only 11 patients. Iratherapy was performed in 88 patients. The remission rate was objectified in 94%. The predictive factors of recurrence were multifocal character ($P = 0.004$), size > 5 mm ($P = 0.002$), and unencapsulated character ($P = 0.001$).
Conclusion
Papillary thyroid microcarcinomas have an excellent prognosis. However, certain predictive factors of aggressive evolution justify a surgical and isotopic maximalist attitude. The limitation of this study was the lack of the genetic study.

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AEP777

Prognostic factors and therapeutic strategy for patients with bone metastases from differentiated thyroid carcinoma

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Thyroid differentiated carcinomas are of good prognosis except in case of metastatic dissemination. These distant metastasis, especially the bone one, are a major cause of altered quality of life and death. This study concerns a cohort of 21 patients treated from 1995 to 2011.The aim of our work is to study the characteristics of patients who had *bone metastases* in association with *thyroid cancer* to determine their prognostic factors. 18 of our patients were over 45 years of age with a majority of vesicular carcinoma (81%). Distribution of patients according to the anatomopathological characteristics of the tumor were: multifocality 28.6%, thyroid capsule invasion 52.2%, complete lymph node chain resection 66.7%. Bone metastases are often multiple. They are located in order of decreasing frequency: limbs 76%, spine 46%, skull 38%, pelvis 33.3% and sternum 28.5%. They have been associated with other types of metastasis, especially pulmonary metastases (13 patients) and brain (2 patients). The mean stimulated thyroglobulin (sTg) level before radioactive iodine therapy was 762.95 ± 484.64 ng/ml with extremes from 3 to 2000 ng/ml. The average number of radioactive iodine therapy (RIT) cures received by patients was 9 ± 8.25. Consequently, bone metastases fixing iodine was noticed for 20 patients. (RIT) had as a result the disappearance of bone uptake in 1 case, reduction in 2, and stabilization in 9. More intensive uptake was noted in 7 cases. Thus, the (sTg) level was declining for 4 patients, stable for 5 and rising for 12 patients. In addition, radiotherapy of bone metastatic sites was performed for 10 patients and Only 4 patients (19%) had metastases removal surgery. The 5-year survival was 74% for patients who have had radiotherapy. After an average delay of 6.4 years from time carcinoma firstly diagnosed and 3.4 years its bone metastases: a partial remission was notable for only 1 patient, a stationary state was observed for 9 patients and clinical aggravation was observed for 11 patients. Overall survival was 65% at 5 years and 49% at 10 years. With a multidisciplinary treatment adapted to each case, it was possible to obtain long survival in 10% of cases.
Conclusion
The treatment of *bone metastasis* in association with *thyroid cancer* represents a difficult challenge requiring, as a result, more extensive treatment.

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AEP778

Thyroid nodule classified as Bethesda III: Our clinical experience and management strategy

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Background
The prevalence of malignancy among Bethesda category III (atypia of undetermined significance) cytologies is variable in different studies.
Objective
The aim of this paper is to evaluate the risk of malignancy of thyroid nodules classified as Bethesda III in our hospital.
Methods
We have reviewed the medical records of 146 patients who underwent FNA with Bethesda III results between January 2017 and June 2020 in our hospital. From those, 26 patients were excluded because they didn't have enough follow -up information ($n = 120$). We analyzed the result of the second FNA (in those patients in which it was performed), then, the histological result from surgery and the echographic characteristics of each nodule.
Results
The mean age of the patients at the time the FNA was performed was 57,16±11,7 years. 71,67% of them were women. A second FNA was performed in 65.83% of the patients (79/120) resulting in Bethesda 1 (non-diagnostic) 29.11% of them, 2 (benign) in 40.51%, 3 (undetermined) in 24.05%, 4 (suspicious for follicular neoplasm) in 1.27% and 5 (suspicious

for malignancy) in 5.06% of them. 33.33% of all the patients suffered from hypothyroidism (40% of them had a benign nodule and 17.5% had a malign one). In 61 patients surgery was indicated: 57.38% had a hemithyroidectomy and 42.62% had a total thyroidectomy. Postsurgical complications occurred in 14.76% of the patients (6.56% suffered from dysphonia, 6.56% partial recurrent laryngeal nerve paralysis and 1.64% hypoparathyroidism). These complications appeared in 19.23% from total thyroidectomized patients, against 11.42% of hemithyroidectomized ones. From the 61 patients undergoing surgery, the histology was benign in 62.29% of the cases and malignant in 36.07% (26.6% were papillary thyroid cancer, 3.27% follicular thyroid cancer, 3.27% NIFTP and 3.27% Hürthle cell carcinoma). In addition, the ultrasound characteristics of benign and malignant nodules were compared. From those with malignant histology, 13.63% showed microcalcifications (compared to 7.89% of benigns); 31.81% had irregular margins (compared to 7.89% of benigns); 54.54% had hypoechoic consistency (vs 36.84% in benigns) and 36,36% showed absent of hypoechoic halo (vs 47.36% of benigns) 52.63% of benign nodules occurred in the context of multinodular goiter (compared to 31.81% of malignant nodules).
Conclusion
More than one third of the Bethesda III patients who underwent thyroidectomy had thyroid cancer.

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AEP779

Management of papillary thyroid carcinoma in children

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Objective
Thyroid cancer is a rare disease in children and adolescents; it accounts for only 1.4% of all pediatric malignancies. Papillary carcinoma is the most common histological type. Furthermore, its treatment remains controversial. The aim of our work is to illustrate the clinical, histological and therapeutic features of pediatric papillary thyroid carcinoma.
Materials and methods
This is a retrospective study of 5 cases of papillary thyroid carcinoma, for which the upper age limit at the time of diagnosis was set at 15 years. This study was carried out over a period of 10 years from 2007 to 2017.
Results
The average age of our patients was 14 years, with a sex ratio of 1.5. No personal history of cervical irradiation or thyroid pathology was found. All of patients consulted for a thyroid nodule, associated with cervical lymphadenopathy in two case. A total thyroidectomy with central compartment lymph node dissection is performed in all cases. Only two patients had a lateral lymph node dissection. The diagnosis of papillary carcinoma was confirmed on the histopathological examination of the surgical specimen. The tumor was multifocal in all cases with capsular invasion and Lymph node metastases. After surgery, I-131 therapy was carried out in all patients. The evolution was favorable in all cases. No case of recurrence was noted with a mean follow-up of 4 years.
Conclusion
Compared with adults, papillary thyroid cancer in children display a greater frequency of lymph node metastases and distant metastases at the time of diagnosis and higher rates of recurrence after treatment. For this reason it should be treated differently with a long-term follow-up. The treatment is based on total thyroidectomy with lymph node dissection followed by I-131 therapy, usually giving a good prognosis.

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AEP780

Parathyroidian cysts: About an observation

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Introduction
The parathyroid cyst is a benign lesion that develops at the expense of the gland parathyroid. It is rarely revealed by palpable cervical swelling and is often a surgical discovery. The purpose of our work is to report an observation of parathyroid cyst, and specify the methods of pre-operative diagnosis and the different therapeutic possibilities.
Materials and methods
We report an observation of a 65-year-old patient with no pathological history individuals who presented for bone pain with functional impotence of the lower limbs.
Results
The cervical examination noted a right lower paramedian cervical swelling of 4 cm large axis, firm, mobile to swallowing. Biological assessment objectivated hypercalcemia with hyperparathyroidism (PTH: 2406 pg/ml). Cervical CT showed a cystic lesion at the lower part of the right thyroid lobe and another heterogeneous on the side left. A resection of the lower right parathyroid gland, which had a wide cystic component, was performed as well as resection of the left parathyroid. The anatomopathological examination concluded in a lower right parathyroid cyst with parathyroid parenchyma hyperplasia of both parathyroid glands. Surgical suites were simple with normalization of calcemia and parathormone levels.
Conclusion
Parathyroid cysts account for 3.2% of parathyroid diseases. They affect preferably women whose age varies between 40 and 50 years. They mainly cause differential diagnosis with isolated thyroid nodules. The treatment is often surgical

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AEP781

Neuroendocrine carcinoma of the thyroid: About of a case

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Goals
The purpose of this work is to study histological, clinical, and therapeutic features neuroendocrine carcinomas of the thyroid.
Materials and methods
We report a case of neuroendocrine carcinoma of the thyroid colliged in ENT department of sousse.
Observation
The case involved an 83-year-old woman with a history of family dysthyroidism who had significant cervical swelling, rapidly increasing in size over the past month, and associated signs of compression (inspiratory dyspnea, dysphagia, and dysphonia). The clinical examination showed an anterolateral cervical swelling, poorly limited, fixed in relation to both planes, more marked on the right side with altered laryngeal mobility. The chest CT scan revealed a latero-cervical 9 cm mass, extended to the anterior mediastinum, pushing back the esophagus and the trachea, and compressing the carotid artery, left subclavian and right internal jugular which is thrombosed, cervical lymphadenopathy: right spinal (20mm) and right upper clavicular (17 mm). There weren't lung parenchyma abnormalities. A biopsy showed a neuroendocrine carcinoma little differentiated expressing chromogranin. The abdominal ultrasound did not object to remote metastasis. The multidisciplinary staff opted for external radiotherapy. The evolution was marked by the rapid increase of the size of the tumor with a significant alteration of the general state. A tracheotomy was performed in emergency before the aggravation of dyspnea. The patient died before she could begin radiotherapy.
Conclusion
Clinical presentation of neuroendocrine carcinomas is aggressive and rapidly progressive with an often invasive tumor and extensive necrosis sites. The immunohistochemical study confirms the diagnosis by showing an expression of neuroendocrine markers. The lymph nodes are almost constant. Given the rarity of this histological type, the treatment remains poorly defined. However, radiation therapy is still more appropriate than surgery. The prognosis is often bad with a high mortality rate.

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Late Breaking

AEP782

Heterozygous 461A> T (p.Asp154Val) Mutation in POR gene in a male case

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Background
Cytochrome P450 oxidoreductase (POR) deficiency is an autosomal recessive steroidogenesis disorder similar to combined deficiencies of 17ήhydroxylase, 17,20-lyase, 21-hydroxylase. POR deficiency (PORD) is a very rare type of congenital adrenal hyperplasia(CAH) characterized by sexual development disorders and skeletal anomalies. We present a case that was evaluated with a prediagnosis of nonclassical CAH and was found to have a heterozygous mutation in the POR gene.
Case report
A 23 years old male patient applied to our clinic with complaint of excessive hair. These symptom had started on her arms and legs at 6 years old, appeared on her back at 8 years old, then spread to all over the body. He has reached his final adult height at about 15 years old. He had no history of chronic illness, his 47 years old mother and 56 years old father were consanguineous. On physical examination, his blood pressure was 120/80mm/hg, height was 161cm, the length of the penis was 9.5cm and testicular volume was 20 ml. Laboratory tests were as follows; glucose 89 mg/dl (70–99), sodium 138 mEq/l (132–146), potassium 4.7 mEq/l (3.5–5.5), cortisol 20.3 µg/dl (5.2–22.4), ACTH 37.8 pg/ml (<46), TSH 1.6 mU/l (0.55–4.78), sex hormone binding globulin 7 nmol/l (10–57), FSH 3.2U/l (1.4–18.1), LH 6.9U/l (1.5-9.3), progesterone 1.26 µg/l (0.28–1.22), total testosterone 383 ng/dl (164–753), dehydroepiandrosteronesulfate 698.72 µg/dl (34.5–568.9), 17-alpha-hydroxyprogesterone (17-OHP) 1.22 ug/l, free testosterone 26.6 pg/ml (15–50), androstenedione 13.5 nmol/l (2.1–10.8). Maximum 17-OHP was 3.36 mg/l after ACTH-stimulation. Abdominal magnetic resonance imaging showed normal adrenal glands. Scrotal ultrasonography was normal. Bone age was 18 years. Genetic testing revealed that the patient was heterozygote for c.461A > T(p.Asp154Val) mutation in exon 5 of POR gene while CYP21A2, CYP17A1, CYP11B1, HSD3B2, STAR genes were normal. Subsequent genetic testing of parents showed that his mother also had POR(NM_000941.3):c.461A > T(exon5) heterozygote mutation, while there was no mutation in his father.
Conclusion
A great number of POR variants affecting more than 130 amino acids in the POR protein have been reported. There is clinical heterogeneity in patients with POR gene mutations, making the diagnosis difficult. Considering that the POR gene mutation shows ethnic differences, we think that the determination of variant cases in our society will clarify its importance in this case in the future.
Keywords: cytochrome P450 oxidoreductase, POR heterozygote mutation.
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AEP783

Cortisol measurement post steroids (Dexamethasone) treatment for COVID-19

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Introduction
We are currently mid Covid-19 pandemic. In the last year there have been 116,135,492 confirmed Covid-19 cases worldwide, with an estimated 2,581,976 deaths.
The RECOVERY trial reported for patients hospitalized with Covid-19, the use of dexamethasone (6 mg for 10 days) resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomisation. Adrenal insufficiency (AI) is a serious, potentially life-threatening side effect of glucocorticoids which cause suppression of the hypothalamic-pituitary-adrenal (HPA) axis.
Objective
We aimed to investigate the effects of Covid dexamethasone protocols on adrenal function.
Methodology
We collected data from patients admitted with a diagnosis of Covid-19 by searching electronic patient records from November 2020 to March 2021 at our institution. We included patients with a diagnosis of COVID-19 treated with Dexamethasone, Hydrocortisone, or prednisolone for 7 days or more. We also recorded factors that may also affect adrenal function including.
• Patients on long term corticosteroids (i.e inhaled, topical, injectable, and oral)
• Patients on CYP3A4 enzyme inhibitors
• Patients on opioids
Adrenal function was screened by 0900 h cortisol, at least 24 hours off of steroids. Cortisol levels >300 nmol/l excluded adrenal insufficiency. levels between 100-300 nmol/l underwent further assessment. Concentration <100 nmol started on hydrocortisones replacement and further surveillance.
Results
77 patients were alive at the time of data collection, data being available for 53. 42/53 patients had 7–10 days 6 mg dexamethasone whilst 9/53 had additional ARDS regimen of dexamethasone (reducing dose over 12 days starting at 33 mg/day). To date 13/50 had suboptimal cortisol level, 5 had cortisol <100 nmol 24–48 hours post stopping Dexamethasone, 4 of these having had ARDS regimen of prolonged dexamethasone. These have been started on hydrocortisone and further testing planned when on lower doses of hydrocortisone. 8 had cortisol 100-300 nmol/l, confirmatory testing is awaited. Data is therefore awaited for 27 patients along with the SST results.
Summary
Whilst this is a small data series it highlights the risk of adrenal insufficiency after treating with dexamethasone, with almost 50% of patients on ARDS regimen on ICU having adrenal insufficiency. It is important to be aware and screen for AI as these patients will be at risk of adrenal crisis if left undiagnosed. These data also suggest that Covid-19 itself does not cause adrenal insufficiency. Larger numbers are needed to confirm these data.
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AEP784

New biomarkers to predict cardiovasculer risk in patients with adrenal incidentaloma; irisin and nesfatin-1

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Objectives
Evidence from recent studies suggests that patients with adrenal incidentaloma have increased cardiovascular risk. In our study, we aimed to investigate the levels of irisin, nesfatin-1 and the relationship between levels of these relatively new molecules with cardiometabolic risk markers; carotid intima-media thickness (CIMT), epicardial adipose tissue (EAT) thickness and abdominal subcutaneous adipose tissue (SCAT) thickness in patients with nonfunctional adrenal incidentaloma (NFAI).
Methods
Patients with NFAI (n = 59) and age-, sex- and body mass index-matched healthy control subjects (n = 59) were enrolled in this study. Serum glucose, insulin, C-reactive protein (CRP), lipid, irisin and nesfatin-1 levels were measured in patients and controls. In addition, echocardiographic CIMT and EAT thickness measurements of patients and controls were made.
Results
The irisin level was 17.58 ± 4.38 pg/ml in the NFAI group and 14.03 ± 4.03 pg/ml in the control group, and it was significantly higher in the NFAI group ($p < 0.001$). Nesfatin-1 level was 194.98 ± 119.15 pg/ml in the NFAI group and 303.48 ± 200.78 pg/ml in the control group, and it was significantly lower in the NFAI group ($P < 0.001$). There were no difference between two group in terms of CIMT and EAT thickness ($P > 0.05$) Positive correlations were found between irisin level and CIMT (r: 0.384, p: 0.003) and EAT thickness (r: 0.333, p: 0.010) in the NFAI group. In addition, positive correlations were also found between nesfatin-1 level and CIMT (r: 0.323, p: 0.013) and EAT thickness (r: 0.292, p: 0.025) in the NFAI group.
Conclusions
In our study, we found that irisin level was higher and nesfatin-1 level was lower in patients with NFAI, and both irisin and nesfatin-1 levels were associated with CIMT and EAT thickness in NFAI patients. Irisin and nesfatin-1 can be used as markers to predict the cardiovasculer risk in patients with NFAI.
Keywords: nonfunctional adrenal incidentaloma, irisin, nesfatin-1, carotid intima-media thickness.
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AEP785

The role of radiological assessment with CT in the characterisation of adrenal nodules: use of size, pre-contrast attenuation and washout studies

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Background
Advances in imaging techniques combined with the increase in the number of patients undergoing radiological investigations have contributed to the increased detection of adrenal nodules. Prior to the publication of the European Society of Endocrinology (ESE) guidelines on the management of adrenal incidentalomas in 2016, there was marked variability in the management of adrenal nodules. The objective of this study is to validate the diagnostic performance of the radiological thresholds (size of nodule, pre-contrast attenuation and washout studies), as per the ESE guidelines 2016.
Methods
The histological diagnosis (gold standard) for 68 patients who had adrenolectomy between January 2011 – February 2020 was obtained from hospital records. CT reports of these patients were reviewed to collate data on size (n = 68), pre-contrast attenuation (n = 47) and absolute washout (AW) (n = 31) and relative washout (RW) (n = 31). Univariate models were used to analyse the diagnostic accuracy of these radiological thresholds. ROC analyses were conducted and standard thresholds were used to derive sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV). We propose new thresholds providing better estimation of these parameters.
Results
The malignancy prevalence in the dataset was 10.4%. Univariate analysis using the chi-squared test, demonstrated that size ($P < 0.0001$) and pre-contrast attenuation ($P = 0.01$) were significant predictors of benign histopathology. Receiver operating characteristic (ROC) area under the curve (AUC) was 0.89 ($P = 0.005$) for size and 0.88 for pre-contrast attenuation ($P = 0.03$). The AUC for RW ($P = 0.08$) and AW ($P = 0.24$) were not significant.
With the size cut off ≥4 cm (current standard) for diagnosing a malignant lesion, the NPV and PPV values were 0.96 and 0.17 respectively (sensitivity 0.80, specifity 0.53). A new threshold of ≥8cm for diagnosing a malignant lesion gave a NPV 0.98 and PPV 0.67 (sensitivity 0.80, specifity 0.95). Similarly, a pre-contrast cut off of >10HU (current standard) for a malignant lesion diagnosis had NPV 1.00 and PPV 0.18 (sensitivity 1.0, specifity 0.59). A new cut off 29.5HU had NPV 0.97 and PPV 0.40 (sensitivity 0.67, specifity 0.91).
Conclusions
These data show that size and pre-contrast attenuation are good predictors of benign histopathology. The low number of patients with cancer in the cohort has an impact on any test sensitivity, but these early data show that different thresholds might be required than currently in use. Larger cohort studies are required to investigate this further and to understand the role of washout studies in determining adrenal histopathology.

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AEP786

Prevalence of primary aldosteronism in patients with acute stroke: A prospective study

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Background
Primary aldosteronism (PA) affects 5-20% of all patients with hypertension, and is likely the most common treatable cause of hypertension. Patients with PA have higher risk of cardiovascular disease, atrial fibrillation and stroke. We aimed to estimate the prevalence of PA in patients with recent stroke.
Methods
We prospectively recruited 300 patients who were admitted to the acute stroke unit of a single tertiary centre with the diagnosis of cerebrovascular accident (both ischemic and haemorrhagic) or transient ischemic attack. At 2-4 months post-stroke, all patients had screening blood tests for serum aldosterone (ng/dl) and plasma renin activity (ng/ml/hr) Patients with aldosterone-renin-ratio (ARR) >10 underwent confirmatory seated salt loading test (SLT). This study was registered with Clinicaltrials.gov (NCT03789357).
Results
300 patients were recruited, of which 192 underwent ARR screening. Mean age of the 192 patients was 56.7 ± 10.6 years, 55 (28.6%) were females, and 130 (67.7%) had hypertension. 156 (81.3%) had ischemic stroke, 20 (10.4%) had haemorrhagic stroke and 16 (8.3%) had transient ischemic attack. 26 of 192 (13.5%) patients had positive ARR. Patients with positive ARR were more likely to have AF, 4 of 26 (15.4%), compared to those with negative ARR, 5 of 166 (3.0%), P =0.021, and they also had higher baseline diastolic blood pressure. 4 of 12 (25%) patients who underwent confirmatory SLT had post-saline aldosterone >5ng/dl. One patient had baseline aldosterone >20 ng/dl with suppressed renin and spontaneous hypokalaemia, which was consistent with diagnosis of PA. In total, 5 patients were diagnosed with PA, giving a prevalence of 2.6% in all stroke patients, and 3.9% amongst those with hypertension. Prevalence rates were higher in certain subgroups of patients: 16.7% (2 of 12) in those with hypertension and hypokalemia, 22.2% (2 of 9) in hypertension and AF, and 6.1% (3 of 49) in young stroke patients aged ≤50 years. If screening for PA was only done in patients with hypokalemia or age ≤50 years, half of the cases would have been missed.
Conclusion
In addition to current guideline recommendations to screen for PA in certain subgroups of hypertensive patients, e.g. resistant hypertension, hypertension with hypokalemia, it will be worthwhile to screen hypertensive patients with previous stroke, who are at high risk of cardiovascular events. In post-stroke patients who have good functional recovery, accurate diagnosis and treatment of PA can improve and potentially cure hypertension, and prevent a subsequent stroke which could be catastrophic.

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AEP787

Prospective clinical trial comparing 11c-metomidate pet-ct and adrenal vein sampling in identifying unilateral surgically-curable primary aldosteronism

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Introduction
Unilateral PA can be cured with unilateral adrenalectomy. Adrenal vein sampling (AVS) is the current reference test to identify unilateral PA, but it is invasive and technically-difficult. 11C-metomidate PET-CT offers a non-invasive alternative to AVS. We compared the accuracy of AVS and PET-CT in identifying patients with unilateral surgically-curable PA.
Methods
In this prospective multi-centre clinical trial, patients with confirmed PA underwent both AVS and 11C-metomidate PET-CT. All results were reviewed at a multi-disciplinary meeting to decide on the final diagnosis and treatment. Primary outcome was the accuracy of each diagnostic test compared to biochemical cure of PA post-surgery as defined by Primary Aldosteronism Surgery Outcomes (PASO) criteria. Secondary outcome was the accuracy of each diagnostic test compared to the final diagnosis (ClinicalTrials.gov: NCT03990701).
Results
25 patients were recruited, and all patients had a successful AVS procedure, and 11C-metomidate PET-CT. Final diagnosis was unilateral in 22 patients, bilateral in two patients, and indeterminate in one patient due to discordant lateralization on AVS and PET-CT. 20 of 22 patients with unilateral PA underwent surgery, and all were biochemically cured six months post-surgery. For the primary outcome, sensitivity of AVS was 15/20 (75%), and PET-CT was 16/20 (80%). For the secondary outcome, the sensitivity and specificity of AVS was 15/22 (68.2%) and 2/2 (100%), and PET-CT was 18/22 (81.9%) and 2/2 (100%), respectively. Six patients had PET lateralization without AVS lateralization, of which four patients had AVS lateralization ratios between 2.8–3.5, while two had bilateral low aldosterone levels on AVS. Three patients had AVS lateralization without PET lateralization. There were no differences in clinical outcomes (blood pressure) using PASO criteria between patients identified on PET-CT and

those with AVS. Patients with higher PET lateralization ratios also had higher AVS lateralization ratios, and higher peripheral aldosterone levels during AVS, but similar aldosterone and cortisol levels during PET-CT, compared to those with lower PET lateralization ratios.
Conclusion
11C-metomidate PET-CT performs comparably with AVS in identifying unilateral PA and can also identify patients not currently detected with AVS. Being non-invasive and non-operator dependent, it may allow identification of more patients with unilateral surgically-curable PA.

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AEP788

Significant regression of primary adrenal lymphoma after acute steroid replacement therapy: a case with an insufficient initial biopsy

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Objective
There is limited clinical data available on bilateral adrenal masses (BAM). Here we present a case with BAC and adrenal insufficiency. The patient's lesions disappeared after steroids, re-grew in the follow-up, allowing a biopsy.
Case
A 60-year-old male patient presented with abdominal pain, nausea, and weakness to another hospital. Hyponatremia and hyperkalemia accompanied by hypotension were detected. Abdominal tomography revealed, "irregularly demarcated hyperdense mass lesions, 60 × 44 mm in the right and 75 × 26 mm in the left adrenal." Upon referral to our hospital, we employed PET-CT, which demonstrated "mass lesions of 49 × 52 × 71 mm in the right and 56 × 57 × 75 mm in the left adrenal as well as pathological hypermetabolism in multiple foci in the skeletal system." After diagnosing adrenal insufficiency, we initially gave the patients intravenous hydrocortisone, followed by oral maintenance. There were no pathological findings in tuberculosis tests, viral and autoimmune panel, and malignancy screening. Urine and plasma catecholamine and 17-hydroxy progesterone levels were normal. CT-guided biopsy of the adrenal mass revealed fat necrosis. After 45 days, we attempted a repeat biopsy without success due to almost wholly regressed adrenal masses. Also, bone lesions could not be visualized. Adrenal MRI showed "14 mm lesion on the right and, only diffuse thickening on the left adrenal." A control PET-CT was obtained. "Evident decrease in the size of the adrenal lesions, in addition to the fairly reduced metabolic activity of adrenal masses and bone lesions." We performed a biopsy from the most active bony lesion; however, it was inadequate. Two months after the initial presentation, he was admitted with abdominal pain. His lesions had progressed. In CT he had, 70 × 41 mm right adrenal mass invading liver and IVC, 56 × 38 mm left adrenal mass, and numerous metastasis in his liver and lungs. Adrenal biopsy, this instance was compatible with "CD20 + B cell lymphoma infiltration." Patient died of cerebrovascular incident, whilst awaiting biopsy results.
Conclusion
Primary adrenal lymphoma is a rare etiological cause of BAM with only a handful of reported cases. Adrenal lesions vanishing after steroids should raise the suspicion of adrenal lymphoma. The shrinkage of tumors may lead to diagnostic difficulties such as our patient.

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AEP789

Admission of patients with chest pain and/or breathlessness from the emergency department in relation to risk stratification and Copeptin; a prospective observational study

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Background
Accurate identification of patients at risk in the Emergency Department (ED) is crucial in order to avoid delays in treatment which may result in poor outcomes. Our aim was to study the association of the decision in ED to admit patients with chest pain and/or breathlessness in the ED to a ward with risk stratification by RETTS or NEWS and level of the surrogate biomarkers Copeptin, MR-proADM and MR-proANP of vasoregulatory hormones.
Methods
Patients presenting at the ED with chest pain and/or breathlessness were enrolled. Vital signs were recorded and patients were triaged accordingly to Rapid Emergency Triage and Treatment System (RETTS). NEWS (national early warnings score) was retrospectively calculated from the vital signs. Levels of Copeptin, MR-proADM and MR-proANP on presentation were analyzed.
Results
334 patients were included. The median age was 64 year. 167 (50%) of them were male. 210 (63%) patients complained of chest pain, 65 (20%) of breathlessness and 59 (18%) of chest pain and breathlessness. Of those 176 (52.7%) patients were admitted to a ward and 158 (47.3%) patients were discharged from ED. In binary logistic models age, gender, vital parameters, NEWS class and Copeptin were associated with admission to award from ED, whereas there was no association with RETTS, MR-proADM or MR-proANP. Assessed by receiver operating characteristic (ROC) curves constructed with: age, gender and vital signs for prediction of admission from ED, addition of copeptin did not significantly increase the area under the curve (AUC).
Conclusions
Age, vital signs, NEWS and copeptin, are related to the decision of admission to a ward from ED for patients with chest pain and/or breathlessness.

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AEP790

Patients susceptible to an adrenal crisis show marked differences in urinary cortisol excretion and glucocorticoid sensitive pathways

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Background
Adrenal crisis (AC) is a life threatening medical situation caused by an absolute or relative cortisol deficiency. A biological predisposition may be of importance, because some patients never experience an AC, whereas others are admitted repeatedly to the hospital for an AC. Differences in cortisol pharmacokinetics (PK) and/or pharmacodynamics (PD) may underlie this vulnerability.
Objective
To study PK and PD data of glucocorticoid sensitive pathways in patients with or without an AC.
Design
An exploratory analysis of well-characterized patients with secondary adrenal insufficiency who participated in a randomized controlled trial investigating the effects of two different hydrocortisone (HC) doses corrected for body weight.
Methods
Analysis of variables was performed on the lower HC dose (0.2–0.3 mg/kg body weight/day) as this was considered to better reflect the state of (relative) hypocortisolism. Variables of interest were also analyzed on the higher dose (0.4–0.6 mg/kg body weight/day). Plasma cortisol and cortisone, 24 hour urinary steroid profile, as well as the glucocorticoid sensitive tryptophan-kynurenine, and renin-aldosterone pathways were determined by LC-MS/MS. In addition, quality of life (QoL) was measured by means of questionnaires. A P-value <0.05 was considered significant. Considering the exploratory study design, a P-value <0.1 was considered to be of interest.
Results
Out of the 52 patients included in this study, 9 (17%) suffered from at least one AC. No differences in baseline characteristics were observed between patients with (AC+) and without (AC-) an adrenal crisis. On the lower HC dose the 24 hour urinary excretion of cortisol and cortisone were found to be lower in AC+ (P = 0.01 and P = 0.04, respectively). No differences in

plasma half-life and other PK parameters of (free) cortisol were observed. Kynurenine was higher in AC+ (P = 0.03), as was 3-OH-kynurenine and the kynurenine-tryptophan ratio (both P = 0.06). In addition, perceived pain (P = 0.08), general fatigue (P = 0.04) and anxiety (P = 0.06) were higher in the AC+ group. On the higher HC dose, the 24 hour urinary excretion of cortisol and cortisone remained lower (both P≤0.01) in the AC+ group, whereas differences in the kynurenine pathway and quality of life were no longer present. A higher plasma aldosterone concentration was found in the AC+ group on the higher HC dose.
Conclusion
Patients susceptible to an adrenal crisis demonstrate lower urinary excretion of cortisol and cortisone as well as differences in the kynurenine pathway and QoL on a standardized lower hydrocortisone substitution dose when compared to patients who never experienced an adrenal crisis.

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AEP791

Histopathology and post-surgical outcomes of surgically treated patients for primary aldosteronism

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Background
Unilateral forms of primary aldosteronism (PA) are usually surgically treated to remove the source of aldosterone excess. After adrenalectomy, aldosteronism persists in a subset of patients indicating abnormal aldosterone production from the unresected gland.
Objective
To retrospectively analyze histopathology and post-surgical outcomes in a 3-year prospective cohort of patients diagnosed with unilateral PA (2016 to 2018).
Methods
Histopathology was evaluated by the international HISTALDO consensus and postsurgical outcomes were assessed by the PASO criteria.
Results
The cohort comprised 60 adrenals categorized as classical or nonclassical histopathology of unilateral PA. The classical group (solitary aldosterone-producing adenoma or nodule) comprised 45 cases (75% of 60). More than half of these adrenals (26 of 45) displayed aldosterone-producing lesions in the adjacent cortex. The nonclassical group comprised 15 adrenals (25% of 60) characterized by multiple aldosterone-producing micro/nodules or aldosterone-producing diffuse hyperplasia. A high proportion of the classical histopathology group achieved complete biochemical success compared with the nonclassical group (97.6% versus 66.7%, P = 0.002). The ratio of the aldosterone concentration in the contralateral adrenal vein to the peripheral vein was increased in the nonclassical group relative to the classical group (3.8 [1.7–6.5] vs 2.0 [1.1–3.1], P = 0.004).
Conclusion
Adrenals with nonclassical histopathology of unilateral forms of PA are associated with disease persistence and abnormal aldosterone production from the unresected adrenal.

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AEP792

Long-term follow-up in primary aldosteronism: the major determinant of the haemodynamic phenotype is volume load

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Background
Aldosterone excess causes volume retention and cardiovascular damage. We evaluated the long-term haemodynamic changes in patients with targeted treatment of primary aldosteronism (PA) (n = 40) in comparison with essential hypertension (EH) (n = 40) and untreated normotensive controls (n = 40).
Methods
PA patients were subjected to adrenal vein sampling and allocated to adrenalectomy (n = 20) or spironolactone-based treatment (n = 20) and followed for 2.8 years (median). In the PA and EH groups, age (55 and 50 years, respectively), sex distribution (30 and 31 males), body mass index (BMI) (31 and 29 kg/m^2), and smoking status (6 and 3 present, 25 and 23 never, respectively) were corresponding. The normotensive controls had similar sex distribution and smoking status but were younger (44 years) with lower mean BMI (26 kg/m^2). Supine haemodynamics were recorded using whole-body impedance cardiography and continuous radial tonometric pulse wave analysis.
Results
The average initial number of antihypertensive medications in the PA and EH groups was 3 vs 1, and the final number was 3 vs 2, respectively, with all major classes of antihypertensives in use. Aortic systolic and diastolic blood pressures (BP) were similarly elevated in the PA and EH groups, and the values were correspondingly reduced by treatment. However, BP remained higher in both hypertensive groups than in normotensive controls. The PA and EH groups presented with similar treatment-induced reductions in systemic vascular resistance without changes in cardiac output. The foremost initial haemodynamic change in the PA patients was about 1 litre (10%) excess of extracellular water volume versus the EH and NT groups (P < 0.001) that was completely normalised by treatment. Before treatment aortic forward wave amplitude (FWA) and backward wave amplitude were correspondingly elevated in the two hypertensive groups. However, when compared with normotensive controls, the treatment-induced decrease in FWA was more pronounced in PA patients (4.1±1.4 vs 0.2±1.4 mmHg, P = 0.043) but not in EH patients (–2.1±1.2 vs 0.2±1.4 mmHg, P = 0.170). In two models of linear regression analysis, extracellular water volume (β=0.255, P = 0.007, R^2 of the model 0.338) and PA (β=0.289, P = 0.013, R^2 0.353) were independent explanatory factors for FWA.
Conclusions
Patients with PA presented with corresponding BP, systemic vascular resistance, and cardiac output, but clearly higher extracellular water volume than patients with EH. Targeted treatment of PA eliminated the volume excess and reduced aortic forward wave amplitude. These findings support the view that systematic evaluation of the volume status would benefit the clinical diagnostics and treatment of PA.

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AEP793

Pheochromocytoma crisis precipitated by invasive coronary angiography in a patient with ventricular tachycardia and raised troponin

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A 63-year-old female with cardiovascular risk factors presented with tremor, sweating, lower back discomfort, nausea and dyspnoea. ECG showed sinus tachycardia with lateral ST-depression. High-sensitivity troponin was dynamically elevated (72 ng/l to 112ng/l on one-hour repeat). Computed tomography aortogram ruled out aortic dissection but identified a 6.6cm lesion in the left adrenal gland. Ventricular tachycardia was detected on cardiac monitoring. Differential diagnoses included acute coronary syndrome and a pheochromocytoma (with arrhythmia and myocardial injury). Invasive coronary angiography demonstrated non-obstructive coronary artery disease. Post-procedure, the patient developed a pheochromocytoma crisis. This was managed with intravenous phentolamine. Our case serves as an important reminder that invasive procedures in these patients can induce potentially life-threatening hyperadrenergic episodes. Pheochromocytomas are usually benign tumours, arising from the chromaffin cells in the adrenal medulla or a paraganglion. The vast majority are hormonally active, secreting catecholamines. The resulting hyperadrenergic state causes the classic triad of symptoms; paroxysms of tremor, headache and diaphoresis. However, presentation can be varied and may mimic other conditions. They are rare, with an estimated annual incidence of 2 – 8 per million population, although this is likely an underestimation based on post-mortem studies and increasing pre-symptomatic diagnosis rates. Whilst most are sporadic cases, at least a third occur as part of a familial syndrome (e.g. von Hippel-Lindau, MEN-2, neurofibromatosis-1). Treatment is firstly medical, but in the absence of metastatic disease, cure can be achieved with surgical resection. Prior to surgery, patients need to be adequately alpha-blocked, typically for 7–14 days with phenoxybenzamine. Lifestyle advice to increase sodium and fluid intake is important pre-operatively to prevent hypotension after resection. Beta-blockers are contraindicated initially as unopposed beta-blockade can trigger

a hypertensive crisis, but can be commenced after adequate alpha-blockade. Suggested treatment of a hypertensive crisis is with intravenous phentolamine boluses followed by infusion as required for maintenance of responsee. There have been a number of published case reports showing pheochromocytomas presenting with chest pain, ECG changes and raised cardiac biomarkers mistakenly being investigated and treated as acute coronary syndromes (ACS). [*e.g.* 5–7] Given the rarity of pheochromocytomas and how common coronary heart disease is, this presentation understandably can lead to delays in the correct diagnosis. Our case report is therefore an important reminder that in those patients with confirmed or suspected pheochromocytomas, invasive procedures such as coronary angiography can trigger hyperadrenergic crises.

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AEP794

Cushing's syndrome presenting with dilated cardiomyopathy: A case report

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Background
Cardiovascular complications of Cushing's syndrome (CS) include; hypertension, left ventricular hypertrophy, and myocardial ischaemia. Also, CS can cause structural and functional changes in the heart, leading to dilated cardiomyopathy in rare cases. Here, we present a case with dilated cardiomyopathy related to Cushing's syndrome.
Case
A 31-year-old male patient applied to the cardiology department with shortness of breath that worsened with exertion for a year. Globally advanced hypokinetic and globally dilated heart was found in echocardiography with ejection fraction (EF) 20%. His medical treatment was arranged by cardiology department and referred to endocrinology clinic due to the 25 kg weight gain in one year, increased appetite and purple striae on the abdomen and shoulder. Laboratory tests revealed that; ACTH was <5 pg/ml, cortisol: 24.3 μg/dl, night cortisol: 24.7 μg/dl. After 1 mg dexamethasone suppression test (DST) and, 2 day 2 mg DST cortisol levels were found 18.9 μg/dl and 31.79 μg/dl, respectively. Because these findings suggest the CS, abdominal MRI was performed and revealed that a mass lesion (adenoma?) with a smooth contour, 37 × 28 mm in size, showing heterogeneous signal loss in the outer phase in the left adrenal gland. No pathological finding was found in pituitary MRI. With these findings, the patient was diagnosed with adreanal Cushing Syndrome. Viral myocarditis, lupus or autoimmune myocarditis was ruled out by negative viral respiratory panel, and negative autoimmune panel respectively. Absence of hilar adenopathy excluded sarcoidosis. Cardiac MRI conducted for cardiac exclusion of mixoma and revealed no findings that were consistent with the mixoma. After the exclusion of other reasons of cardiomyopathy the patient was diagnosed with dilated cardiomyopathy. In the control echocardiography 2 months after heart failure treatment, EF was found 40%. Metyrapone therapy was started gradually to lower the risk of surgery by lowering the patient's preoperative cortisol load. The cortisol level was found to be 17.4 μg/dl, 2 hours after the first metyrapone treatment. 10 days after metyrapone treatment, when the cortisol level decreased by 14.8 μg/dl, left adrenal gland excision was performed. Postoperative cortisol was found to be 1.8 μg/dl and 3.2 μg/dl. Pathology result was compatible with nodular diffuse hyperplasia.
Conclusion
Dilated cardiomyopathy and left ventricular failure are rare presentations of CS. Since cardiomyopathy can be reversed following successful treatment of Cushing's syndrome it is important to consider this diagnosis in patients with both heart failure and signs of CS.

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AEP795

Severe hypercholesterolemia with primary sclerosing cholangitis

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Introduction
Hypercholesterolemia may develop due to primary and secondary causes. Diabetes mellitus, hypothyroidism, nephrotic syndrome and liver diseases are among the most common causes of secondary hyperlipidemia. Here, we will present a case with severe hyperlipidemia due to primary sclerosing cholangitis(PSC).
Case
A 36-year-old male patient was admitted to our outpatient clinic due to severe hypercholesterolemia. It was learned in his history that he had increased liver enzymes for 3 years. He was diagnosed with PSC 4 months ago and liver transplantation was planned. The patient was using ursodeoxycholic acid 2x500 mg treatment. On physical examination, blood pressure was 120/70 mmHg, heart rate was 78 beats/minute and he had icteric appearance. Xanthoma, xanthelasma, arcus cornea was not observed. In laboratory tests, AST, ALT, ALP, GGT, total bilirubin, total cholesterol, LDL, triglyceride, VLDL, HDL were 111 U/l, 108 U/l, 1037 U/l, 301 U/l, 17 mg/dl, 574 mg/dl, 499 mg/dl, 348 mg/dl, 70 mg/dl, 5 mg/dl, respectively. The patient had no other comorbid diseases other than PSC. There was no history of early cardiovascular disease or sudden death in family members. It was learned that the patient's LDL value was 102 mg/dl 5 years ago. The cause of hypercholesterolemia in the patient was considered depending on the PSC. Statin therapy was not considered due to impaired liver function tests. We planned to start cholestyramine 12 grams per day.
Conclusion
PSC is a liver disease with biliary obstruction. Lipid disorder due to biliary obstruction is associated with lipoprotein X (LpX). LpX is a abnormal low density lipoprotein. It is unable to exert negative feedback on the cholesterol synthesis rate limiting enzyme hydroxymethyglutaryl coenzyme A (HMG-CoA) reductase. In contrast, the presence of LpX increases the activity of HMG-CoA reductase in the liver with increased hepatic cholesterol synthesis. Patients with biliary obstruction have increased LDL and decreased HDL. Hypercholesterolaemia improves with removal of obstruction or liver transplantation. LDL apheresis, statins and cholestyramine decrease cholesterol levels in patients with PSC.

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AEP796

A case of non-familial pheochromocytoma presenting one of the identical twin at young age

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Background
Pheochromocytomas are rare tumors originating from chromaffin cells and characterized by excessive catecholamine synthesis. They are usually benign lesions. Hypertension(HT), tachycardia, sweating and headache are frequently observed. We aimed to present a high malignancy suspected pheochromocytoma case diagnosed in a young age female.
Case presentation
A 20-year-old female patient was admitted to the emergency department due to high blood pressure, tinnitus and headache. The patient was hypertensive (220/110 mmHg) and had tachycardia (130/bpm). For the etiology of HT, renal doppler USG was performed. An extra-renal solid mass lesion (pheochromocytoma?) was reported. She was referred to our clinic. Surrenal MRI revealed a lesion in the left paraaortic area with 40 × 37 mm enhancement in the area corresponding to the adrenal region. 24-hour urinary normetanephrine and metanephrine levels were found 10 times higher than upper limit of the reference range. Laparoscopic partial adenomectomy was performed by the urologist. After surgery, blood pressure was return to normal range without any medication. In histopathology, Ki 67 proliferation index was reported as 20%. Periadrenal adipose tissue invasion, atypical mitosis, lymphovascular invasion and capsule invasion were found positive. Calculated PASS score was reported 6/21 and it was evaluated as high suspicion of malignancy. Genetic analysis (VHL, MEN, SDH) result was negative. The patient had an identical twin. Pheochromocytoma symptoms of the identical twin were not present**.** In the literature some cases of identical twins which have concominant pheochromocytoma were reported. We performed pheochromositoma screening tests for identical twin and no pathology was found.
Conclusion
Although pheochromocytoma is most common in the 4th and 5th decades, it can be seen in all age ranges. The majority of patients are sporadic, there are

also hereditary forms. Genetic background should be investigated in patients diagnosed with pheochromocytoma at the young age. Although our case was diagnosed with pheochromocytoma at a young age, her genetic tests was not showed any mutation.

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AEP797

Effect of dexamethasone's and triptorelin's treatment in 9-year-old girl with congenital adrenal hyperplasia due to 21- hydroxylase deficiency-case report

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Congenital adrenal hyperplasia due to 21-hydroxylase deficiency is the most common disorder, in which lack of the enzyme causes deficiency aldosterone and cortisol. The result of this deficiency is an increased level of ACTH. The classic form appears in early childhood and may be associated with the development of abnormal genitalia. Clinically older patients present the GnRH-independent precocious puberty with rapid growth and advanced bone age. We present the case of 9-year-old girl, who was treated of the congenital adrenal hyperplasia due to 21- hydroxylase deficiency. When the girl was 5 years old, she was diagnosed because of precocious puberty. The height and weight were over 97 percentile, bone age – 11 years, advanced puberty by Tanner stages: Th1, Pub 3, Ax 1, enlarged clitoritis. In laboratory tests the patient had normal cortisol level in serum and elevated adrenal androgens. Congenital adrenal hyperplasia was confirmed in steroid profile in urine. The hydrocortisone had been administered orally in dosages of 8-12 mg/m^2/day in three divided doses. The side effect of that therapy was hypertension. The result of using hydrocortisone was slow down progression of bone age. When the girl was 7.5 years old, because of progress precocious puberty, the test with GnRH was performed. Central precocious puberty was treated with triptorelin to achieve gonadotropin inhibition. Due to insufficient improvement after treatment with hydrocortisone the using therapy with dexamethasone (0.5 mg daily orally) caused decreased level of androgens, slowed growth during first year of treatment and normalization steroid profile in urine.

Results

1). The preferred glucocorticoid for chronic treatment of the congenital adrenal hyperplasia due to 21- hydroxylase deficiency is hydrocortisone. 2). For the purpose of prevented hyperandrogenism in children and adolescents it is important to treat the patient by antiandrogenic drugs. 3). Sometimes, precocious puberty should be treated centrally in children.

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AEP798

Evaluation of subclinical cardiovascular disease by carotid intima media thickness, epicardial adipose tissue thickness, serum endocan, and nesfatin-1 levels in patients with primary hyperparathyroidism

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Background

Primary hyperparathyroidism (PHPT) is known to be associated with cardiac and metabolic morbidities. Chronic hypercalcemia in PHPT patients has been reported to be associated with an increased risk of mortality, particularly due to cardiovascular disease, during long-term follow-up. Endocan is secreted by vascular endothelial cells and is involved in the regulation of important endothelial functions. Endocan secretion increases in a variety of endothelium-related pathological conditions such as atherosclerosis, inflammation, infections, and tumor progression. Nesfatin-1 was found to be expressed in the hypothalamus and involved in regulating food intake. Nesfatin-1 has also been found to have some cardiovascular effects such as regulation of blood pressure and heart rate, role in cardiomyocyte metabolism, and protection against ischemia / reperfusion injury.

Objective

The aim of our study was to evaluate the clinical relevance of serum endocan and nesfatin-1 levels, EAT thickness and CIMT as markers of increased CVD risk in patients with PHPT.

Materials and methods

In this case-control study, 44 patients with clinical evidence of PHPT, and 40 healthy control subjects were enrolled from October 2019 to October 2020. Serum concentrations of endocan and nesfatin-1 were measured by ELISA.

Results

CIMT values were statistically significantly higher in the PHPT group compared to the control group (P = 0.001). EAT thickness values were higher in the control group compared to the PHPT group, but there was no statistically significant difference (0.454). Serum endocan level was measured as 824.8±351 pg/ml and 826.68±373.65 pg/ml in PHPT patients and control group, respectively. Serum nesfatin-1 level was measured as 148.8±4.5 pg/ml and 149.14±5.66 pg/ml in PHPT patients and control group, respectively. There was no difference between the two groups in terms of serum endocan and nesfatin-1 levels (P = 0.963 and P = 0.510, respectively). In correlation analysis, a negative correlation was found between PTH and LDL cholesterol levels (P = 0.001). No significant relationship was found between other parameters.

Conclusions

No significant difference was found between PHPT patients and healthy controls in terms of serum endocan and nesfatin-1 levels. CIMT, which is a marker of CVD risk, was found to be increased in mild PHPT patients and consequently, CVD risk is high in these patients, but no relationship was found in terms of serum endocan and/or nesfatin-1 levels.

Keywords: primary hyperparathyroidism, carotid intima media thickness, epicardial adipose tissue thickness, endocan, nesfatin-1, cardiovascular disease risk.

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AEP799

Comparison of patients with normocalcemic and hypercalcemic primary hyperparathyroidism

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Objective

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia. A group of patients who were followed up with a diagnosis of PHPT had normal calcium levels with high parathyroid hormone (PTH) levels. For the diagnosis of normocalcemic PHPT, secondary causes of hyperparathyroidism such as vitamin D deficiency should be excluded. In this study, the data of 318 PHPT patients who were operated were retrospectively analyzed, and biochemical and clinical characteristics of hypercalcemic and normocalcemic patients were compared.

Methods

The data of patients who were admitted to our hospital's endocrinology clinic between January 2012 and January 2019, diagnosed with PHPT and operated according to guidelines (all symptomatic patients and asymptomatic patients with at least one operation indication) were retrospectively evaluated. A total of 318 patients were divided into two groups as hypercalcemic and normocalcemic according to the corrected calcium level. The two groups were compared according to clinical and biochemical properties.

Results

Female gender was dominant in both groups (P = 0.07). The mean age was similar in both groups (P = 0.36), while it was 54.0 ± 10.3 in the hypercalcemia group, and 55.4 ± 12.8 in the normocalcemia group. As expected, serum corrected calcium (Ca), PTH levels and urinary Ca excretion were higher in the hypercalcemia group (P < 0.01). While phosphorus (P) level was lower in the hypercalcemia group (P < 0.01), urinary P excretion was similar between the two groups (P = 0.77). There was no difference between the two groups in alkaline phosphatase, creatinine, and vitamin D levels. Percentage of localization with preoperative ultrasonography and mean adenoma size were similar. Also, there was no difference in adenoma features (echogenicity, cystic appearance) and localization, thyroid nodules and thyroiditis prevalence on ultrasonography. The positive result obtained on neck MRI and MIBI scanning was similar. There was no difference between the two groups in terms of stone incidence and osteoporosis prevalance (P = 0.72 and P = 0.08, respectively).

Conclusion
In our cohort, corrected Ca and PTH levels and urinary Ca excretion were high in the hypercalcemic group, as expected. But, the phosphorus level was significantly lower in the hypercalcemia group. In the normocalcemic group, the PHPT phenotype was found to be similar to the hypercalcemic group. These findings suggest that the frequency of surgical indications is similar in normocalcemic PHPT patients to that in hypercalcemic PHPT patients.

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AEP800

Vitamin D deficit in type 2 diabetes patients during the winter in Northern Gran Canaria with and without supplementation

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Introduction
Vitamin D deficiency is associated with higher risk of COVID-19, and type 2 diabetic patients are a vulnerable group. We described an alarming rate of vitamin D deficiency (81.0% < 30 ng/ml plasma calcifediol) in unsupplemented type 2 diabetes patients during the 2020 spring lockdown in Northern Gran Canaria. During the winter period (December 2020 to February 2021) some restrictions for social gatherings and a nightly curfew have been enforced but there was no mandatory lockdown.
Objectives
To assess the prevalence of vitamin D deficiency in type 2 diabetic patients from Northern Gran Canaria during the winter period (December 2020 to February 2021).
Methods
Plasma calcifediol levels were sampled in an unselected type 2 diabetic population, along with age, gender and vitamin D supplementation status.
Results
Data were obtained from 227 consecutive patients, 133 female (58.6%), mean age 59.7 ± 14.7 years. 103 (45.4%) were taking vitamin D supplements. Mean plasma calcifediol was 31.2 ± 13.0 ng/ml; but it was lower than recommended (<30 ng/ml), in 50.2% of the patients, deficient (<20 ng/ml) in 20.3% and severely deficient (<12 ng/ml) in 5.3%. In supplemented patients, calcifediol was mostly adequate (mean 41.1 ± 10.7 ng/ml, with 15.5% < 30 ng/ml, 3.9% < 20 ng/ml, none < 12 ng/ml and none > 80 ng/ml) but low in unsupplemented patients (mean 23.0 + 8.2 ng/ml, with 79.0% < 30 ng/ml, 34.7% < 20 ng/ml and 9.3% < 12 ng/ml). Plasma calcifediol was significantly higher in supplemented patients (mean difference 18.1 ng/ml, unpaired *t*-test, $P < 0.0001$) and the proportions of low, deficient and severely deficient patients were significantly lower (Fisher's exact test, $P < 0.0001$, $P < 0.0001$ and $P = 0.0006$, respectively). Female patients had slightly higher plasma calcifediol than males (mean difference 4.1 ng/ml, unpaired t-test, $P = 0.019$). There was an inverse correlation between age and plasma calcifediol (coefficient -0.091, $P = 0.004$).
Conclusions
Even without a mandatory lockdown, the prevalence of low calcifediol levels during the winter months in our unsupplemented type 2 diabetic population is extremely high. However, when taking vitamin D supplements their vitamin D status is satisfactory with < 4% deficient patients and none severely deficient. Their use was effective to prevent the deprivation associated with voluntary lockdown, social gathering restrictions and low insolation during wintertime.

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AEP801

A case report of Primary hyperparathyroidism presenting as a brown tumor in the mandible

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Brown tumor (BT) is a rare bony benign lesion caused by excess osteoclast activity and hemosiderin deposition because of uncontrolled primary or secondary hyperparathyroidism. 71-year-old man with no significant pathological history, twelve months before admission presented with growing mandibular brown tumor and bone pain in lower limbs. He was referred to Endocrinology unit. Physical examination found left facial paralysis, absence of horizontal branches and left jaw ascending. A total parathyroidectomy was performed without implantation of a parathyroid fragment into the forearm muscle. PTH was monitored intraoperatively, and the PTH level decreased. A histopathological examination of the mass confirmed the diagnosis of parathyroid adenoma with a tumor result of giant cells of 1.8 × 5 × 4 cm with necrotic and hemorrhagic areas and serum PTH level continued to decrease after surgery. Surgical resection of a brown tumor is generally not recommended and should only be considered if the patient wants quick resolution, if the bony lesion is compromising body functions or promoting facial deformation, or if the lesion fails to regress after 1–2 years. The 10-year duration of our case was too long, reflecting the inadequacy of preventing and managing brown tumors in underdeveloped countries like Peru where is from our patient. In developed countries, PHPT is mostly diagnosed by routine biochemical screening without clinical signs suggesting the disease, so the classical manifestations of PHPT are very uncommon. The case of an older adult patient with an unusual presentation of primary hyperparathyroidism by a mandibular-level brown tumor is present as an initial manifestation, which should be considered in differential diagnosis when evaluating a patient with a bone tumor at the maxillary level presenting with multifocal osteolytic bone lesions, although bone metastases and multiple myeloma still should be considered first.

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AEP802

Hypovitaminosis D in patients with SARS-CoV2: Correlation with inflammatory markers and severity of the disease

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In March 2020, the infection due to **COVID-19** spread as a pandemic emergence showing a mutable phenotype ranging from asymptomatic to lethal severe acute respiratory syndrome coronavirus 2 **(SARS-CoV-2).** Among multiple biological and environmental investigated factors, **vitamin D status was proposed as a credible candidate**, since hypovitaminosis D could be identified as a modifiable risk factor and a potential tool in SARS-CoV-2 prevention or ancillary treatment.
The aim of this study is to analyse the relationship between vitamin D status and a complete biochemical panel of immune system markers (pro and anti-inflammatory factors), in a cohort of patients with SARS-CoV-2. This was a **retrospective, observational study** conducted on available serum samples from consecutive patients with COVID-19 related pneumonia, admitted from March to May 2020 in two Hospital Units (Pulmonary and Geriatric Unit) in Pisa.
A total of 93 patients were included in the study, they were mainly males ($n = 64$, 68.8%) with a mean age of 68±16 years (median 69 i.r 57–80). Mean 25OHD was 17.3±10.7 ng/ml, with a median of 16.5 ng/ml (i.r. 7.9–23.2). Eighty-three patients had 25OHD levels ≤ 30 ng/ml (89%), 61 patients (65%) had 25OHD levels £20 ng/ml and 27 patients (29%) had 25OHD £10 ng/ml (severe vitamin D deficiency). Inflammatory markers were measured in all patients and compared between patients with 25OHD levels >20 ng/ml and those with ≤ 20 ng/ml. The latter showed significantly higher IL-6 [20.8 (10.9–45.6) vs 12.9 (8.7–21.1) pg/ml $P = 0.02$], CRP [10.7 (4.2–19.2) vs 5.9 (1.6–8.1) mg/dl $P = 0.003$], TNFα [8.9 (6.0–14.8) vs 4.4 (1.5–10.6) pg/ml $P = 0.01$], D-dimer [0.53 (0.25–0.72) vs 0.22 (0.17–0.35) mg/l $P = 0.002$] and IL-10 [3.7 (1.8–6.9) vs 2.3 (0.5–5.8) pg/ml $P = 0.03$] (Figure 1 panel A-E). In the overall group, an inverse correlation was found between 25OHD and IL-6 ($r = –0.22$, $P = 0.03$), between 25OHD and CRP ($r = –0.21$, $P = 0.04$), between 25OHD and D-dimer ($r = –0.43$, $P = 0.001$), between 25OHD and IL-10 ($r = –0.25$, $P = 0.02$) (Figure 2 panel A-D). These correlations remained statistically significant in a multivariate linear regression analysis, adjusted for age and gender [β=-0.64, $P = 0.04$ IL6; β=-0.17, $P = 0.03$ CRP; β=-0.017, $P = 0.001$ D-Dimer; β=-0.11, $P = 0.02$ IL-10]. In conclusion, hypovitaminosis D is related to the negative prognostic inflammatory status in patients with SARS-Cov2.

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AEP803

Physical activity and female sexual dysfunction: too much of a good thing?

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Background
Research on the relationship between physical activity (PA) and female sexual dysfunction (FSD) is lacking.
Aim
To investigate the clinical, psychological, and sexual correlates of PA in women with FSD.
Methods
A non-selected series of n = 322 pre- and post-menopausal patients consulting for FSD was retrospectively studied. Regular involvement in PA and its frequency (<1 hour/week: sedentary, 1–3 hours/week: active, 4–6 hours/week: very active, >6 hours/week: extremely active) were investigated with a specific question.
Outcomes
FSDs, including HSDD (Hypoactive sexual desire disorder) and FGAD (Female genital arousal disorder), were diagnosed according to a structured and clinical interview. Participants underwent a physical examination and a clitoral Doppler ultrasound, and were asked to complete the Female Sexual Function Index (FSFI), Female Sexual Distress Scale-Revised (FSDS-R), Body Uneasiness Test (BUT), and Middlesex Hospital Questionnaire (MHQ).
Results
At multivariate analysis, women engaging in PA (67.4%, n = 217) scored significantly higher in several FSFI domains - including desire, arousal and lubrication - and showed lower sexual distress and lower resistance of clitoral arteries, as compared to sedentary women. A significant, inverse association between PA and HSDD was observed. Mediation analysis demonstrated that the negative association between PA and HSDD was partly mediated by body image concerns (BUT Global severity index), psychopathological symptoms (MHQ total score) and sexual distress (FSDS-R score). These latter two factors also partly mediated the association between PA and a reduced risk of FGAD, whilst a lower BMI was a full mediator in the relationship between PA and FGAD. Finally, extreme PA was associated with significantly worse scores in several psychosexual parameters (i.e. sexual satisfaction and histrionic/hysterical symptoms), even compared to a sedentary lifestyle.
Clinical Implications
Women consulting for FSD may gain benefits on desire, arousal, lubrication and sex-related distress from regular PA; however, physicians should remain alert to the downsides of excessive exercise.
Strengths & Limitations
The main strength lies in the novelty of the findings. The main limitations are the cross-sectional nature, the clinical setting, the small sample size of the different PA groups, and the use of self-reported instruments for the evaluation of PA.
Conclusion
In women with FSD, PA was associated with better sexual function and clitoral vascularization, lower sexual distress and reduced odds of HSDD and FGAD; the benefits of PA on sexuality were mediated by both psychological and organic determinants; excessive PA was related with a poor overall sexual function and with a low sexual satisfaction.

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AEP804

Effects of Christian Orthodox versus intermittent fasting on plasma irisin concentrations in overweight adults

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Irisin is an adipomyokine produced during physical activity and implicated in the browning of adipose tissue. Existing evidence suggests an inverse relationship between irisin plasma levels and adverse metabolic outcomes; however, the exact impact of diet on irisin levels remains unclear. We aimed to assess the effects of two dietary patterns, Christian Orthodox fasting (OF) and 16:8 time-restricted eating (TRE), on irisin concentrations among overweight, metabolically healthy, subjects. Plasma irisin, glycemic indices, lipid parameters, calcium homeostasis markers, and anthropometry were measured in 29 Orthodox fasters and 14 age- and body mass index (BMI)-matched TRE controls (mean age and BMI 48.8 years and 28.7 kg/m^2, respectively) at three time points: before the implementation of the energy-restricted diets (baseline), at the end of the dietary intervention (7 weeks) and 5 weeks after participants returned to their standard dietary habits (12 weeks from baseline). At 12 weeks, the OF group had higher irisin concentrations than both its baseline values (64.3 ± 54.4 vs 43.6 ± 42.2 ng/ml, P = 0.01) and those of the TRE group at the same time point (64.3 ± 54.4 vs 44.2 ± 26.6 ng/ml, P = 0.04). Glycemic, lipid, and anthropometric markers were not found to correlate with irisin levels. Parathyroid hormone (PTH) concentrations at 12 weeks correlated with irisin levels (P = 0.04), with lower values of irisin expected for higher PTH. Our findings suggest favorable long-term effects of OF on irisin status. The interaction between irisin, PTH, and nutrition deserves further investigation.

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AEP805

Self-management behavior of the patients with type 2 diabetes: A cross-sectional survey in the eastern european population (Belarus)

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Background
The prevention of complications and improvement of metabolic control and state of health in diabetes cannot be effective only with medications. And now we need to develop different approaches – not only up to date pharmacological treatment of diabetes, but change the Self-Management Behavior among patients with Type 2 Diabetes.
Aims
To assess the current status of diabetic self-management behavior and the factors responsible for such knowledge among type 2 diabetes patients in Minsk, Belarus.
Methods
A correlational, exploratory, quantitative research design was utilized. We used the Diabetes Self-Management Questionnaire (DSMQ) and a questionnaire with free questions related to diabetes to investigate patients with T2DM from August to December 2020 in Minsk, Belarus.
Results
We enrolled a total of 206 patients in the present study. The median score of self-management behavior was 5.48 (10 maximum point), the interquartile range was 4.64–6.04 points. An analysis of subscale was: "Glucose Management" was 7.33 (6.00; 8.00) (P -value: < 0.001); "Dietary Control" 5.00 (3.33; 5.83) (P-value: < 0.001); "Physical Activity" 4.44 (2.22; 5.56) (P -value: < 0.001); "Health-Care Use" 5.56 (3.33; 6.67) (P -value: < 0.001). Answers for the 16th item "My diabetes self-care is poor" were: "Applies to me very much" 27.20%; "Applies to me to a consider-able degree" 4.76%; "Applies to me to some degree" 33.80%; "Does not apply to me" 34.27%. Further, a correlation was made between the onset of the disease, the patient's age, the degree of cognitive impairment, the average mean of hemoglobin A1c and DSMQ subscales.
Discussion
Self-Management Behavior in Patients with Type 2 Diabetes was negatively correlated with: the duration of the course of diabetes; the patient's age; the degree of cognitive impairment; the existing disorders of carbohydrate metabolism.

Conclusion
There are a number of reasons that could affect on changes in Self-Management behavior. It is likely that the maximum Self-Management behavior changes are available to the patient in the early stages of the onset of type 2 diabetes. Given the limited capacity of any national health care system, it is worth paying attention to the possibility of making maximum efforts to change Self-Management behavior among patients in whom the period of diagnosis of diabetes mellitus is from 1 to 2 years.
Keywords: type 2 diabetes mellitus, DSMQ, self-management, behavior, self-care management, eastern europe.
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AEP806

Rapid onset of severe diabetes in adult patients with prior, mild SARS-COV-2 infection

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COVID-19 is affecting Northern Italy since early 2020 and long-term consequences of the pandemia are progressively coming to light. Over the past months, a marked increase in the number of adults with rapid-onset severe diabetes has been observed at the Diabetes Clinic thus prompting an evalutation into possible links with COVID-19. Of note, diabetes and hyperglycaemia are known to worsen during COVID-19 and there are several reports of new-onset hyperglycaemia during SARSCoV2 infection, possibly due to the links between SARS-CoV-2 and pancreatic islet damage. Aim of the present study was to review charts of adult patients with newly diagnosed, severe diabetes recorded after the first pandemic wave.
Methods
Data relating to diabetes and SARS-CoV-2 infection was reviewed in patients attending the Diabetes Clinic from September 2020 to March 2021.
Results
Out of 120 patients who attended the clinic in the 7-month span, four (2 men and 2 women, age 51–71 years) presented with recent-onset, severe diabetes. None had previous history for hyperglycaemia or diabetes. Features of uncontrolled hyperglycaemia (e.g., weight loss, glycosuria, polyuria) had developed over the prior 2–3 months; patients were normal-weight or midly overweight and did not report significant changes to their eating habits. HbA1c ranged from 10.7% to 14.1%, fasting glucose from 300 to 410 mg/dl. Testing for autoantibodies common to Type 1 diabetes proved negative. Two patients had previously presented mild symptoms of COVID-19 and tested positive for SARS-Cov-2 whereas the other two reported close contacts with SARS-CoV-2 positive individuals during past months. None of the patients had been hospitalized or required any treatment for COVID-19-related symptoms.
Conclusions
This report describes an increased incidence of rapid-onset, uncontrolled hyperglycaemia in adults with no known risk factor for diabetes in the aftermath of the first COVID-19 pandemic wave. Severe diabetes developed months after mild or asymptomatic SARS-CoV-2 infection and mandates the need for an increased awareness among physicians given the sheer number of individuals who came and will come in contact with SARS-CoV-2.
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AEP807

Abstract withdrawn
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AEP808

Significance of technology in diabetes care during pandemic in our county hospital

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Introduction
In last two decades, new technological advances have permitted the use of novel approaches to the management of diabetes. Continuous Glucose Monitoring (CGM) has been linked to improved HbA1c and overall quality of life. The evidence, however, is limited to retrospective studies. This audit was designed to evaluate the effectiveness and impact of CGM before and after on HbA1c and quality of life in clinical practice setting during pandemic in our county for 12 patients in our local Diabetes Day Centre (DDC).
Methods
Data of diabetes patients identified from medical notes of DDC in Our Lady's hospital of Navan for patients commenced on DEXCOM CGM since we started using CGM in 2019. Total number of patients recruited for this audit is12. All patients have type I diabetes mean age of participant is 38 years for 10–12 months duration.
Patients Contacted by phones to answer the following questions:
- Frequency of hypoglycemia (<4 mmol) episodes before and after getting CGM?
- HbaA1C before and after CGM? Collected from our lab system.
- Lifestyle quality after getting CGM system?
- Satisfaction: Are patients satisfied with DEXCOM CGM (less hypoglycemia, less stress in diabetes control, more confidence)? With rating (0–10) Score.

Table 1 Hypoglycemia before and after, Hba1c before and after CGM

Number	Hypoglycemia before CGM	Hypoglycemia after CGM	HbAlc before CGM (mmol/mol)	HbAlc after CGM (mmol/mol)	Life quality after CGM	Satisfaction score 0–10
1	up to few limes aclay,	Twice a month	92	78	improved	7
2	up to 5 times a month	Nil	94	64	improved	10
3	Once a month	Once a month	74	70	Improved	10
4	Once a clay	Once a month	66	55	Improved	10
5	Tree times/clay	3 times/week	88	73	Improved	10
6	4 times/week	One time/week	66	58	improved	9
7	Once every week	Once every 3 months	80	64	improved	8
8	Up to 8 per week	Up to 2 per week	59	70	improved	10
9	Once per month	No hypoglycemia	113	91	improved	8
10	Almost every day	No Hypoglycemia	91	101	improved	10
11	Once per month	No hypoglycemia	85	70	improved	8
12	Once every week	No Hypoglycemia	50	Not done	improved	

Results
Among 12 patients with type I diabetes who were commenced on CGM, it shows:
- All patients have no or very little hypoglycemia after CGM with hypoglycemia confidence.
- 90% of patients had reduced overall HbA1c after CGM and less diabetes distress.
- All patients noted remarkable improvement in quality of life.
- All patients satisfied with CGM technology and more than half of patients have 100% satisfaction and others more than 80% satisfaction.

Figure 1 Satifaction score of patients on technology.

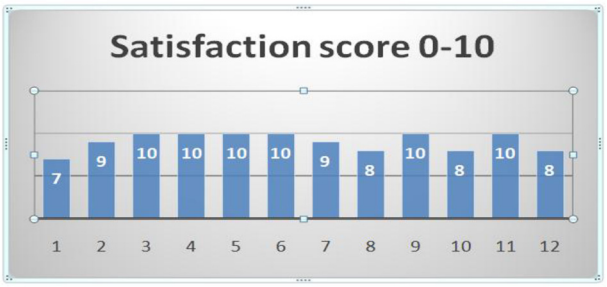
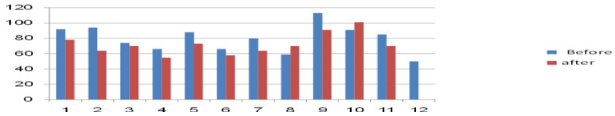


Figure 2 Average HbA1c pre and post CGM.



Conclusion
Obviously, it is highly recommended to consider CGM a common and useful tool in diabetes care who was at high risk of dysglycemia. It showed significant improvement in less time spent for day and nocturnal hypoglycemia. Patients feel safer and more confident during pandemic where the diabetes care facilities are very limited. It provided remarkable

glycemic control and positive effects on HbA1c levels. Less dysglycemia, as a result, improved life quality.

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AEP809

Comparison of the clinical efficacy of Semaglutide between DPP4-inhibitor-naive and DPP4-inhibitor-experienced patients in a real world setting in Spain

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Introduction

Glucose and weight control effectiveness in patients with Type 2 diabetes (T2D) in treatment with DPP4 inhibitors (DPP4i) that switch to semaglutide is scarce. We aim to assess it in a real-world setting of DPP4i-experienced patients and compare it to DPP4i-naive patients.

Methods

Patients with T2D that were prescribed Once-Weekly semaglutide in 4 hospitals in Madrid-Spain were identified. Patients with another new glucose-lowering-agent prescription and GLP1-experienced patients were excluded. A total of 250 patients were included. The Changes at 6 months of follow up (Paired T-test, Exact McNemar), and comparison between groups (T-test and Chi^2) were analysed. A multiple linear regression model to assess HbA1c change in both DPP4i groups (naive vs experienced) adjusted by age, T2D duration, BMI, baseline-HbA1c, insulin use, SGLT2-inhibitors use and semaglutide dose was perfomed.

Results

Baseline weight and BMI was higher in DPP4i-naive group and HbA1c was higher in DPP4i-experienced group. A higher proportion of patients in the DPP4i-naive group had a baseline-HbA1c <7% compared to DPP4i-experienced. There were no other baseline differences (Table 1). At 6 months of follow up boths groups achieved significant reductions in HbA1C, Glucose, weight, BMI and fat mass, but there were no differences between groups. The proportions of patientes that achieved a HbA1c <7% was higher in the DPP4i-naive group (Table-2). Only patients in the DPP4i-naive group achieved a signifficant reduction in insuline dose. After adjusment, the HbA1c reduction in the DPP4i-experienced group was 0.36% lower than in DPP4-naive (IC95%: 0.14% to 0.59%).

Conclusions

Switching to semaglutide is an effective glucose and weight lowering treatment in DPP4i-experienced patients with T2D.

Table 1 Baseline Characteristics

	DPP4i-Naïve n = 153	DPP4i-experienced n = 97
Age(years)	60.1±11.0	62.0±9.5
Male	55.6%	52.6%
T2D duration (years)	9.2±7.4	11.13±7.6
Weight (kg)$^{\omega}$	100.4±18.4	94.2±13.7
BMI (kg/m^2) $^{\omega}$	37.0±6.0	34.8±4.1
Metformin treatment	88.2%	82.5%
SGLT2-inhibitors treatment	40.0%	32.0%
Insulin treatment	35.3%	41.2%
HbA1c (%) $^{\omega}$	7.6±1.4	8.0±1.3
eGFR (ml/min/1.73 m^2)	85.7±20.1	80.2±24.3
HbA1c <7% $^{\omega}$	43.1%	22.7%

Table 2 6-month Clinical Outcome

	DPP4i-Naive *n* = 153	DPP4i-experienced *n* = 97
Glucose(mg/dl)	-29.0 (-37.4 to –20.7)*	–26.1 (–35.4 to –16.9)*
HbA1c (%)	–1.15 (–1.35 to –0.94)*	–0.98 (–1.24 to –0.74)*
Weight (kg)	–5.3 (–6.1 to –4.4)*	–4.0 (–5.1 to –3.0)*
BMI (kg/m^2)	–1.9 (–2.3 to –1.6)*	–1.5 (–1.9 to –1.1)*
Fat mass(kg)	–1.54 (–2.84 to –0.24)* *n* = 54	–1.96 (–3.66 to –0.27)* *n* = 28
Lean mass(kg)	–0.97 (–2.06 to 0.10) *n* = 49	+0.25(–1.31 to 1–83) *n* = 27
HbA1c <7% $^{\omega}$	74.5%*	57.7%*
Insuline dose(IU) $^{\omega}$	–11.3 (–18.1 to–4.5)*	–0.9(–5.8 to 4.0)

*P<0.05 (6 months vs baseline).
$^{\omega}P$ <0.05 (DPP4i-Naive vs DPP4i-experienced).

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AEP810

Peripheral serotonin and its interaction with other hormones, in male Wistar rats with obesity and obesity-induced diabetes, studied by using of LP533401

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Background and aims

95% of serotonin is produced in the periphery. Serotonin system in the periphery regulates multiple physiological aspects. In previous researches that we made, using the Tph1 inhibitor - LP533401 (peripheral serotonin inhibitor) it shows that this agent could be use for treatment of obesity and obesity-induced diabetes in male Wistar rats. With current study we aimed to look more detailed in to fine mechanisms of action of serotonin related with other hormones such as ghrelin and leptin.

Materials and methods

We used forty Wistar rats separate in 2 groups- rats with induced obesity and diabetes and healthy rats (control group). Each of this groups was separated in other 2 - one with daily intraperitoneal injection of LP533401 (0.5 mg/kg) and one without. In 4 weeks period, we were tracking different factor-blood glucose level, insulin secretion, rats weight, blood levels of ghrelin and leptin. We measured the level of ghrelin and leptin in the beginning of the study and in the beginning of every week just before the meal.

Results

After application of LP533401, the blood levels of ghrelin starts to change. In the group with diabetic and obese rats using LP544401, the levels of ghrelin decreased of 5.4% for the first week till 12.2% in the fourth week (P<0.05), and with 9,4% (in total) in the control group. No significant dynamic in the groups without daily intraperitoneal injection of LP533401. Also there were significantly reduction of hyperglycemia and peripheral insulin resistance and reducing body weight in the obese and diabetic rats group, but also in the control group using LP533401. In the beginning of the study, the levels of leptin were around 3 times higher in the diabetic and obese rats' groups both using LP533401 or not. During the study, the leptin level in the diabetic and obese rats group using LP533401 decrease with 54.4% (P <0.05). In the diabetic and obese rats group in which we were not using LP533401, the levels of leptin raised with 5.4%.

Conclusion

Using LP533401 inhibitor significantly decrease fasting blood level of ghrelin in rats with induced obesity and diabetes, which corresponded with their weight loss and reduction of hyperglycemias. The level of leptin in the group whit diabetic and obese rat using LP533401, also decrease significantly together with their weight loss, which leads us to the conclusion for decreasing of leptin resistance in this group.

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AEP811

Post-transplant dyslipidemia in two cases

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Introduction
Lung transplantation was associated with a 32% prevalence of hypercholesterolemia and a 41% prevalence of hypertriglyceridemia. The prevalence of dyslipidemia in liver transplant recipients is 43% and 31% –51%. In this report, we present 2 cases who developed dyslipidemia after transplantation.
Case 1
The blood test of a 73-year-old male patient who had lung transplantation about 3 years ago revealed Triglyceride (TG) 475 mg/dl (<150), LDL-Cholesterol: 382 mg/dl (<100), HDL 53 mg/dl (>40), Total cholesterol 431 mg/dl (<200) and HbA1C: 8.3. Six months ago, he was diagnosed with diabetes mellitus by his primary physician. He was on everolimus, prednisolone, and mycophenalate sodium therapy, and was referred to us. There were no cutaneous findings related to hyperlipidemia. After the diet and blood sugar regulation, the tests were repeated; TG was 422 mg/dl and LDL was 366 mg/dl. He had elevated liver function test (LFT) levels, and hepatitis panel and liver auto antibodies were negative. Atorvastatin 1× 10 mg was initiated on 14/02/2020. TG was 210 mg/dl (<150), and LDL cholesterol level was 123 mg/dl (<100).
Case 2
A 65-year-old female patient underwent liver transplantation from a cadaver on 12/09/2019 due to toxic hepatitis and on 25/09/2019 due to hepatic vein thrombosis after transplantation. Receiving tacrolimus and mycophenolic acid treatments after transplantation, she developed refractory dyslipidemia after the second transplant. Tests performed in February 2020 showed levels of Triglyceride 474 mg/dl (<150), LDL-Cholesterol 512 mg/dl (<100), Total Cholesterol 815mg/dl (<200) and HDL cholesterol 11 mg/dl (>50). Pravastatin 1 × 40 mg was initiated in February 2020 and intermittent lipid apheresis was performed. In April 2020, ezetimibe 1 × 10 mg was added to her treatment. In May 2020, LDL level was determined 186 mg/dl.
Discussion
Maintaining or improving allograft function after transplantation and reducing cardiovascular risk are main objectives during follow-up. Interventions for dyslipidemia have the effect of reducing cardiac events in clinical studies specific to transplant population.

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AEP812

Psychological factors in type 2 diabetes mellitus: A cross-sectional survey in the eastern european population (Belarus)

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Background
It has often been argued that important psychosocial factors such as depression, anxiety and emotional stress can influence self-help behavior and therefore negatively affect glycemic control. In turn, the reduced quality of life due to chronic illness is a mediated cause of poor glycemic control. Also, attention is drawn to the prevalence of cognitive impairments and dementia.
Aims
1) to assess the psychological status of patients with diabetes; 2) to describe subgroups of patients with anxious and depressive reactions; 3) to assess quality of life. To assess the current status of diabetic self-management behavior and the factors responsible for such knowledge among type 2 diabetes patients in Minsk, Belarus.
Methods
Questionnaires were used to assess cognitive impairment (MoCA), depressive disorders (PHQ-9), anxiety disorders (GAD-7), quality of life (RU-ADDQol).
Results
We examined a total of 206 patients in the present study. The prevalence of cognitive decline was 79.07±3.10% (136/172) (25 and below points) in patients with type 2 diabetes. The average score was 19.00 (18.00; 25.00). The average value of depressive reactions on the PHQ-9 scale in the study group was 11.00 (8.00; 13.00). Mean of anxious reactions on the GAD-7 scale in the study group was 8.50 (5.75; 11.00). The average value of the quality of life on the RU-ADDQol scale in the study group was –3.21 (–3.68; –2.84); the average value for men is –2.63 (–3.12; –2.42), for women –3.39 (–3.74; –3.04). The differences are statistically significant between men and women (W-statistic: 4144.50, p-value: <0.001). The lowest score was obtained for the parameter motivation (–4.11), freedom to eat (–4.48), financial situation (–4.18), feelings about future (–3.87). We also analyzed the correlation of the level of glycated hemoglobin with the level of cognitive decline, depressive and anxiety reactions, and the level of quality of life.
Discussion
The prevalence of cognitive impairments, anxiety and depressive reactions in the population of patients with type 2 diabetes mellitus is higher than among a similar sample of healthy people. Psychological factors (cognitive impairment, anxiety and depressive reactions) negatively affect metabolic parameters, motivation and limit the ability to adapt to type 2 diabetes. In addition, mental factors were directly correlated with poor glycated hemoglobin levels and quality of life.
Keywords: behavior, RU-ADDQol, diabetes/quality of life, depression, anxiety, psychology, type 2 diabetes mellitus, eastern europe.

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AEP813

Three faces of the metabolic syndrome in children

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Introduction
As the incidence of pediatric obesity is increasing, so is the incidence of metabolic syndrome in the pediatric population. We present the management of 3 such cases.
Case report
Three 14 (D.D), 15 (C.A.), 16 (C.M) year-old males presented for weight and metabolic management.DD had a medical history weight gain since 2 years old, obesity, dyslipidemia, hyperuricemia. C.A., obese since 2018, with hypertriglyceridemia and insulin resistance (HOMA-IR of 3.71). C.M., obese since 2015, with a Bethesda II 1.5 cm thyroid nodule (right lobe), hyperuricemia since 2017. All three had important first degree antecedents of type 2 diabetes, hypertension and metabolic syndrome. The clinical examination showed in all three boys normal pubertal Tanner stage (P4–5G4), D.D: BMI 35.5, 1.68 m (+2SD), 44% fat, 179% obesity degree, BP 130/80 mmHg and a waist circumference: 113 cm, C.A.: BMI 30.2, 1.82 m (+2.5DS), 22.9% fat, 137% obesity degree, BP 147/78 mmHg, important acanthosis nigricans, waist circumference: 106.5cm and C.M.: BMI 35.4, 1.83 m (+2DS), 38.7%fat, 161% obesity degree, BP 145/88mmHg, waist circumference: 120 cm.
Laboratory
Dyslipidemia with HDL: 35/26/39, TG: 71/250/190, insulin resistance in C.M.-HOMA-IR: 5.8, type 2 diabetes in C.A: HbA1c= 7.4%, blood glucose 135, hepatic cytolysis in C.A. (TGO= 118, TGP= 182) and D.D. (TGP= 48.6, TGO= 26 UI/l,) 25-OH vitamin D – between 17 and 25 ng/dl and hyperuricemia 10.53 in D.D., 7.4 in C.A. and 8.4 mg/dl in C.M. The abdominal ultrasound: severe liver steatosis, BP monitoring showed 1st degree hypertension in all three patients. The basal metabolic rate (indirect calorimetry) - low in D.D. (85%), correlated with the low muscle mass, normal in the other 2 boys – 94 and 99%. We began a hypocaloric Mediterranean diet (400 calories daily deficit), moderate physical activity (45–60 minutes), low sodium intake. All three received Omega 3(2000 mg), 2000 UI vitamin D, vitamin E and hepatic protectors for the liver cytolysis. After 1 month of diet and 2% of body fat loss the BP, cytolysis and fasting glucose normalized.
Conclusion
The metabolic syndrome is a frequent condition in adults with increasing prevalence in children and teenagers, but there is no common definition and treatment of the conditions associated with this syndrome. A new guideline for the metabolic syndrome in the pediatric population is needed to manage and monitor the effects of this syndrome and avoid the serious health risks in our children and teenagers.

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AEP814

Awareness of normal weight, overweight and obese patients about complications, risk factors and prevention of obesity

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Background
We aimed to determine the awareness of obese, overweight and normal weight patients about the complications, causes and prevention of obesity.
Methods
Patients who admitted to our clinic during a four months period were included. Demographical features, familial histories of obesity, smoking, alcohol use, chronic diseases, medications, medical nutrition therapy and exercise habits were determined. Answers of agree, not agree or no idea were obtained for 40 questions regarding the definition, consequences, risk factors and prevention of obesity. Patients were grouped as normal, overweight and obese according to the WHO criteria.
Results
Data of 352 patients (282 female and 70 male) were analyzed. There were 51(14.5%) normal weight, 72 (20.5%) overweight and 229 (65.0%) obese patients. Median ages were 49, 44 and 33 in obese, overweight and normal patients, respectively (P <0.001). Education level was lower and familial history of obesity was higher in obese patients (P <0.001). The rates of agreeing that obesity may cause insulin resistance, type 2 diabetes, cardiovascular disease, hypertension, dyslipidemia, fatty liver, sleep apnea, asthma, gastrointestinal problems, depression, mental problems, limitation of movement and mortality varied between 69.60% and 92.61%. Only 130 (36.93%), 138 (39.20%) and 191 (54.26%) patients agreed that obesity is associated with cholelithiasis, pancreatitis and cancer, respectively. The rate of patients who thought that obesity may cause death, sleep apnea and asthma were significantly higher in obese compared to normal weight patients. Approximately half of the patients agreed that obesity in family, eating too much, skipping meals, and engaging in other activities during eating are risk factors for obesity. Rates of agreement about risk factors for obesity were similar in three groups. More than 2/3 of patients agreed with how a healthy diet should be, and believed in the benefit of exercise. The rate of those who agreed that 4–6 meals/day and not to miss snacks are important for a healthy diet was highest in the obese group (72.92%, P = 0.043). There was no significant difference between groups in terms of other questions regarding a healthy diet.
Conclusion
While awareness about some of the obesity associated complications are high, awareness about others such as gall bladder disease, pancreatitis and cancer are low. Obese patients have higher awareness that obesity can cause death, sleep apnea and asthma. The knowledge about risk factors of obesity related with eating habits was relatively low. It is important to raise awareness of both obese and non-obese patients for the prevention and appropriate treatment of obesity.

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AEP815

Correlation between the wrist circumference and waist circumference in patients with and without diabetes

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Introduction
Contemporary literature highlights the importance of wrist circumference as an easy-to-use marker of general and abdominal obesity
Methods
We measured the wrist circumference and the waist circumference in a heavy volume outpatient department of a specialised endocrine centre in 467 subjects with and without diabetes over a period of one month. Patients with known medical conditions, that were confounding and influencing anthropometric parameters like body weight, including thyroid related disorders, genetic disorders were excluded. A dedicated nurse assistant was trained to eliminate the observer bias. The measurements were by standard protocols using calibrated instruments. Descriptive statistics and Pearson r was used for the statistical analysis.
Results
We evaluated 467 patients (with diabetes n = 252, without diabetes n = 215). The mean body weight (kg) in patients with diabetes 72.43 kg (±14.44, 95% CI 70.64 to 74.22) was more than those without diabetes 67.73 kg (±15.38, 95% CI 65.6 to 69.8), P = 0.0007. The mean age of the cohort was 46 years (±17, 95% CI 44 to 47). The mean age (years) of diabetics was more (51 ± 0.78, 95% CI 49.54 to 52.63) than the non-diabetics (39.8±1.43, 95% CI 37.01 to 42.63), P <0.0001. There was a significant positive correlation between the wrist circumference and the waist circumference, irrespective of diabetes (Pearson r 0.50, 95% CI 0.4388 to 0.5686 P <0.0001). The mean wrist circumference (cm) was significantly higher in the diabetics (16 ± 1.4, 95% CI 16.24 to 16.59) than the non-diabetics (15.94±1.33, 95% CI 15.77 to 16.12), P = 0.0003.
Conclusion
The results of our study suggest that wrist circumference is a useful index for assessing obesity irrespective of the diagnosis of diabetes. It is easy, quick, and convenient to measure than the waist circumference. This might make wrist circumference as a routine measurement in daily clinical practice. The results of our study need corroboration with larger epidemiological studies, involving varied population with multi-ethnic population.

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AEP816

24-week impact of dapagliflozin treatment on body weight, body composition, and cardiac risk indicators of patients with type-2 diabetes mellitus

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Aims
We aimed to reveal the impacts of dapagliflozin, a sodium glucose transporter inhibitor (SGLT2i), on the body weight and body composition, cardiovascular risk indexes, and carotis intima-media thickness (CIMT).
Methods
Body weights, body compositions measured by means of bioelectrical impedance, and CIMT in the baseline, the 12th, and the 24th week of 42 patients with type-2 diabetes mellitus receiving SGLT2i treatment along with medication were measured. Visceral adiposity index (VAI), lipid accumulation product (LAP), and atherosclerotic index of plasma (AIP) were measured according to lipid measurements and anthropometric values.
Results
Mean change in total body weight and total fat mass was –2.96 and –1.97 kg, respectively (P <0.001). There was a reduction in total fat mass of 1.23 kg (from 31.4 to 29.3 kg, P <0.001) and in body fat percentage of 2.5% (from 35.8% to 34.4%, P <0.001) in the first 12 weeks. A mild increase was observed in both total fat mass and body fat percentage between the weeks of 12 and 24, which was not statistically significant (P = 0.783, P = 0.925 respectively) whereas there was a statistically significant reduction in hsCRP, AIP, and CIMT values (P = 0.006, P = 0.035, P = 0.007, respectively). No change observed in VAI and LAP values (P = 0.985, P = 0.636).
Discussion
We detected in our study that dapagliflozin causes a weight loss in the 24-week follow-up period. The rate of weight was explicit particularly in the first 12 weeks and it was observed with the reduction in total fat mass and body fat percentage. Apart from the studies on SGLT-2 inhibitors, we detected an increase in total fat mass and body fat percentage in spite of the fact that there was no reduction in weight in the follow-ups after the 12th week. According to our ideas, that our patients made less physical activity as a consequence of Covid-19 pandemic process, which had started during our follow-ups must have caused this situation. However, adding dapagliflozin to the current treatment was associated with the reduction in cardiovascular risk factors like hsCRP, CIMT, and PAI.
Conclusions
We have observed that dapagliflozin not only contributes to weight and fat loss but also has positive impacts on cardiovascular and atherosclerotic indicators.

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AEP817

Vitamin B12 deficiency in type two diabetes patients using metformin at kenyatta national hospital

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Background
Metformin is most frequently prescribed first line therapy for individuals with type 2 diabetes. Continuous use of metformin is associated with vitamin B12 deficiency, yet the prevalence of this side effect and subsequent clinical implications has not been estimated.
Objective
To determine the prevalence of vitamin B12 deficiency and the variables associated with it in patients with type 2 DM on metformin at Kenyatta National Hospital.
Design
A cross-sectional, descriptive study.
Setting
Diabetes out-patient clinic of Kenyatta National Hospital, Nairobi, Kenya.
Subjects
A total of 190 patients with type 2 diabetes on metformin for more than one year attending the out- patient clinic, were enrolled into the study.
Results
Of the patients studied the peak age was around 50–59 years, and majority (61%) were women. The mean duration of metformin use was 5.6 years. Eight percent (n =14) of diabetic patients had confirmed B12 deficiency. With vitamin B12 levels < 208 pg/ml, 18% (32) of the study population had lower/normal levels 208–300 pg/ml and 74%patients had normal levels > 300 pg/ml. No significant correlation between vitamin B12 levels and dosage and duration of metformin use, Hb, MCV or peripheral neuropathy was found.
Conclusion
Vitamin B-12 deficiency is rare in diabetics treated with metformin at an average dose of 1gram per day. A possibility that an individual's diet, duration of exposure to metformin, and dosage may have been responsible for the low prevalence of Vitamin B12 deficiency.
Keywords: metformin, type 2 diabetes, vitamin B12.
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AEP818

Relevance of non-invasive central pressure measurements with vascular stiffness indicators to predict future cardiovascular risk in children with type 1 diabetes

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Introduction
Modern diabetology is focused on preventing late complications of diabetes and to find research tools to detect discrete changes, with the possibility of early entry with treatment. Type 1 diabetes (DM1) causes oxidative stress, affects the cardiovascular system and increases vascular stiffness. The non-invasive measurement of central blood pressure (CBP) together with augumentation and aplification indicators, more accurately reflects the condition of blood vessels and can be useful in monitoring patients with DM1.
Aim
Evaluation of central blood pressure parameters in children with DM1
Materials and methods
The study was conducted in 101 children selected for age, weight and height, without hypertension (mean age 13 years). They were divided into a control group (A) of healthy children (n = 21) and patients with DM1 with short <5 years ((B) n = 37) and long > 5 years ((C) n = 43) duration of the disease, under the care of the Diabetes Clinic and the Department of Pediatrics, Endocrinology and Diabetology udsk in Bialystok. Based on HbA1c levels, all DM1 patients were divided into 2 groups with good HbA1c <7.5% (D) and insufficient HbA1c > 7.5% (E) metabolic control. Three CBP measurements were taken at 5-minute intervals using the Centron Diagnostic and then averages were calculated. The statistical analysis was performed using the Stat12.5 (U Mann-Withney test).
Results
Peripheral and central blood pressure were comparable in patients with type 1 diabetes mellitus and control group. The Augumentation rate was significantly higher in children with DM1 who had short-term patients (0.62 vs 0.56, P = 0.02). Statistical significance was not demonstrated in cbp parameters between groups of children with diabetes mellitus, while both vascular stiffness indicators showed a positive trend with regard to vascular elasticity in the group of children with DM1 long-suffering (AUG 0.62 vs 0.58, AMP 1.65 vs 1.76). In patients with HbA1c, >7.5% hba1c correlates with CBP.
Conclusions
Vascular stiffness rates of Augumentation and Aplification showed improvement during therapy and were higher in the group of children with DM1<5 years, perhaps as a residue after ketoacidosis at the time of diagnosis of the disease. Significant vascular changes may not occur early in DM1 in children with good metabolic control.
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AEP819

The impact of endocrine-disrupting chemicals on the prevalence of diabetes

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Introduction
Endocrine-disrupting chemicals (EDCs) are a heterogeneous group of exogenous chemicals or chemical mixtures that interfere with the action of hormones and cause adverse effects. Humans are constantly exposed to hundreds of EDCs mainly through air, water, and food. Pregnant women are exposed to multiple EDCs that can cross the placenta and enter the fetus. The developing fetus and neonate are more sensitive than adults to perturbation by EDCs. The prevalence of diabetes has risen dramatically over the last several decades.
Methods
A systematic search of literature was conducted using the search terms endocrine-disrupting chemicals, obesogens, prenatal exposure, type 1 diabetes, type 2 diabetes, and vulnerable populations.
Results
The number of EDCs has markedly increased over the past 60 years. The potential contribution of several EDCs (e.g., bisphenol A, dioxins, phthalates, polychlorinated biphenyls, and organochlorine pesticides) to the development of diabetes has been proposed by several epidemiological studies. Prenatal and early-life exposures to EDCs can promote the development of type 1 diabetes by increasing the risk of autoimmunity and affecting ńcell development and function. EDCs with androgenic activity (e.g., bisphenol A) may interfere with β-cell function, impair insulin secretion by accelerating insulitis, and cause type 1 diabetes. Several EDCs called obesogens may promote the development of type 2 diabetes through weight gain and the resulting insulin resistance. The higher burden of diabetes in the vulnerable populations of the USA (e.g., Latinos, African Americans, and low-income individuals) may be partly due to a higher exposure of these populations to diabetogenic EDCs.
Conclusion
Exposure to EDCs may be a significant component of the environmental origin of diabetes. Promotion of public knowledge and initiation of preventive measures, especially in the vulnerable populations, will help minimizing the exposure to EDCs and the resulting diabetes.
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AEP820

Ethnicity and its influence on post-oral glucose tolerance test glucagon-like peptide-1 responses

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Introduction
Glucagon-like peptide-1 (GLP-1) plays an important role in the pathophysiology of type 2 diabetes mellitus (T2DM). Results from some

studies on post-OGTT GLP-1 responses involving East Asians with abnormal glucose tolerance states tend to differ from the West. This may be attributed to the different diabetic phenotypes found in East Asians.
Aim
To examine post-OGTT GLP-1 responses in subjects with normal glucose tolerance (NGT) and T2DM among three major ethnic groups in Malaysia.
Methods
A total of 120 Malaysians consisting of Malays (n = 41), Chinese (n = 43) and Indians (n = 36), were categorised based on their glucose tolerance states following a 75g OGTT. There were 58 NGT and 62 T2DM subjects. Plasma total GLP-1 concentrations were measured at 0, 30 and 120 minutes during OGTT.
Results
Overall, T2DM had higher GLP-1 responses to OGTT compared to NGT. GLP-1 levels were positively correlated with insulin levels and HOMA-IR. Among NGT, Malays had lower post-OGTT GLP-1 levels than Chinese and Indians whereas Chinese and Indians had comparable GLP-1 levels. Among T2DM, Malays appeared to exhibit higher GLP-1 levels at 30 minutes post OGTT than Chinese and Indians. There was a significant ethnic difference in incremental GLP-1 levels at 120 minutes in T2DM group (P = 0.024), where the levels were higher in Malays than in Chinese and Indians. Indians were the most insulin resistant while Malays were the most insulin sensitive.
Conclusions
Insulin resistance was associated with compensatory increased GLP-1 secretion in T2DM. Malays with NGT had lower post-OGTT GLP-1 responses. In contrast, Malays with T2DM had higher GLP-1 responses compared to Chinese and Indians to compensate for their prevailing insulin sensitivity.
Comparisons of post-OGTT GLP-1 responses by ethnicity and glucose tolerance states.

	NGT (n = 58)			T2DM (n = 62)		
	Malays (n = 19)	Chinese (n = 20)	Indians (n = 19)	Malays (n = 22)	Chinese (n = 23)	Indians (n = 17)
Fasting GLP-1 (pmol/l)	13.32 (9.47,16.32)	12.99 (10.34, 19.28)	17.28 (11.83, 26.82)	19.97 ł * (14.68, 26.88)	28.89 (24.06, 35.42)	26.03 (20.95, 37.84)
$GLP\text{-}1_{30min}$ (pmol/l)	22.87 * ł (15.41, 28.39)	26.85 (20.84, 38.47)	26.58 (20.75, 49.28)	51.15 (29.66,68)	48.25 (40.89, 55.82)	48.77 (39.2, 70.71)
$GLP\text{-}1_{120min}$ (pmol/l)	17.54 (13.22,22.79)	21.19 (16.54, 27.03)	21.98 (19, 32.91)	26.43 (17.4, 33.15)	21.81 (16.53, 31.19)	29.18 (19.55, 51.83)
$\Delta GLP\text{-}1_{30min}$	8.71 ł (3.19, 12.63)	11.86 (8.22, 19.3)	10.56 (6.19, 20.23)	24.66 (10.75, 34.15)	18.66 (9.44, 26.98)	23.8 (10.56,3 3.32)
$\Delta GLP\text{-}1_{120min}$	2.62 (-2.78, 11.99)	8.17 (1.92,17.52)	5.38 (-1.32, 11.29)	1.66 ł (-4.3, 11.74)	-6.62 (-10.57, 0.52)	-1.13 (-6.93, 721)

Data are expressed as median (interquartile range). * P < 0.05 versus Indians, ł P<0.05 versus Chinese. ΔGLP-1, incremental GLP-1.

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AEP821

Gender differences in ghrelin levels in patients with type 2 diabetes mellitus

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Introduction
Ghrelin has an important role in insulin resistance, glucose and lipid metabolism and cardiovascular morbidity and mortality. It is still unclear whether insulin and glucose per se play a direct inhibitory role in ghrelin secretion. The decrease in ghrelin levels after an oral glucose load is modulated by sex, status of obesity, and level of insulin resistance. The aim of our study was to evaluate gender differences in ghrelin levels in type 2 diabetes mellitus patients.
Methods
109 women and 32 men with type 2 diabetic mellitus were included to the study. The age of the participants was 62 (59–68) years old, mean body mass index – 32.2 (29.0–35.7) kg/m^2 with no statistical gender differences in parameters (U=1587.5; P = 0.173, U=1689.0; P = 0,373). The serum levels of ghrelin were analyzed by the sandwich ELISA method.
Results
Fasting concentration of ghrelin in diabetic patients was 0,78 (0.57–0.98). The level of ghrelin in women with type 2 diabetes mellitus was 0.79 (0.55–0.96), in men with type 2 diabetes mellitus was 0.78 (0.64–1.06). The results revealed no gender differences in ghrelin levels (U=1410.0; P = 0.100).
Conclusion
The study did not reveal gender differences in fasting ghrelin concentrations in type 2 diabetes mellitus patients.

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AEP822

Influence of physician-related factors on the "Glycemic Happiness" of persons with T2DM: Interim analysis of an observational survey

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Background
Apart from long-term complications associated with diabetes(T2DM), the psychological impact also significantly contributes to poor outcomes in persons living with diabetes. An observational survey was undertaken to assess various physician-related factors that can help define "glycemic happiness" for persons living with T2DM.
Methods
A prospective, multicentric, cross sectional, observational survey involving 40 physicians from 40 tertiary care centers in India. Interim analysis of 12 centers is presented here. Survey (Box 1) was based on a simple questionnaire developed by an expert panel and administered by designated personnel at study centers.
Results
Of the 12 responses from physicians obtained to date, all of them feel that physician's belief in one-self to make a difference in life of person with T2DM and satisfaction from being able to help the person with T2DM can influence glycemic happiness of person with T2DM. In addition, 10 (83.33%) and 6 (50%) agree that professional satisfaction and physical/mental exhaustion at work can affect glycemic happiness of person with T2DM respectively.
Conclusion
Apart from good glycemic control, glycemic happiness of persons with T2DM can be influenced by physician's belief in his role in T2DM management, professional satisfaction and ability to cope with physical and emotional professional demands.
Funding
Dr Reddy's Laboratories

Box 1. Questionnaire of the Glycemic Happiness Survey – Physician Component

- Do you feel happy and satisfied that you chose to be a diabetes care professional?
- Do you get satisfaction from being able to help T2DM patients?
- Do you feel you can make a difference in life of with T2DM patients through your work?
- Do you get physically and emotionally exhausted at work?
- Do you feel you are losing enthusiasm at work?
- Do you feel you are in control dealing with complex problems of T2DM management?
- Do you feel worn out by your job as a care provider?
- Do you feel overwhelmed because Diabetic patients load seems endless?
- Do you feel depressed by the traumatic stress of T2DM patients whom you try to help?
- Do you feel less empathetic and connected with your colleagues and friends?

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AEP823

A case of euglycaemic ketoacidosis and concomitant acute pancreatitis in a diabetic patient treated with SGLT2i and GLP-1RA

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Introduction
Glucagon-like peptide 1 receptor agonists (GLP-1RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) are the two novel classes of anti-diabetic agents with compelling efficacy, in terms of glucose-lowering and cardio-renal protection. Euglycemic diabetic ketoacidosis (EDKA) is a serious rare adverse effect of SLT2i while the use of GLP-1RA has been scarcely linked with acute pancreatitis in humans.
Case presentation
We present the case of a 50-year old, overweight man who was admitted to the Emergency Department due to diffuse abdominal pain radiating to the back, nausea, appetite loss and bile vomiting. He had a 20-year history of Type 2 Diabetes (T2D) and was on triple anti-diabetic regimen with dulaglutide, empagliflozin and metformin which he continued to take, despite a marked decrease in food intake over the last 5 days. Clinical examination was remarkable for rapid heart rate, Kussmaul breathing, signs of extracellular volume depletion (dry skin and mucosa) and breath smell of acetone. Initial laboratory work-up revealed metabolic acidosis (pH 7.053) with increased anion gap (22.3 mmol/l), ketonaemia (4.9 mmol/l) and ketonuria (4+ in urine dipstick), in the setting of mild hyperglycaemia (glucose 204 mmol/l) and normal renal function (eGFR 126 ml/min/1.73 m^2). Meanwhile, computed tomography of the abdomen revealed misty mesentery and significant stomach dilation; therefore, a nasogastric tube for drainage was placed. EDKA was managed with intravenous administration of 5% dextrose solution, fixed-rate insulin infusion, 0.9% normal saline and potassium. Following the above protocol, b-hydroxybutyric acid gradually decreased, blood glucose level was maintained stable (130–180 mg/dl), and acidosis was reversed within 12 hours (pH 7.330). However, serum and urine amylase demonstrated a gradual increase during the first 24 hours (peak levels of 654 U/l and 1423 U/l respectively). Gastroenterology review established the diagnosis of acute pancreatitis, thus intravenous esomeprazole and metoclopramide were initiated. The patient demonstrated rapid clinical improvement and feeding restarted after 48 hours. As for the cause of acute pancreatitis, all other etiologies (lithiasis, alcohol, autoimmune, trauma) were excluded and it was attributed to GLP-1RA use.
Conclusions
The possibility of EDKA due to SGLT2i must be kept in mind when evaluating a patient with long standing T2D and unexplained metabolic acidosis. Acute pancreatitis due to GLP-1RA exists in humans, although several studies did not verify an increased risk. This case highlights that all anti-diabetic agents must be applied in a patient-tailored way, accompanied by appropriate sick day rules.

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AEP824

Diabetes care during COVID-19 pandemic using a telehealth approach

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Introduction
COVID-19 pandemic has rapidly changed the landscape of diabetes care to quickly adapt to continue providing optimal care to patients with diabetes in an efficient and effective manner
Methods
We describe a retrospective assessment of patients with diabetes, with and without COVID-19 infection, during the lockdown period March 2020 to February 2021 managed through a dedicated comprehensive dedicated telehealth platform. The virtual health applications comprised of telephone consultations and video telehealth consultations
Results
The total patients who were managed by teleconsultation were 765 (30 T1DM), (440 males). 250 patients were COVID-19 with type 2 diabetes, and 15 patients were type 1 diabetes. The mean age (years) was 60 (±14, minimum 10, maximum 88, 95% CI 58 to 62). There were 49% (375/765) patients with age less than 60 years. The mean number of teleconsultations per patient were 1.5 (±0.97, minimum 1, maximum 6, 95% CI 1.4 to 1.7). There were 235 patients who sought at least 1 repeat virtual consultation, of which 145 had two virtual consultations. The mean number of virtual consultations were comparable in patients with (1.6±0.94, 95% CI 1.3 to 1.8) or without COVID-19 (1.4±0.97, 95% CI 1.2 to 1.6), $P = 0.41$ ns. The mean age was comparable in patients with (58±15.5, 95% CI 54.47 to 63.04) or without COVID-19 (60.45±12.81, 95% CI 57.91 to 62.9), $P = 0.47$ ns. The mean number of virtual consultations were comparable in elderly >60 years (1.4±0.78, 95% CI 1.2 to 1.5) and in age group <60 years (1.6±1.1, 95% CI 1.3 to 1.8), $P = 0.22$ ns. The mean number of virtual consultations were similar in males (1.4±0.77, 95% CI 1.2 to 1.5) and in females (1.6±1.1, 95% CI 1.3 to 1.9), $P = 0.11$ ns.
Conclusion
Digital – virtual diabetes clinic has a potential to provide efficient method of consultative service. Virtual electronic consultation mitigated the lockdown induced disruption in diabetes care activities and appears to be a reliable approach. Beyond the pandemic, we suggest that annually per patient, two virtual consultations would complement the two in person consultations, that would suffice to maintain the continuity of care and deliver optimal diabetes care

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AEP825

Mucormycosis in a patient with newly diagnosed diabetes mellitus and diabetic ketoacidosis

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Background
Mucormycosis is an opportunistic fungal infection that can be aggressive and mortal. Diabetic ketoacidosis(DKA) is a risk factor for mucormycosis. We present a case with mucormycosis presenting with newly diagnosed diabetes mellitus and DKA.
Case presentation
A 34-year-old male patient presented with confusion and vomiting. He had no comorbiditiy. On admission the patient was afebrile, hypotensive (85/55 mm/hg) and had tachycardia (120/bpm). Laboratory investigations revealed hyperglycemia (673 mg/dl), severe metabolic acidosis (pH:6.86, bicarbonate:2.6 mmol/l) and urinary ketones. The patient was intubated due to cardiac arrest and followed up in the intensive care unit for 15 days. After that, the patient with newly diagnosed diabetes was admitted to our clinic for blood glucose regulation. During follow up, he described a feeling of swelling in the left half of the face and blurred vision. There was an erythematous appearance on the left eyelid. Diagnostic nasal endoscopy showed widespread crusting filling left nasal cavity and necrosis in the adjacent septum and middle meatus which was suggestive of mucormycosis. Paranasal sinus CT revealed mucosal thickening in the left frontal sinus, left anterior-posterior ethmoidal cells, sphenoid sinus in the left compartment and in the left maxillary sinus, causing almost complete loss of ventilation. Mucosal thickening was observed in the left compartment of the sphenoid sinus and the ethmoidal cells on the left. Left frontal and left sphenoethmoidal recesses were obliterated. Left precentral fatty tissue and left pterygopalatine fossa, around the sphenopalatine foramen were dirty. Orbital CT was normal. Cranial MRI showed 22 × 10 mm flair hyperintensity accompanied by effacement in the sulcus in left frontal lobe, frontobasal-orbitofrontal level, cortical-subcortical located in the medial part. In this location, frontal bone integrity was not clearly differentiated, and signs of inflammation were observed in the adjacent frontal sinus. The patient was operated urgently. Histopathology confirmed the diagnosis of mucormycosis. Liposomal amphotericin-B treatment was started. The patient was discharged with intensive insulin treatment after five weeks.
Conclusion
Mucormycosis is an invasive and progressive disease which requires immediate diagnosis and treatment including surgical debridement. Although uncontrolled and long standing diabetes is a well-known important risk factor for this opportunistic infection, it is rare to see it in patients with newly diagnosed diabetes. Our case is important in terms of showing that this infection can also occur in newly diagnosed diabetes.

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AEP826

The promising role of Agouti related peptide in the differentiation of ACTH-independent Cushing syndrome

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Background
Agouti related peptide (AgRP) is a neuropeptide, produced by the hypothalamus and by the adrenal glands. AgRP is an antagonist of proopiomelanocortin (POMC) and its principal role is to stimulate appetite. Although current evidences suggest that AgRP levels are influenced by glucocorticoids, it is still not clear, whether they depend on adrenocorticotropic hormone (ACTH) or cortisol. One of the aims of this study was to address this issue. Furthermore an analysis of AgRP in the differentiation of Cushing´s disease (CD), ectopic Cushing syndrome (ECS), adrenocortical adenoma (ACA), and adrenocortical carcinoma (ACC) was performed.
Methods
We performed a retrospective analysis of AgRP levels in blood samples of 103 patients with proven Cushing syndrome (CS), including 44 with ACTH-dependent CS (n = 33 CD, n = 11 ECS) and 59 ACTH-independent CS (n = 21 ACA, n = 38 ACC). Levels of AgRP were measured with ELISA. Considering the AgRP fluctuating levels throughout the day, the analysis was performed on midnight serum samples for all patients. Correlation with midnight cortisol levels, basal ACTH, and in ACC with tumor burden and overall survival (OS) were investigated.
Results
Considering the entire cohort, a negative AgRP-ACTH correlation (rs = –0.60, $P < 0.001$) and a moderate positive AgRP-cortisol correlation (rs = 0.25, $P = 0.02$) was identified. Levels of AgRP did not differ between CD and ECS [median 0.39 (0.23–0.57). ng/ml vs 0.43 (0.34–0.65) ng/ml, respectively, $P = 0.99$]. Concerning the ACTH-independent CS, ACC were characterized by significant higher levels of AgRP compared to ACA [median 1.38 (0.22–8.71) ng/ml vs 0.45 (0.25–0.79) ng/ml, respectively, P = 0.035] with a mean ACC/ACA fold change of 4.7. Furthermore, AgRP levels were significantly higher in ACC in comparison to both CD ($P < 0.0001$) and ECS ($P = 0.014$). Among ACC, AgRP levels were higher in patients with a higher tumor burden (considered as two or more site of metastasis) compared to those with a lower tumor burden ($P = 0.025$). No difference in terms of OS was observed between patients with low AgRP levels (considered as <1.38 ng/ml) in comparison to those with high AgRP levels (≥1.38 ng/ml) (median survival 14 vs 15 months, respectively, P = 0.47).
Conclusions
AgRP seems to play an intriguing role in the pathophysiology of cortisol-secreting ACC and could be an interesting marker in the differentiation of the ACTH-independent CS. On the other hand, the analysis of AgRP seems not to be beneficial in the differentiation of ACTH-independent CS. Further analyses on a larger population are necessary to confirm our results.

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AEP827

Germline variants of the MEN1 gene in 132 subjects with clinical indication of genetic diagnosis, born in Argentina

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Multiple Endocrine Neoplasia type 1 (MEN1) is an autosomal dominant inherited disease with a high degree of penetrance. The three most common locations of tumors are the parathyroid glands, the gastro-duodenum pancreas and/or the anterior pituitary gland. The gene involved in this disease is MEN 1, a tumor suppressor gene located on chromosome 11q13. The objective of our work was to describe the genotype of patients with MEN 1 born in Argentina.
Subjects and Methods
We studied 132 possible carriers of MEN1 born in Argentina: 56 index cases (31 women; mean age 40.42 years (SD 16.2); r: 2–75 years) and 76 asymptomatic first-degree relatives (41 women; age 33.70 (SD 19.1); 2–69 years). The coding region (exons 2–10), the promoter, exon 1 and, the flanking intronic regions of the MEN1 gene were sequenced by the Sanger method. MLPA was used in patients with no mutation findings.
Results
We found mutations throughout the entire gene, in the coding regions, the flanking intronic and splicing sites as reported in the literature. Forty mutations were found in 56 patients (71.4%). The prevalence of mutations was 92% in familial cases and 54.5% in sporadic cases. Of the 31 different pathogenic variants, 11 (38.7%) were reading frame alterations (38.7%) (9 microdeletions, 1 microduplication and 1 microinsertion), 7 (22.6%) were nonsense variants, 7 nonsense (22.6%), 3 mutations in splicing sites (9.7%) and 2 large deletions (6.4%). We found nine novel pathogenic variants.
Conclusions
The genetic diagnosis of this population of 76 with MEN1 allowed us to confirm the diagnosis in 71.4% of the patients and to identify 38% of the first-degree relatives as asymptomatic carriers. Carriers of the mutation may be studied annually according to international guidelines that would improve their survival through early diagnosis of tumors.

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AEP828

Duodenal neuroendocrine tumor (siNET) and Rothmund-Thomson syndrome: a new association of a rare genetic disorder

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Rothmund-Thomson syndrome (RTS) usually presents with physical stigmata (poikiloderma, ectodermal dysplasia, juvenile cataracts…) and it´s associated with malignancies in patients with homozygous or compound heterozygous mutations in the *RECQL4 helicase* gene (RTS-II). Neoplasms include osteosarcoma in childhood and skin cancer later in life, with occasional malignancies affecting other tissues (leukemia, lymphoma and gastrointestinal adenocarcinomas). To our best knowledge, its association with neuroendocrine tumors has not been reported. We present one patient with this association. A 33-year-old woman was admitted in February 2020 for diarrhoea (4–5 stools/day) with urgency and mucus. At six she had been diagnosed with RTS-II after detecting osteosarcoma of the right femur, treated with amputation and chemotherapy with no evidence of disease in check-ups. In 2015, an ultrasound showed two liver lesions in segment VI and biopsy of the larger one was reported as a benign hepatocyte proliferation. In 2018, a cutaneous squamous cell carcinoma on the left heel had been resected and a CT scan showed a tumor in the duodenal setting, with two endoscopic US-guided FNAC obtaining insufficient cytological material for diagnosis. Colonoscopy disclosed a 1.8 cm tubule-villous adenoma with high-grade dysplasia and gastroscopy showed a tumor located posterior to the duodenal bulb, about 15 mm in diameter. Endoscopic biopsy showed a well-differentiated NET (G2). Biochemistry revealed dissociated cholestasis and elevation of chromogranin A (3,001ng/ml; NV<100) with slightly elevated glucagon (153 pg/ml; NV<100). SPECT-CT with Tektrotyd confirmed the uptake of the lesion, as well as of adjacent adenopathies, without hepatic involvement. Operated on May 2020, a hard lesion on the posterior aspect of the duodenal bulb and adjacent adenopathies were resected. Intraoperative ultrasound showed more than 10 liver lesions in both lobes, whose biopsy confirmed their metastatic nature. Pathology diagnosed a well-differentiated NET of 2 cm, infiltrating up to muscularis propria, with lymphatic invasion and lymph nodes affected. Ki-67:15%. Genetic study discovered two variants of the RECQL gene in compound heterozygosis: c.1620+1G>C (NM_004260.3) and c.2547_2548delGT (NM-004260.3). After surgery, two sessions of transarterial chemoembolization with adriamycin were performed. Seven months later, a SPECT-CT with Tektrotyd shows uptake in non-treated hepatic segments and regional periduodenal adenopathies. CgA levels have reduced to 923 ng/ml. In conclusion, this is the first reported case of NET in a patient with RTS. Duodenal malignancy was previously reported in association with RTS-II. Increased awareness of the risk of gastrointestinal malignancy in patients with RTS could improve detection and outcomes in these patients.

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AEP829

Papillary thyroid cancer in adolescents after neuroblastoma in childhood: Description of the two cases

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Background
It is known that the thyroid gland is sensitive to the damaging effects of irradiation, and patients who have received radiotherapy for tumor treatment require regular thyroid screening subsequently. A few cases of thyroid cancer after receiving 131I-metaiodobenzylguanidine (MIBG) therapy in the treatment of neuroblastoma in childhood have been described (HM van Santen et al 2012; SC Clement et al, 2013). Here, we report the two cases of papillary thyroid cancer in adolescents after treatment of neuroblastoma in childhood without applied of 131I-MIBG therapy.
Patient findings
A 14-year-old girl, treated neuroblastoma at the age of 11 months, and a 17-year-old girl, treated at the age of 9 months, were both diagnosed with papillary thyroid cancer at 12 and 13 years, respectively. In both cases surgery and chemotherapy have been used to treat neuroblastoma in childhood (without 131I-MIBG therapy). Thyroid cancer was discovered in nonpalpable nodules by thyroid ultrasound. Papillary thyroid carcinoma with capsular invasion was detected after surgical treatment in both, with lymph node metastasis in the second patient, what required 131I-therapy.
Conclusions
In this cases the development of thyroid cancer in adolescents is not associated with the treatment of neuroblastoma with 131I-MIBG in childhood, as described in previous articles. The development of several types of cancer is possibly associated with the presence of the hereditary tumor syndromes and requires further diagnostic molecular genetic research.

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AEP830

Clinical case of insulinoma in patient with germline mutation in the ADCY1 gene

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Introduction
The clinical cases of insulinoma patients with well-studied hereditary syndromes due to mutations in the *MEN1, VHL, TSC1,* and *TSC2* genes are repeatedly described in the literature. At the same time, the hereditary nature of the pathology is highly probable in young patients with primary multiple lesions without mutations in these genes. In such cases, one can assume the presence of germline mutations in genes with the described somatic mutations accompanying tumorigenesis and insulin hypersecretion.
Objectives
To search for novel germline mutations associated with insulinoma.
Methods
Based on the literature data, we have compiled a genetic panel that includes 10 genes. *MEN1, VHL, TSC1,* and *TSC2,* and candidate genes, which were reported to contain changes in the tissue of sporadic insulinoma (*KRAS, YY1, CDKN2A, MLH1, ADCY1, CACNA2D2*). Targeted sequencing of these genes was performed in a 38-year-old woman with insulinoma of pancreatic head (the disease manifested at the age of 26 years with hyperglycemia). The diagnosis was confirmed by results of histological and immunohistochemical studies (tumor size: 10×4 mm, ki67 – 4%, Grade 2). The concomitant pathology included gastric polyp, kidney cyst, autoimmune thyroiditis; heredity was burdened by diabetes mellitus.
Results
we revealed the heterozygous variant *c.789+114A>G (rs536921599)* of unknown significance in the *ADCY1* gene (NM_021116.4) in intron 2. The *ADCY1* gene encodes adenylate cyclase 1, which is not expressed by normal pancreatic tissue. This protein is regulated by the concentration of calcium and calmodulin. When the gene is mutated, sensitivity to calcium concentration is likely to be lost, which leads to overstimulation of insulin secretion (regardless of glucose level) and proliferation of pancreatic β-cells. The variant found in the patient has not been described in the literature. Germline biallelic or compound heterozygous mutations in *ADCY1* are known to lead to hereditary hearing loss (autosomal recessive inheritance). The patient and her relatives have no pronounced hearing impairment. No changes were found in the rest of the genes included in the panel. We continue the monitoring of the patient.
Conclusion
we revealed the germline variant *c.789+114A>G* in the *ADCY1* gene, which is involved in regulation of insulin secretion and pancreatic β-cells proliferation, in patient with insulinoma. The identified variant is possibly a novel genetic marker of tumor: we plan to clarify its clinical significance. Identification of genetic predictors of insulinoma will allow predicting the course of the disease and developing optimal tactics for managing the patients.

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AEP831

Paraneoplastic Cushing syndrome: Diagnostic and management challenge

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Introduction
Paraneoplastic Cushing syndrome (CS) due to ectopic ACTH secretion is a rare syndrome usually associated with severe hypercortisolism which is responsible for life-threatening comorbidities. These tumors are often difficult to locate. Among all ACTH-secreting thoracic tumors,well differentiated neuroendocrine tumors located in the bronchi are the most common and account for 20% to 40% of all cases.
Case
A 36-year old man,was admitted on June 2020 for exploration of a CS. His medical history dates back to July 2019 with the diagnosis of insulin-requiring diabetes and a resistant severe hypertension with symptomatic hypokalaemia, all associated with morphological changes suggesting a CS. The drug history excluded an exogenoous exposure to glucocorticoids. Clinical examination revealed *facio-truncular obesity*, thin arms and legs,muscular atrophy, «moon face», buffalo neck, steroid acne on the trunk, fragile and poorly healing skin,large violaceous striae over the abdomen and axillary area, spontaneous bruising.Biochemical findings confirmed the diagnosis of CS: urine free cortisol was elevated (3880 µg/24 h□over 53 times of normal); the circadien cortisol secretion was disturbed. Adrenocorticotropic hormone (ACTH) level was high (254.5 ng/ml□five times normal). Clinical assessement for complications(in addition to diabetes and hypertension) found a left ventricular hypertrophy, dyslipidemia, functional hypogonadism,diffuse bone demineralization, *chronic hypocalcemia*, hypercoagulability,anxious and depressive symptomatology with insomnia. Based on the rapid deterioration of our patient's general condition,severity of clinical manifestations,a negative nocturnal 8 mg-DST(cortisol level: 421 µg/l)and a negative pituitary imaging,an ectopic CS was suspected.Thus,a chest CT-scan had shown a solid peripheral nodule of the postero-basal segment of the right lung of 20 mm with heterogeneous enhancement on injection of iodinated contrast agent, suggesting a neoplasic origin. Due to the unavailability of octreoscan preoperatively as well as the severity of clinical and biological signs resisting to medical treatment, the patient was operated. He underwent a video-assisted thorocoscopic surgery with total resection of the tumor. Histological examination revealed a low grade pulmonary neuroendocrine tumor measuring 17 mm. *Tumor* cells were positive for chromogranin, synaptophysin and ACTH on *immunohistochemistry*. Post-operative evolution was marked by improvement of diabetes and hypertension,normokaliemia and adrenal insufficiency was obtained within the second week.Octreoscan performed after the surgery did not show a metastatic localisation or residual tumor. We observed that *physical* features were ameliorated at 3 months and resolved at 6 months.
Conclusion
Ectopic ACTH secreting tumors are rare and severe. The ideal treatment is their excision. In addition to symptomatic treatments, hypercortisolism must be controlled rapidly as a pre-operative management or if surgery is impossible. However, these tumors carry an excellent prognosis especially localized and well-differentiated bronchial tumors.

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AEP832

The management of pituitary macro adenoma in a patient with multiple myeloma-a diagnostic and treatment dilemma and a 2 year journey

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Introduction
Multiple myeloma is a haematological malignancy arising from plasma cells. It accounts for 10% of all haematological malignancies. Myeloma usually occurs in people over the age of 65, however, we have noted an increase occurrence of people with a younger age.
Case Report
A 68 year old male, with background of hypertension and right total hip replacement, was referred to the outpatient haematology; as his blood results

revealed IgGK monoclonal bands(18 g/l) following a GP appointment. Further testing also confirmed Bence-jones protein in the urine sample. A skeletal survey was requested, which showed some soft lucencies in the skull. Subsequently, a CT head was organised, however this did not show any skull lucencies. Despite the absence of skull lucencies on the CT head, lytic lesions in C1 vertebral body were present as well as an incidental finding of macroadenoma pituitary adenoma compressing the optic chiasm. This was confirmed with an MRI scan. Further discussions were made with neurosurgeons, who also noted the incidental pituitary adenoma. In spite of this, the neurosurgeons were strongly convinced that this was likely a pituitary plasmacytoma given the patients latest diagnosis of multiple myeloma. Therefore, neurosurgeons suggested to start the patient on treatment for multiple myeloma. The patient responded very well to the chemotherapy however, he later developed some blurring of his vision which prompted an optician review. This confirmed bitemporal visual field defects with no reduction in pituitary tumour size on MRI. As a result, the patient underwent transsphenoidal surgery with improvement in visual field.
Discussion
A common diagnostic criteria for multiple myeloma include: □10% clonal plasma cells on bone marrow examination or presence plasmacytoma following biopsy, hypercalcemia, renal failure, anaemia, and lytic bone lesions. Pituitary adenomas are often misdiagnosed. Sella and Parasellar plasmacytomas are rare tumours, that can progress to multiple myeloma or even be present in the midst of a diagnosis of multiple myeloma. The clinical presentation of patients with sellar or intrasellar plasmacytoma are headaches due to the mass effect or visual disturbances. Due to the mimicry nature and similarity in clinical presentations accurate diagnosis is essential for successful management.
Conclusion
This case delayed definitive treatment of non-functioning pituitary adenoma for almost 2 years. This highlights the importance of having the correct diagnosis, to avoid delayed treatment.

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AEP833

Treatment of severe symptomatic hyponatraemia using hypertonic saline; real world findings from 2017–2020 in two university hospitals in the UK

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Introduction & aim
Hypertonic saline (HTS) is an effective treatment for severe symptomatic hyponatraemia. European Society of Endocrinology (ESE) published guidelines to standardise HTS administration in 2014, however, evidence behind the guidelines is limited by virtue of being largely derived from small retrospective studies and expert opinion. The aim of this study was to evaluate the 'real-world' safety and efficacy of these guidelines.
Methods
This was a retrospective, observational, cohort study. We examined use of HTS for severe symptomatic hyponatraemia at two University hospitals between 2017–2020 that had uniformly adopted ESE guidance. Patients were identified via a centralised pharmacy database and data was collected to record demographic and clinical variables in addition to treatment details. The primary outcome was rate of overcorrection after first and second HTS boluses (defined as rise in sodium >5 mmol/l), and at 24 and 48 hours (rise in sodium >10 and 18 mmol/l) respectively. Secondary outcomes were inpatient mortality rate, all-cause mortality rate at 12 months, and rate of osmotic demyelination syndrome (ODS).
Results
In total 112 patients (Females: Males = 61:51) met the inclusion criteria for the study. Their mean age ± SD was 66.4 ± 16.0 years with mean body mass index ± SD of 24.8 ± 5.6 kg/m^2. Mean serum sodium ± SD at baseline was 113.8 ± 6.4 mmol/l. Less than 1/5th of the patients were administered treatment to mitigate overcorrection (dextrose infusion/desmopressin). *Primary outcome:* Overcorrection rates after first and second boluses were 22.6% and 34.6%, respectively, while overcorrection rates at 24 and 48 hours were 44.9% and 19.6%, respectively. *Secondary outcomes*: 7.1% patients died during the same admission, while the mortality at 12 months was 18.7%. No cases of ODS were reported. A bivariate regression analysis including various categorical and continuous variables was unable to define characteristics of a high-risk group. Finally, a significant correlation was noted between paired serum and venous blood gas sodium (n = 36, Spearman's correlation r = 0.956; P<0.001), although the latter was, on average, 1.9 mmol/l lower than for serum.
Conclusion
This is the first study to comprehensively evaluate ESE guidelines in a real-world setting. Rate of overcorrection at various endpoints is significantly high without long-term sequelae. We recommend liberal use of overcorrection treatments, especially in the first 24 hours, to keep the sodium rise within the suggested cut-offs. Accounting for a correction factor of ~2 mmol/l, a venous gas sodium check between the first two boluses is useful in practice.

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AEP834

Perception of the speciality of endocrinology and nutrition among students training for the medical internship examination

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Introduction
The choice of a specialty in medicine is a decision that is imposed on new graduates. The aim of our study was to assess the perception of the specialty of Endocrinology and Nutrition among a large sample of medical students in their final year of their degree or prior to taking their Medical Internship Examination in order to know if they would choose Endocrinology and Nutrition for their specialised training, as well as the most and least attractive factors of the specialty.
Materials and methods
We designed an anonymous survey with seven questions that was distributed via telematics among the students of one of the main Spanish academies dedicated to preparation of exam that allow access to specialised medical training.
Results
A total of 2193 responses were obtained. Of these, 63.1% corresponded to "junior doctors" (who would take their exam in 2021) and 36.9% to final-year medical students (who would take their exam in 2022). 2.6% of the students surveyed considered the speciality of Endocrinology and Nutrition as their first choice for their specialised training at the time of the survey. Those students who rated the specialty of Endocrinology and Nutrition as their first choice considered the importance of the teaching of the subject in their decision with average value of 7.8 (SD: 2.2) being 10 extremely important. The most attractive aspect of the speciality among the students is that "it has a logical pathophysiological basis" (53.6%) followed by "the work is dynamic, varied and with great scientific soundness of its benefits" (28.0%). The least attractive aspect of the speciality among the students is that "it has few interventional techniques" (44.9%). Finally, students considered the most attractive part of the speciality to be hypothalamic-pituitary pathology (26.6%), diabetes mellitus (22.0%), thyroid pathology (17.8%), clinical nutrition (11.1%) and adrenal pathology (9.7%). Among students intending to choose Endocrinology and Nutrition for their specialised training, the most attractive part of the specialty was diabetes mellitus (35.1%), clinical nutrition (17.6%), hypothalamus-pituitary pathology (15.8%), thyroid pathology (14.0%) and obesity and dyslipidaemias (14.0%).
Conclusions
The teaching of the subject is an important factor in the choice of speciality. It would be interesting to increase and show the different interventional techniques in Endocrinology and Nutrition.

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AEP835

Preliminary evidence of the role of circulating testosterone levels in a cohort of women with SARS-CoV-2 infection

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Purpose
Objective of this study was to assess the association between testosterone (T) levels and biochemical markers in a cohort of female patients admitted for SARS-CoV-2 infection in a respiratory intensive care unit (RICU).
Methods
A consecutive series of 17 women affected by SARSCoV-2 pneumonia and recovered in the RICU of the Hospital of Mantua (Italy) were analyzed. Biochemical inflammatory markers as well as total testosterone (TT), calculated free T (cFT), sex hormone–binding globulin (SHBG), and luteinizing hormone (LH) were determined.
Results
TT and cFT were significantly and positively associated with PCT, CRP, and fibrinogen as well as with a worse hospital course. We did not observe any significant association between TT and cFT with LH; conversely, both TT and cFT showed a positive correlation with cortisol. By LOWESS analyses, a linear relationship could be assumed for CRP and fibrinogen, while a threshold effect was apparent in the relationship between TT and procalcitonin, LDH and ferritin. When the TT threshold value of 1 nmol/l was used, significant associations between TT and PCT, LDH or ferritin were observed for values above this value. For LDH and ferritin, this was confirmed also in an age-adjusted model. Similar results were found for the association of cFT with the inflammatory markers with a threshold effect towards LDH and ferritin with increased LDH and ferritin levels for values above cFT 5 pmol/l. Cortisol is associated with serum inflammatory markers with similar trends observed for TT; conversely, the relationship between LH and inflammatory markers had different trends.
Conclusion
Opposite to men, in women with SARS-CoV-2 pneumonia, higher TT and cFT are associated with a stronger inflammatory status, probably related to adrenal cortex hyperactivity.

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AEP836

Lithium-induced hypercalcaemia

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Introduction
Lithium remains a first-line treatment for several mental disorders. Hypercalcaemia has been associated with long-term lithium treatment, yet it is often unrecognized. The manifestations of hypercalcaemia can develop insidiously and mimic psychiatric disturbances.
Cases
Case Report 1 – A 53-year-old Caucasian gentlemen referred by his GP following routine bloods with an adjusted calcium of 3.46 mmol/l (2.2–2.6), PTH of 8.7 pmol/l (1.6–6.9), and a lithium level of 0.56 mmol/l (0.4–1). The patient was asymptomatic and clinically well. With a background of depression and right-sided hydrocele, this patient was on the following medications: lithium, atorvastatin, folic acid, mirtazapine, olanzapine and venlafaxine. An ultrasound of the parathyroid showed a small hypoechoic ovoid lesion adjacent to the inferior pole of the right lobe of the thyroid measuring 7 mm × 4 mm, suspicious for a small parathyroid adenoma. He was treated with IV fluids and given IV pamidronate prior to discharge. Additionally, his lithium dose was reduced and sodium valproate was initiated. Case Report 2 – A 73-year old Caucasian gentlemen was admitted with confusion and acute kidney injury on a background of Chronic Kidney Disease. Prior to admission, he described being generally unwell for the last two months, with poor oral intake and appeared significantly unkempt. His past medical history was notable for primary hyperparathyroidism secondary to a parathyroid adenoma, type 2 diabetes mellitus with retinopathy, severe depression with previous psychotic symptoms and hypertension. He was taking lithium, sitagliptin, venlafaxine, aspirin, and gliclazide. Blood tests results revealed an elevated calcium at 3.25 mmol/l (2.20–2.60), a raised PTH of 71.1 pmol/l (1.3–6.8) and a lithium level of 1.16 mmol/l (0.4–1). This patient's lithium was stopped, and he was treated with IV fluids and pamidronate. His AKI resolved and his discharge calcium was 3.11 mmol/l.
Discussion
While primary hyperparathyroidism usually arises from parathyroid adenomas, in patients on lithium, drug-induced hypercalcaemia should be considered and ruled out. Lithium is thought to cause hyperparathyroidism by altering the set points of extracellular calcium-sensing receptor (CaSR). This promotes excess parathyroid release. Thus, consistently elevated PTH levels may lead to hypercalcaemia.
Conclusion
Lithium-induced hypercalcaemia is likely more common than reported. Many patients are asymptomatic, with diagnosis only becoming apparent on routine blood tests. These cases and previously reported cases highlight that either reduction of lithium dosing or cessation of lithium can be effective management strategies. Regular measurement of serum calcium, PTH, as well as thyroid function test upon commencing lithium treatment is advisable.

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AEP837

How has the covid-19 pandemic affected training in endocrinology and nutrition

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Introduction
The pandemic has altered the day-to-day running of hospitals and most of the material and human resources have been made available for COVID-19 care. So have the residents in Endocrinology and Nutrition (MIR), who have been working on the front line, and this has led to alterations in their training programme. In addition, this unexpected and stressful work situation has had psychological consequences. The Spanish Society of Endocrinology and Nutrition (SEEN) wanted to evaluate how the pandemic has affected the residents in our speciality in Spain.
Material and methods
From 9 to 22 November, all MIR in were invited to participate anonymously. A survey was created using Google Forms and the MIR members of SEEN and heads of departments and tutors were contacted. Surveys were collected with demographic data (age, sex, year of training), location and size of hospital, alteration of internal and external rotations and training, participation in teleconsultation, infection by COVID, participation in COVID teams and emotional involvement.
Results
Eighty-seven surveys were received: -67.8% female. MIR: 81.6% 3–4th year (60% 4th). -Size: 88.5% >500 beds. Cancellation of rotations: 70.1% in own speciality, 43.7% in their own centre, 37.9% another centre. Participation in teleconsultation: 93.1%. Training courses, congresses: 97.7%. Perception of training impact: 78.1%. COVID infection: 21.8% and quarantine: 28.7%. Participation in COVID teams: 83.9% (53.5% for more than two months). Feeling supported by tutor: 67.8% A lot - Quite a lot. Affected mood: 75.8% A lot - Quite a lot.
Conclusions
This study shows the disruption that the residents have suffered in their training programmes, due to the health care collapse generated by the pandemic. In 4th- year residents, the loss of important rotations in the speciality could affect their future professional activity. The psychological impact of the pandemic should not be forgotten. The positive aspects to be highlighted are having had experience in Teleconsultation and having participated in multidisciplinary teams in an exceptional pandemic situation. New training scenarios (online, virtual reality, etc.) that can replace or complement the classic models should be considered to ensure the correct training of the residents. Assuming that, after the 3rd wave, the impact on training and rotations may have been even greater than described with these data, the SEEN requests that consideration be given to extending

the residency period for those who have lost more than 3 months due to participation in COVID teams.
Keywords: resident, training, COVID-19.
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AEP838

Consecutive development of adrenal Cushing´s syndrome and Cushing´s disease in a female patient with somatic CTNNB1, USP8, and NR3C1 mutations

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Context
The occurrence of different subtypes of endogenous Cushing's syndrome (CS) in single individuals is extremely rare. We here present the case of a female patient who was successfully cured from adrenal CS 4 years before being diagnosed with Cushing's disease (CD).
Case Description
A 50-year-old female was diagnosed with ACTH-independent CS and a left-sided adrenal adenoma in January 2015. After adrenalectomy and histopathological confirmation of a cortisol-producing adrenocortical adenoma, biochemical hypercortisolism and clinical symptoms significantly improved. However, starting from 2018, the patient again developed signs and symptoms of recurrent CS. Subsequent biochemical and radiological workup suggested the presence of ACTH-dependent CS along with a pituitary micoradenoma. The patient underwent successful transsphenoidal adenomectomy, and both postoperative adrenal insufficiency and histopathological workup confirmed the diagnosis of CD. Exome sequencing excluded a causative germline mutation, but showed somatic mutations of the β-catenin protein gene (*CTNNB1*) in the adrenal adenoma, and of both the ubiquitin specific peptidase 8 (*USP8*) and the glucocorticoid receptor (*NR3C1*) genes in the pituitary adenoma.
Conclusion
Our case illustrates that both ACTH-independent and ACTH-dependent CS may develop in a single individual even without evidence for a common genetic background.

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AEP839

Neuroendocrine neoplasm of the pancreas as a manifestation of familial isolated pituitary adenoma: A case report

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Context
Germline mutations in the aryl hydrocarbon receptor-interacting protein (*AIP*) have been identified in patients with pituitary adenomas, most frequently presenting as somatotropinomas in the setting of familial isolated pituitary adenoma (FIPA). Our current understanding of *AIP* related tumorigenesis indicates that it leads to isolated pituitary adenomans, while other associated tumors have not typically been considered part of the clinical spectrum. pancreatic neuroendocrine neoplasms (panNENs)
Case description
We report a unique case of an advanced pancreatic neuroendocrine neoplasm (panNEN) in a patient from a 3-member kindred. Germline DNA revealed a heterozygous pathological *AIP* variant c.910C > T (p.R304*) in the affected family members; no germline multiple endocrine neoplasia type 1 (*MEN1*) or cyclin-dependent kinase inhibitor 1B (*CDKN1B*) variants were seen. The tumor DNA sequencing confirmed the *AIP* c.910C > T (p.R304*) change in a liver metastasis, accompanied by loss of heterozygosity at the *AIP* locus. Furthermore, the liver metastasis showed an additional somatic variant in *MEN1* c.1289_1291del (p.E430del).
Conclusions
Genetic testing and tumor histopathology in this FIPA kindred suggest that in this case, the panNEN might represent a rare new *AIP*-associated malignancy.

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AEP840

Markers of humoral and cell-mediated immune response in primary autoimmune hypophysitis: A pilot study

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Introduction
Primary autoimmune hypophysitis (PAHs) is a rare inflammatory disease of the pituitary gland. Although largely investigated, the pathogenesis of PAH is not completely clarified. We aimed to investigate the immune response in PAHs.
Material and methods
Serum anti-pituitary and anti-hypothalamus antibodies (respectively APAs and AHAs) were investigated though an indirect immunofluorescence on monkey hypophysis and hypothalamus slides, serum cytokines though an array membrane and cell-mediated immunity though the white blood cells count.
Results
Nineteen PAH cases entered the study. APA or AHA were identified in all cases. APA were detected in 13 patients (68.4%) and AHA in 13 patients (68.4%). Ten patients (52.6%) were simultaneously positive for both APA and AHA. The prevalence of APAs and AHAs was higher as compared to those observed in 50 health controls (respectively 14% $P < 0.001$ and 24% $P = 0.004$) and in 100 not-secreting pituitary adenoma (NFPAs) (respectively 22% $P = 0.002$ and 8% $P < 0.001$). Similarly, the prevalence of simultaneous positivity for APA and AHA (52.9%) was higher as compared to the those detected in patients affected by NFPAs (0%; $P < 0.001$) and in health controls (16% $P = 0.002$). No differences were identified between PAHs and controls at qualitative and quantitative analysis of serum cytokines and white blood cells count.
Conclusions
This study suggest that APA and AHA may be detected in an high percentage of PAH cases and that their simultaneous identification may be useful for the differential diagnosis between PAH and NFPAs, in an appropriate clinical context.

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AEP841

Natural course and surveillance of non-functioning pituitary microadenomas

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In the current era of multi-modal imaging being performed for various pathologies, incidental non-functioning pituitary microadenomas (NFPAs) are being increasingly identified. The available literature and guidance is limited on the long-term surveillance and monitoring and hence there is a wide variation in clinical practice across the UK. We conducted a

retrospective study in our institution to compare the outcome in our cohort to the current literature.
Method
Keyphrase "pituitary adenoma" was used to select 1700 patients over a 10-year period (2010–20) from pituitary MDM, radiology database and electronic patient records. Macroadenomas, functioning tumours, Rathke's cleft cysts, MEN syndrome and patients with < 2 pituitary screening (imaging and biochemistry) were excluded. Retrospective analysis was conducted on 43 patients with a mean age of 51 ±13 years (32F and 11M). NFPA diameter ranges were 1 – 5 mm in 24 (56%) and 6 - £10 mm in 19 patients (44%).
Results
Mean follow up period was 28.5 months (range 3 – 96) equating to 102 patient years. Although 20% of cases progressed in size (0.72 mm/year), overall net growth was negative (- 0.13 mm/year) as 80% regressed or remained unchanged. The maximum dimension reached during surveillance was 11mm in 1 NFPA from a baseline of 10mm.
Surveillance summary
1 – 10 mm: Regression in 30%, unchanged 50% and progression in 20%.
1 – 5 mm: Regression in 25%, unchanged in 60% and progression in 15%.
6 – 10 mm: regression in 30%, unchanged in 40% and progression in 30%.
Conclusion
Compared to the largest meta-analysis of 14 multi-centre observational studies that consisted of 229 NFPAs, our single centre case series of 43 NFPAs demonstrated 20% (vs 10%) progression, 30% (vs 7%) regression and 50% (vs 83%) unchanged with stable size. None of the NFPAs in our series came into contact with the optic chiasm and all the patients remained eupituitary throughout. Our study further reaffirms the benign course of NFPA if £10 mm, however, further up to date multi-centre data collation is essential for predictive modelling based on size and age at presentation and standardisation of follow up and discharge protocols.

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AEP842

The first comprehensive study of the clinical response of a cohort of acromegalic patients with somatostatin responsive headache

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It is known that acromegaly may be associated with headache as a significant co-morbidity. Amongst all acromegaly headache patients, there is a unique group with specific types of severe headache that fail to improve despite acromegaly therapy and are resistant to conventional analgesics, however, immediately respond to subcutaneous short-acting (SA) somatostatin analogue (SSA) treatment. We have surveyed 8 tertiary specialist UK centres and identified 18 patients (6 females) on the basis of their presentation with SSA-responsive acromegaly associated headache. The phenotype was mostly chronic migraine (78%) and International Headache Society pituitary-tumour associated headache (22%). All patients reported a daily, persistent headache (apart from those on long-acting (LA) SSA) with intense severity (mean 9 on 0–10 pain scale). No headache cessation after surgery was observed (although in 27.8% improvement was reported). All patients presented with macroadenoma, mostly after incomplete resection (94.1%) and headache ipsilateral to remnant tissue (93.8%). All patients failed to respond to conventional analgesic treatment. However, they all observed headache relief after SA-SSA injection within minutes, lasting up to 6 hours. The frequency of SA-SSA injections was higher when taking SA-SSA alone (n = 8), than in combination treatment with SA- and LA-SSA (n = 10) for disease control (mean 10.4 [range 3–6] SA-SSA alone; vs mean 3.7 [range 0–7] SA with LA-SSA). Headache was long-lasting, persisted up to 33 years after diagnosis (mean 18 [range 6–33]), and only 4 patients were in headache remission. 77.8% of patients achieved biochemical control, although 71.4% of this group still had headache despite normal IGF-1. Elapsed time after radiotherapy in patients with headache remission was higher than in patients still struggling with headache (median 21 vs 10 years). Headache, as a significant co-morbidity in a specific group of patients with acromegaly can be persistent, severe, unrelieved after surgery, and not correlated with biochemical control, while reacting to SA-SSA, which appears to have a modulatory role with its still unknown mechanism.

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AEP843

The stimulatory effects of glucagon on cortisol and GH secretion occur independently from FGF-21

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Aim
Glucagon stimulation test (GST) is used to assess hypothalamo-pituitary-adrenal (HPA) and GH axis with an incompletely defined mechanism. Glucagon has physiological effects on body weight and metabolic parameters and some of these effects are suggested to occur via fibroblast growth factor-21 (FGF-21) which is a circulating hepatokine. FGF-21 was also shown to affect HPA and GH axis in rodents. The aim of the present study was assess if glucagon acted through FGF-21 to stimulate the cortisol and GH secretion. Secondary outcome was to determine the relationship of FGF-21 with variable GH responses to GST in obesity.
Material and methods
A total of 26 healthy participants were included in the study. 11 participants were obese (Body Mass Index (BMI) > 30 kg/m^2) and 15 had a normal weight (BMI <25 kg/m^2). Basal pituitary and target hormone levels were measured and glucagon stimulation test (GST) was performed. During GST, glucose, insulin, cortisol, GH and FGF-21 responses were measured.
Results
Glucagon resulted in significant increases in FGF21, glucose, insulin, cortisol and GH levels. Serum glucose levels showed variations during GST. Peak GH and area under curve $(AUC)_{(GH)}$ responses to GST in the obese group were lower than those of the normal weight group with a different pattern of response. Cortisol responses were similar in two groups. Obesity was associated with significantly increased glucose and insulin responses and slightly decreased FGF-21 response to glucagon. But neither cortisol nor GH response to the GST was related to FGF-21, deeper hypoglycemia may be related to increased GH response to GST in lean individuals.
Conclusion
Obesity was associated with blunted and delayed GH, but preserved cortisol responses to GST. This is the first study, at least according to our knowledge, to show that glucagon stimulates the HPA and GH axis independently from FGF21. The delayed GH response to GST in obesity does not seem to be related to FGF-21.

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AEP844

The relative's viewpoint on acromegaly in remission : A psychosocial dimension of a chronic disease

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Aim of the study
A relative can be an asset in dealing with chronic illnesses such as acromegaly where quality of life is altered even after remission. However, it has been shown that quality of life of caregivers can also be impacted. Our

main objective was to explore the consequences of acromegaly in remission in the patient-relative dyad in a matter of quality of life and self-esteem.
Methods
In this French monocentric observational study, to better characterize the perception of the disease by the relative, patient's body image (Stunkard figurines) and self-esteem were evaluated from the patient's point of view and from the relative's (n = 27 dyads, including 77.7% partners and 22.2% children) using the same questionnaires with modified instructions. Both evaluations were correlated in an original approach to try to understand the differences of the perception of acromegaly in remission seen by the partner when he/she was asked to think of what would be the answer given by the patient. The patient and the relative were also asked to fulfil quality of life, anxiety/depression and coping strategies questionnaires.
Results
The relative had an overall accurate estimation of the patient's body image (P = 0.171 in comparison with the patient). However, there were individual variations between the patient's and the relative's answers for self-esteem and body perception from an individual viewpoint. The relative's quality of life was not altered and was significantly higher in the social domain than for the patient. As expected, patients had a significantly lower quality of life and body satisfaction than the French population: in multivariate analysis, self-esteem was associated with an impaired psychological quality of life score. Finally, the adaptation strategy preferentially adopted by the relative was positive thinking. Problem solving came in second position, and seeking social support in third.
Conclusions
Our study is the first to analyse the consequences of acromegaly of the patient-relative dyad in a matter of quality of life and self-esteem. Despite inter-individual changes between the patient's and the relative's view, our results show that the relative appeared to have an accurate estimation of the patient's body image. However, the relative was not fully aware of the consequences of body changes on the patient's self-esteem. The relative should thus be educated in all the steps of the management of acromegaly, and be encourages not to postpone seeking social support.
Funding
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AEP845

Importance of proper diagnosis and treatment challenges in a 16-year-old patient with ectopic posterior pituitary and panhypopituitarism - a rare case report

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Background
Posterior pituitary ectopia is a rare congenital condition that consists of the abnormal position of the distinctly hyperintense signal suggestive of the posterior pituitary gland on magnetic resonance imaging. The classical features include the ectopic location of the posterior pituitary gland, pituitary stalk abnormalities and associated clinical manifestations related to isolated growth hormone deficiency. In rare cases, some patients suffering from this condition may develop panhypopituitarism.
Case report
The present paper aimes to present a rare case of a late-diagnosed ectopic posterior pituitary with an absent pituitary stalk and panhypopituitarism, in a 16-year-old male patient with severe mental retardation, under the care of a non-compliant mother. The initial physical examination showed short stature, mild facial dysmorphism, absence of both expressive and receptive language, micropenis and cryptorchidism. Laboratory investigations showed multiple anterior pituitary deficiencies: growth hormone deficiency (GHD), with a corresponding low insulin-like growth factor-1 (IGF-1), low free-thyroxine-4 (FT4), low follicle-stimulating hormone (FSH), and luteinizing hormone levels (LH), low total testosterone level, low serum cortisol level, hyperprolactinemia and severe 25-hydroxivitamin D deficiency. The radiographic anatomy of the hand estimated a bone age between 6 and 7 years. A pituitary magnetic resonance imaging revealed the absence of the pituitary stalk, hypoplastic anterior pituitary and the ectopic location of the posterior pituitary near the mammillary bodies. Initially, the patient was treated with prednisolone 5 mg/day, levothyroxine 50 mg/day, and cholecalciferol 1000 IU/day. At the 3-month follow-up, no significant improvement could be observed, due to lack of compliance from the patient's mother regarding treatment administration. The decision to add human growth hormone and later on human chorionic gonadotropin to the current treatment was taken. Parent counseling was provided. At the 6-month follow-up, a slight improvement in the patient's height and general condition was observed.
Conclusion
Taken together, our findings support the theory that in rare cases, an absent infundibular stalk is associated with panhypopituitarism. Based on the clinical and hormonal findings, magnetic resonance imaging for hypothalamic-hypophyseal abnormalities was the key investigation to determine the underlying cause of these aspects. If diagnosed early and with adequate treatment adherence, the therapy can ensure normal psychiatric and somatic development in pediatric patients. Parent compliance is crucial for successful outcomes.

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AEP846

Hemorragic degeneration after covid-19 infection in microprolactinoma

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Introduction
Pituitary apoplexy is seen in 1.5–27.7% of pituitary adenomas. Common etiologies include hypertension, diabetes mellitus, radiotherapy, contrast-enhanced MR, surgery, drugs, anticoagulant, antithrombotic, estrogen, head trauma and pregnancy. SARS-CoV-2 had spread rapidly, and caused COVID-19 pandemic. Although it mainly causes respiratory problems, there may also be extrapulmonary involvement. COVID-19 infection is associated with hemorrhagic complications, cardiac and renal infarction and cerebrovascular hemorrhage. In this report, we present a patient who was followed up with microprolactinoma and developed hemorrhagic degeneration in adenoma after Covid-19 infection.
Case
A 26-year-old female patient was found to have serum prolactin of 94.19 mg/l (4.79–25.3) in the tests performed due to menstrual irregularity and complaints of galactorrhea by provocation. Control prolactin was 104 mg/l, and macroprolactin was negative. Other anterior pituitary hormones, kidney and liver function tests were normal. A 4 × 6 mm microadenoma was detected on pituitary gland in pituitary MRI. Cabergoline 0.5 mg/week was initiated in March 2019 with the diagnosis of microprolactinoma. The pituitary MRI taken in February 2021 revealed a 7 × 5.5 mm lesion in the adenohypophysis with the presece of hemorrhagic degeneration. There were no complaints of severe headache, nausea, vomiting, or visual impairment during system inquiry. Anterior pituitary hormone levels were normal. Medical history showed that she was diagnosed with Covid-19 in September 2020. She used hydroxychloroquine sulfate 2 × 200 mg (5 days) and enoxaparin sodium 2 × 0.6 mg (10 days) and then acetylsalicylic acid for 10 days. It was thought that hemorrhagic degeneration might be due to the antiaggregant/antithrombotic treatment she had received or the Covid-19 infection itself.
DISCUSSION
Case reports of pituitary apoplexy following Covid-19 infection have been presented in the literature. It is unclear whether this infection occurs as a contributing factor to pituitary apoplexy or coincidentally. It is possible that coronavirus infection could cause an acute hemorrhagic infarction of the gland. This risk increases with anticoagulant and antiaggregant treatments used during Covid-19 infection. Although bleeding into adenomas is spesific to macroadenomas, it should be kept in mind that it may also occur with microadenomas.

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AEP847

Two thyrotropin secreting pituitary adenoma cases diagnosed after response to the somatostatin analogue

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Introduction
Pituitary adenomas secreting TSH (TSHoma) are a rare cause of hyperthyroidism. They account for approximately 0.5–3 % of functioning pituitary tumours and much less than 1% of all cases of hyperthyroidism. TSHoma should be considered in all hyperthyroid patients, especially those with diffuse goitre and no extrathyroidal signs of Graves' disease.
Case 1
A 30-year-old female applied to the internal medicine department with complaints of palpitations, diarrhea, sweating and weight loss. In repeated examinations, high levels of TSH, fT3 and fT4 were detected, TSH, fT3 and fT4 values examined in 3 different centres and again found to be high.The serum sex hormone-binding globulin concentration was slightly elevated. In family screening, no thyroid dysfunction was detected. In pituitary MRI, 5 mm adenoma was detected.The serum α-subunit level was 2.4 ng/ml (normal < 1.2), and the α-subunit/*TSH molar* ratio (α-subunit × 10/*TSH*) was 4.3 (normal < 1).We performed an analysis for mutations in the *THRB* gene; no mutations found. The serum TSH concentration didn't increase in response to the thyrotropin-releasing hormone, while a fall in serum TSH concentrations was detected in response to administered T3. Since the tests showed discordance, a short course of long-acting (LAR) somatostatin analogue (SSA) was administered. Thyroid function tests returned to normal with LAR-SSA therapy and strengthened the diagnosis of TSHoma. Surgery was planned.
Case 2
A 35-year-old male patient was referred to the endocrinology department when elevated TSH, fT3 and fT4 values were detected in the smoking cessation outpatient clinic. Repeated examinations in the same centre and two different centres showed high TSH, fT3 and fT4 levels. No thyroid dysfunction was found in first-degree relatives.The serum sex hormone-binding globulin concentration was normal,and the serum ńsubunit level was 0.7 ng/ml (normal<0.5). In pituitary MRI, 7 mm adenoma was detected. The serum TSH concentration didn't increase in response to the thyrotropin-releasing hormone,while a fall in serum TSH concentrations was detected in response to administered T3. Since the tests showed discordance,a short course of LAR-SSA was administered. Thyroid function tests returned to normal with LAR-SSA therapy and strengthened the diagnosis of TSHoma. Surgery was planned.
Conclusion
Most *TSHomas* are detected as pituitary *macroadenomas***.** The presence of a microadenoma on MRI is not specific for a TSH-secreting tumour and can be seen as an incidental finding in 10 per cent of normal individuals. The rutin tests used for the differential diagnosis of TSHoma and Thyroid hormone resistance sometimes may be discordant. In such cases, performing the LAR-SSA test strengthen the diagnosis.

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AEP848

EGFR (Epidermal Growth Factor Receptor) expression in tumor microenvironment of pituitary adenomas – pathogenic and therapeutic implications

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Background
Pituitary adenomas are general benign tumors. However, gross invasion at time of operation is observed in up to 35% of pituitary adenomas. The new WHO classification describes pituitary tumor subtypes along with histological markers, such as Ki67 > 3%, that may suggest a potential for aggressive clinical behavior. The expression of EGFR in tumor microenvironment of pituitary adenomas ant its correlation with tumor behavior have been poorly characterized.
Materials and methods
Our study included 92 selected cases (10 normal pituitary glands, 82 pituitary adenomas extracted through transsphenoidal approach). We used standard morphological stain- hematoxylin-eosin to determine the tinctorial classification and the growth pattern of the adenomas. We used the immunohistochemical method to obtain the hormonal profile; we determined the mRNA for the well known growth factors (VEGF, VEGF165b, PDGF A, PDGF B/PDGFR BETA, EG-VEGF) through ISH, respectively the RNA scope technique. We also characterized S100 -positive folliculo-stellate cells and tumor associated macrophages.
Results
We identified 2 types of cells, with positive immunohistochemical reaction to EGFR in pituitary tumors with negative reaction to EGFR. In some adenomas, we identified, at the periphery of the tumor, an important accumulation of tumor associated macrophages. In these cells,we identified a strong expression of the receptor EGFR. We identified a strong expression of EGFR in folliculostellate cells with a homogenous or granular cytoplasmatic pattern.Both adherent and gap junctions are between folliculostellate cells and between folliculostellate cells and endocrine cells. These cells are also positive for GFAP (glial fibrillary acidic protein), suggesting that this cell type may represent an astrocyte – or microglia – like cell type. Our observations support older findings, notably the increased activity of folliculostellate cells under pathological conditions, their phagocytic activity and their capacity to secrete angiogenic growth factors, suggesting that folliculostellate cells may be involved in basement membrane remodeling, tumoral neoangiogenesis and tumoral expansion.
Discussions and conclusions
The role of folliculostellate cells expressing EGFR in pituitary adenomas has not been studied until now. Clearly, the tumor microenvironment is a major component of pituitary adenomas that holds promise for targeted therapies. We need to better characterize the composition of this microenvironment ,influencing the tumor behavior and the response to therapy

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AEP849

Pituitary diseases registry study in latvia. Part 2

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Introduction
Pituitary diseases result in clinical consequences and increased mortality due to tumors mass effects and also due to pituitary hypersecretion and insufficiency. Pituitary tumors registry enables identification of diagnostic and prognostic markers. The registry improves long-term clinical outcomes, pituitary diseases care and management.
The aim of this study
Our registry study is designed to create a unified database of pituitary disease patients in Latvia for the first time.
Materials and methods
We collected 3 yrs data from pnts medical records with pituitary diseases and tumors from Clinical University Hospital Outpatient Clinic and from 4 Outpatients Clinics in Riga and in Jelgava, which were the workplaces of both authors. Prospective cohort analysis was performed based on demographic data, MRI and lab. data, data on medications, doses, and regimens, information on co-morbidities and concomitant medications. We collected pnts with pituitary diseases and tumors: prolactinomas, CNFA, acromegalies, empty sella syndr., Cushing's disease (CD), Ratke's pocket cysts, meningiomas, craniopharyngioma, pituitary aplasia or hypoplasia, TSH-omas, germinoma, glioma, chondrosarcoma, pericytoma.
Results
355 pnts (71.7% women) with pituitary diseases were registered from July 2016 to July 2019. The mean age was 43.4 yrs (range 18–83 yrs). Prolactinomas were the most common adenomas (40.8%), followed by CNFA (28.5%), acromegaly (16.1%) and than empty sella syndrome (5.1%), CD (2.3%), Ratchet pocket cysts (2.3%), meningiomas (1.4%), craniopharyngiomas (1.1%), pituitary aplasia and hypoplasia (0.8%), TSH-omas (0.6%), germinoma (0.3%), glioma (0.3%), chondrosarcoma (0.3%), pericitoma (0.3%). Patients in this cohort most often received drug therapy with any medication alone or in combination (octreotide LAR, lanreotide, bromocriptine, cabergoline, pegvisomant) in 50.5% of cases. The majority of 94.7% of patients (n = 336) had 1 or more co-morbidities. The most common group of comorbidities was the thyroid disease group (n = 289). The next - the cardiovascular diseases group (n = 273), vitamin D deficiency 76.2% (n = 256), dyslipidaemia 59.2% (n = 199), various types of diabetes mellitus/carbohydrate metabolism disorders 36.3% (n = 122), non-alcoholic steatohepatosis (NASH) 19.3% (n = 65), osteoarthritis 17.9% (n = 60), primary/secondary osteoporosis/osteopenia 7.1% (n = 24), gallstone disease 10.4% (n = 35), etc. The majority of pnts (81.7%) were treated with 1 or more concomitant medications.
Conclusions
As a result of this study, a unified database of pnts with pituitary diseases has been created, and data on 14 different pituitary diseases has been collected in register, which allows analyzing the population characteristics

of the pituitary diseases, the applied treatment schemes for the treatment of pituitary diseases; types of neurosurgery, medications data.

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AEP850

A case of pituitary xanthogranuloma diagnosed with diabetes insipidus

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Background

Pituitary xanthogranulomas are extremely rare tumors of the sellar region. A cystic mass lesion was found in the pituitary MRI of our patient diagnosed with central diabetes insipidus (DI). We aimed to present a case who was operated for a pituitary mass and diagnosed with sellar xanthogranuloma.

Case presentation

37-year-old female patient was applied to our outpatient clinic with complaints of polydipsia, polyuria and headache for 8 months. The anterior pituitary hormone levels were in normal. Plasma osmolarity: 291 mOsm/kg, urine osmolarity: 130 mOsm/kg, urine density: 1006 and serum electrolytes were in normal range. Pituitary MRI revealed a cystic mass lesion with prominent hyperintense mucoid content in T1-weighted sequences with a diameter of approximately 10 × 11 mm and completely obliterating the neurohypophysis in the posterior of the adenohypophysis. Also the cystic mass lesion showed expansion towards the posterior suprasellar system. Her visual field examination was found normal. The patient was admitted to our clinic for the water deprivation test. Complete central DI was diagnosed. Desmopressin treatment was started on. The clinic and laboratory findings of DI were improved after desmopressin treatment. The patient was evaluated by neurosurgery department. Transsphenoidal surgery was performed for the mass lesion in the pituitary. The pathology result was reported as sellar xanthogranuloma. Desmopressin therapy was continued in the postoperative period. Clinical and laboratory findings were found normal under desmopressin treatment. Pituitary MRI performed 3 months after the operation, no finding of residual-recurrent adenoma was detected in the sellar region.

Conclusion

Sellar xanthogranulomas are very rare seen intracranial tumors. They have not any typical radiological feature. Patients can present with clinical signs such as headache, visual disturbance, vomiting, DI and hypopituitarism.

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AEP851

A man with adenocarcinoma metastasis to the pituitary gland presenting with panhypopituitarism and double vision

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A 76 year old man known to have coronary heart disease, hypertension and chronic kidney disease due to hypertensive nephropathy admitted to the nephrology clinic with fatigue, nausea and dizziness. His creatinine level was detected to be increased (from 1.5 to 2.5 mg/dl) and was he was hospitalized. The cranial magnetic resonance imaging (MRI) performed after neurology consultation for dizziness showed a pituitary mass. When asked, the patient described bitemporal hemianopsia for 2 months and double vision for the last 3 days. During eye examination bitemporal hemianopsia and VI. nerve palsy were detected. Pituitary MRI showed a 18.2 × 18.6 × 17 mm, bilobular, heterogenous mass with cystic and necrotic areas invading and expansing sella turcica. The lesion also compressed optic chiasma and stretched out pituitary stalk. ıt was interpreted as a macroadenoma but a metastasis could not be excluded. Pituitary hormones revealed panhypopituitarism; cortisol 1.92 mg/dl, ACTH<5 pg/ml, TSH 0.207 uIU/ml, triiyodothyronin 3.46 pmol/l (3.5–6.5), thyroxin 9.31 pmol/l (11.5–22.7), IGF-1 48.8 ng/ml (35–216), LH 0.389 mIU/ml (3.1–34.6), total testosteron< 7.00 ng/dl (86.4–788), PRL 43 ng/dl. The patient was started L-thyroxin subsequently methyl-prednisolon. The patient underwent pituitary biopsy; the tumor, within a desmoplastic stroma, was composed of malignant epithelial cells forming large glandular structures with intraluminal mucin. The neoplastic cells were positive for Cytokeratin 7 and TTF1, was negative for Cytokeratin 20, CDX2, Thyroglobulin, Synaptophysin, Chromogranin and CD56. The tumor was consistent with an adenocarcinoma metastasis. Positron emission tomography-fluorodeoxycortisol (PET-FDG) was performed to reveal the possible primary source of the tumor. PET-FDG showed bone metastases at the dorsal, lumbar vertebrae, left scapula, right acetabulum and left hip (SUVmax: 8.6) and a thyroid nodule at right lobe with normal FDG uptake. Cyber-knife neurosurgery was made to the pituitary lesion of the patient. The pituitary gland is an unusual location for any metastatic spread. Metastases to the pituitary gland represent 0.4% of all intracranial metastatic tumors. Symptoms and signs of pituitary metastases include diabetes insipitus, visual damage, ophtalmoplegia, headache, fatigue, weight loss, nausea and cognitive deterioriation. Anterior pituitary deficiency is common and hyperprolactinemia can be seen.

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AEP852

Rare hypophysis tumor arising in a case with diabetes incipidus: Granular cell tumor

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Introduction

Pituitary gland tumors constitute approximately 10–15% of primary brain tumors, and posterior pituitary tumors are extremely rare. Granular cell tumor (GCT) is a low grade non-neuroendocrine neoplasm. Here, we will present our case who was found to have GCT during follow-up of diabetes insipidus (DI).

Case

A 23-year-old male patient applied to our outpatient clinic for routine control. 12 years ago, he was diagnosed with growth hormone deficiency and central hypothyroidism during tests performed for short stature, and used growth hormone and levothyroxine treatments, and it was learned that these treatments were discontinued after puberty, and he had been using desmopressin for partial DI for 10 years. He was using desmopressin 240 mg/day at presentation. His height and weight were 165 cm and 60 kg, his blood pressure was 120/80 mm Hg, and his pulse was 72 beats/min. Systemic examination was normal. Serum Na level was 142 mEq/l, serum osmolality was 291 mOsm/kg, spot urine osmolality was 693 mOsm/kg, and urine density was 1020 (Table 1). On the neurohypophysis lodge, a high-signal lesion area (granular cell tumor?) was observed with magnetic resonance imaging in T1A and T2A series with 1.4 × 1 × 0.6 cm dimensions, which created convexity at the base of the sella contour. When the pituitary images of previous years were examined, it was reported that neurohypophysis was normal in 2010 and 2016, tubular structure showing loss of signal in all sequences in the neurohypophysis (vascular structure?) was observed in 2013, and in 2019, it was determined that a lesion (lipoma?, terotoma?, dermoid cyst?) was detected in the neurohypophysis lodge, which showed suppression (?) in a fat-suppressed sequence of 13 × 7 mm in size, and did not form a distinct opacification pattern in dynamic study. He was evaluated in a multidisciplinary council and follow-up was planned.

Discussion

DI was seen in 3–5% of GCT cases. In our case, no tumor was observed on neurohypophysis at the time of diagnosis, but GHT was detected during follow-up. We are of the opinion that periodic pituitary imaging in DI cases may increase the possibility of detecting rare tumors such as GHT.

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AEP853

Giant invasive prolactinoma –a dramatic quick response to medical therapy

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Giant prolactinomas are rare tumours, accounting for only 2–3% of all prolactin (PRL)-secreting tumours which can pose therapeutic challenges. It has a higher preponderance in men with a male to female ratio of about 9:1. A 70year old gentleman initially presented to the ophthalmology department with blurred and reduced colour vision. He denied any headache, galactorrhoea or gynaecomastia however he noticed reduced libido and difficulties with erections. His past medical history included hypertension, Type 2 Diabetes and renal stones. He reported no family history of endocrine disease or tumours. On examination, his weight was 92 kg, with a BMI of 31.A mild temporal left visual field defect was noted with normal eye movements. In view of the visual defect he had a brain MRI which demonstrated a large mass centred on the body of the sphenoid extending laterally into both cavernous sinuses the sphenoid wings and roof of the orbits with extension into the ethmoid air cells and left frontal air cells. The mass elevated the chiasm, floor of the third ventricle and anterior frontal lobes. He was subsequently referred to the pituitary service and initial biochemistry showed a random cortisol of 237 nmol/l, FSH 2.0 iu/l ,LH 1.1 iu/l, TSH 1.42 mu/l (0.34–5.6), T4 8.5 mu/l (7.7–15), IGF-1 17.4 nmol/ (5.3–29), ACTH 23 ng/l (0–46), Testosterone 2.1 nmol/l (10.0–27.6), prolactin (post dilution) : 411, 237 mu/l (55–276), Renal, calcium and liver function profiles were normal. In liaison with neurosurgery he was commenced on cabergoline at a dose of 500 micrograms once weekly with views to increase to 500micrograms twice weekly as tolerated. He was also started on hydrocortisone given the indeterminate cortisol level and a short synacthen test was arranged. He was also started on levothyroxine 50 micrograms once daily for secondary hypothyroidism. He responded very well to medical therapy and his prolactin levels dramatically improving to 6911 mu/l.An interval pituitary MRI at 6 weeks showed modest reduction in the bulk of the macroprolactinoma with resolution of chiasmal compression. His subsequent prolactin levels were suppressed to latest of 97 mU/l and serial MRI scans showed progressive shrinkage of the giant tumour.

Conclusion

Dopamine agonists remain the first line treatment for giant macroprolactinoma in tumour size reduction and normalization of prolactin levels. Neurosurgical interventions are associated with high morbidity and mortality and best reserved when medical therapy is ineffective or not tolerated. Patients should be managed in Tertiary Centres within an MDT setting.

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AEP854

Examination of pituitary adenomas and non-adenoma lesions

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Introduction

Pituitary adenomas generate 10–15% of primary brain tumors. Most of these adenomas are benign and orginate from the epithelial cells of the adenohypophysis. Pituitary adenomas can occur in all age groups, but most common in the third and sixth decades. In this study, we are investigated the demographic characteristics of pituitary adenomas and non-adenoma lesions that admission to the Bozyaka Education and Research Hospital Endocrinology and Metabolic Diseases outpatient clinic between 2018–2019.

Materials and methods

93 patient who have pituitary adenomas and non-adenoma lesions that admission to the Bozyaka Education and Research Hospital Endocrinology and Metabolic Diseases outpatient clinic between 2018–2019; detailed anamnesis, pituitary hormone results and pituitary MR images were retrospectively analyzed.

Results

The mean age of patients was 44, 7 (range 19–93). Of 93 patients, we were seen 70% were female (n:66) and 29% were male. (n:27) We were found that microadenoma 56% (n:53), macroadenoma in 31% (n:29), empty cella 2% (n:2), partial empty cella 6%(n:6), craniopharyngioma 3% (n:3), rathke cleft cyst 1% (n:1) of the patients who admitted to the study. Among the patients diagnosed with macroadenoma, the mean age of male patients was 58, 3 (n:13), and the mean age of female patients was 48.9 (n:16). The mean age of female patients who diagnosed with microadenoma was 38 (n:44), and the mean age of male patients who diagnosed with microadenoma was 46, 1. (n:9). When the patients were evaluated according to hormone secretion function; 68% (n:64) of the patients examined were prolactinoma, 6,4% (n: 6) acromegaly, 13,9% (n:13) were nonfunctional adenoma. Majority of the patients (%77,9) who diagnosed with prolactinoma were female. (n: 53)

Conclusion

When both macroadenoma and microadenoma were evaluated, we found that the average age in men was higher than in women. As a result of the study, we determined microadenomas were more common in women and noticed at an younger, however; observed less frequently in men, but diagnosed in older ages. When pituitary lessions were evaluated according to hormone secretion function, prolactinoma was the most common. As a result of our study, the majority of patients followed up with the diagnosis of microadenoma with medical treatment (n:43) while the majority of patients diagnosed with macroadenoma are followed together with surgical and medical treatment.(n:16). In this study, we aimed to make demographic analysis of patients with pituitary adenoma and non adenoma lesions who applied to our hospital. The results of our study were found to be consistent with the literature.

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AEP855

An unusual presentation of a metastatic typical bronchial carcinoid

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Introduction

Lung Neuroendocrine tumors (NETs) range in aggressiveness from low-grade typical carcinoid (TC) and intermediate-grade atypical carcinoid (AC) to the high-grade large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC). TC have excellent prognosis post-surgery and European Neuroendocrine Tumor Society (ENETS) recommands no adjuvant therapy for these well diferentiated tumors.

Case report

A 67-year old, hypertensive woman was referred to our Institute for assessement of thyroid function, accusing exertional dyspnea and chronic hypokalemia. She has a recent history of thyreotoxicosis, treated with antithyroid drugs for a few months. Also, two months before presentation, she underwent a cardiac tamponade with emergency pericardial drainage by left anterolateral thoracotomy. The patient is oncologically monitored for a typical bronchial carcinoid, surgically treated 9 years ago. Her oncologist yearly recommended computer tomography of chest and abdomen, who revealed at the last assessement a left adrenal mass and two hepatic lessions. Soon after that, she performed a FDG-PET CT, which did not show a metabolic active lesion. Her physical examination was normal, except a slightly elevated blood pressure, 140/90 mmHg, and an grade I WHO thyroid goiter. Biochemistry confirmed the hypokalemia (plasma K= 2.9 mmol/l, normal range 3.5–5). Thyroid function was normal, spontaneously. TSH receptor antibodies and ATPO were negative. Thyroid ecography revealed a hypoechoic, pseudonodular echogenicity. Her plasma metanephrines and normetanephrines, basal cortisol, cortisol after 1mg overnight supression test, ACTH, prolactin and PTH, were also in the normal range values. Plasma Aldosteron level was high (377 pg/ml, normal range 18.8–256.7) and plasma renin level supressed (0.68 pg/ml, normal range 2.64–27.66), but taken under antihypertensive agents known to interfere with these hormons and under hypokalemia. Her neuroendocrine markers were as follows: Cromogranin A level was 116.9 ng/ml (normal range 20–100), serotonin level was 78 ng/ml (normal range 80–400), neuron specific enolase level was 15.01 mg/l (normal range 0–18.3) and urinary 5 hydroxiindolacetic acid level was in the normal range. Octreoscan showed single hepatic and pericardial lesions with somatostatin receptor expression, suggestive for secondary determinations of typical pulmonary carcinoid. She was discharged with the recommendation to increase the dose of antialdosteronic diuretic, potassium supplements, repeat thyroid function after 8 weeks and a recommendation of a hepatic biopsy, followed by resection of the lesion if secondary hepatic determination confirmed. Also, a somatostatin analog therapy was initiated.

Conclusion

For the optimal management of NETs, a detailed anamnesis is necessary and requires decision-making within a multidisciplinary team.

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AEP856

A rare case of glucagonoma presented with high serum amilase and lipase

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Introduction
Glucagonoma is an extremely rare type of functional pancreatic neuroendocrine tumor that is characterized by distinctive clinical manifestations such as diabetes mellitus, weight loss, deep vein thrombosis, and necrolytic migratory erythema which represents the hallmark clinical sign of glucagonoma syndrome. Here, we report the case of a 53-year-old male patient who presented with high amilase and lipase levels. In further investigation a pancreatic tumor was determined and after pancreatic surgery it was diagnosed as glucagonoma.
Case
A 53-year-old male patient was examined routinely in cardiology. In the laboratory analysis, amilase and lipase were detected as above the upper limit of normal [amilase: 212 (Normal range: 30–118 U/l), lipase: 224 (Normal range: 12–53 U/l)]. He did not have any symptoms or signs associated with pancreatitis. Glycosylated A1c was 6.5%. In his past history he did not have diabetes mellitus. In the family history, he reported that his mother had diabetes. He referred to our outpatient clinic for prediabetes. Furtherly, 75 gr oral glucose tolerance test was performed. It was evaluated as impaired fasting glucose (0.min glucose: 115 mg/dl, 120.min glucose: 93 mg/dl). In the investigation of pancreatic enzyme abnormalities, abdominal ultrasound was performed. In the ultrasound, Grade 2 hepatosteatosis and a heterogenous weakly hypoechoic solid mass located in proximal pancreatic body which was 20x14.5 mm in diameter were detected. In abdominal MRI, a 21x16 mm mass located in posterior part of the pancreatic body which was mildly hyperintense in T2A and hypointense in T1A images was reported, and in contrasted images the tumor was found as prominent minimally according to parachyme, and had also diffusion restriction. For the investigation of neuroendocrine tumor, Ga-68 DOTA-PEPTIDE PET/CT was performed and it demonstrated a high pathologic Ga-68 enhancement in the pancreatic mass (SUVmax: 21.92). Then, the patient was operated. Distal pancreatectomy and splenectomy was performed. The histopathology was reported as grade 1 glucagonoma. Postoperatively, he had diabetes mellitus, he was under insulin treatment. His postoperative amilase, lipase values were normal. The postoperative glucagon value was 248 (normal range: 25–250 pg/ml).
Conclusion
Glucagonoma is a rare pancreatic neuroendocrine tumor. Most common presentation is the skin lesions. Our patient was diagnosed after investigation of biochemical abnormality. He presented atypically as he did not have most typical presentations like most patients in the literature.

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AEP857

SHBG as a Q1 marker of NAFLD and metabolic impairments in women referred for oligomenorrhea and/or hirsutism and in women with sexual dysfunction

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PCOS (Polycystic Ovary Syndrome) is one of the most common endocrine disorders and NAFLD (Nonalcoholic Fatty Liver Disease) is one of its most dangerous metabolic consequences. The diagnosis of NAFLD is not a practical task and the condition is at risk of being overlooked. The use of simpler but still reliable surrogate markers is necessary to identify women with a high likelihood of NAFLD. The aim of this study was to evaluate the clinical correlates of NAFLD Liver Fat Score (NAFLD-LFS) in women with oligomenorrhea and/or hirsutism. Furthermore, the study aimed to evaluate whether, among the hormonal parameters evaluated in such women, possible hallmarks of NAFLD may be identified. To this purpose, 66 women who attended our Outpatient Clinic for oligomenorrhea and/or hyperandrogenism were included in the study. In order to validate the results obtained in the first cohort, a second independent sample of 233 women evaluated for female sexual dysfunction (FSD) was analyzed. In cohort 1, NAFLD-LFS positively correlated with metabolic and inflammatory parameters. Among the hormone parameters, NAFLD-LFS showed no significant relationships with androgens but a significant negative correlation with SHBG (Sex Hormone Binding Globulin) ($P < 0.0001$) that therefore appeared as a candidate hallmark for pathologic NAFLD-LFS. The ROC analysis showed a significant accuracy (81.1%, C.I. 69.1–93.0, $P < 0.0001$) for SHBG in identifying women with a pathological NAFLD-LFS. In particular, a SHBG 33.4 nmol/l was recognized as the best threshold, with a sensitivity of 73.3% and a specificity of 70.7%. In order to validate this SHBG as a marker of metabolic impairment possible related with the presence of NAFLD, we tested this threshold in cohort 2. FSD women with SHBG <33.4 nmol/l had worse metabolic parameters than women with SHBG ≥33.4 nmol/l and a significantly higher NAFLD-LFS even after adjusting for confounders (B=4.18 [2.05; 6.31], $P = 0.001$). In conclusion, this study provides a new evidence in the diagnostic process of NAFLD, showing that the measurement of SHBG, which is routinely assessed in the workup of women referred for possible PCOS, could identify women at higher metabolic risk, thus detecting those who may deserve further targeted diagnostic assessment.

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AEP858

Abstract withdrawn

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AEP859

Infertility revealing a classical form of congenital adrenal hyperplasia in a 39 years old man

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Classical forms of congenital adrenal hyperplasia (CAH) are generally diagnosed in neonates (salt wasting form) or in early childhood (pure virilizing form). Here, we report the case of a 39 years old man from Sri Lanka in whom a classical CAH has been diagnosed during the exploration of infertility with azoospermia, along with extremely low gonadotropins contrasting with a normal level of testosterone. Hormonal tests revealed high serum 17-hydroxyprogesterone levels (255 ng/ml) and an extremely low level of cortisol with no response to the ACTH stimulation test and high levels of ACTH. The genetic study of CYP21A2 gene found 3 different mutations (c.1066C>T, c.166G>A, c.126C>T), 2 of which are associated with the classical form of 21 hydroxylase deficiency. The patient has never received glucocorticoids, and has never presented signs of adrenal insufficiency or adrenal crisis, suggesting the role of adrenal steroid precursors in the activation of glucocorticoid receptors.

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AEP860

Superoxide dismutase activity of testicular organs after intervention with fermented soy milk on hyperlipidemic rats

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Background
Oxidative stress in hyperlipidemic conditions can affect superoxide dismutase (SOD), a natural antioxidant in the body. One of the organs affected by increased oxidative stress due to hyperlipidemic conditions is the testicular organ. Increased oxidative stress in the testicular organ can damage to sperm cell and increase the risk of infertility. Soy milk is a beverage product made from soybeans which are widely consumed as an alternative to cow's milk. Fermented soy products can improve nutritional quality and have beneficial effects on health.
Aim
The aim of this study was to determine SOD inhibition rate in the testicular organs of hyperlipidemic rat after intervention with fermented soy milk.
Method
The subjects are three-month-old rats (*Rattus norvegicus*) male Wistar strain with body weight 200–300 grams divided into 3 groups (Negative Control (NC), Positive Control (PC), and Intervention group). PC and intervention group were given quail egg yolk for 2 weeks with a dose of 5 ml for hyperlipidemic induction while group of NC were only given fed ad libitum. After hyperlipidemic induction, the intervention group was given fermented soy milk (5 ml) from *Lactobacillus bulgaricus* and soybean. All rats then terminated to taken the testicular organ to measure the level of SOD inhibition rate. All data were statistically analyzed with One-Way ANOVA and Bonferroni Post-Hoc test. Values were considered significant at $P<0.05$.
Results
Mean of SOD inhibition rate (%) in rats was 82.03±1.62 in NC group, 17.97±2.06 in PC group, and 70.31±2.38 in intervention group. The One-Way ANOVA test showed significant differences activity between group with $P<0.001$ and the Bonferroni Post-Hoc test $P<0.001$.
Conclusion
Intervention with fermented soy milk can increase superoxide dismutase inhibition rate in the testicular organs of hyperlipidemic rats.
Keywords: fermentation food, hyperlipidemia, soy milk, superoxide dismutase, testicular organ.

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AEP861

Insight on the intracrinology of menopause: androgen production within the human vagina

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In this study, we investigated steroidogenic gene mRNA expression in human vagina and verified the ability of human vagina smooth muscle cells (hvSMCs) to synthesize androgens from upstream precursor dehydroepiandrosterone (DHEA). As a readout for androgen receptor (AR) activation, we evaluated the mRNA expression of various androgen-dependent markers. hvSMCs were isolated from vagina tissues of women undergoing surgery for benign gynecological diseases. In these cells, we evaluated mRNA expression of several steroidogenic enzymes and sex steroid receptors using realtime reverse transcription-polymerase chain reaction. Androgen production was quantified with liquid chromatography tandem-mass spectrometry (LC-MS/MS). In vaginal tissues, AR mRNA was significantly less expressed than estrogen receptor α, whereas in hvSMCs, its mRNA expression was higher than progestin and both estrogen receptors. In hvSMCs and in vaginal tissue, when compared to ovaries, the mRNA expression of proandrogenic steroidogenic enzymes (HSD3β1/β2, HSD17β3/β5), along with 5α-reductase isoforms and sulfotransferase, resulted as being more abundant. In addition, enzymes involved in androgen inactivation were less expressed than in the ovaries. The LC-MS/MS analysis revealed that, in hvSMCs, short-term DHEA supplementation increased Δ4-androstenedione levels in spent medium, while increasing testosterone and DHT secretion after longer incubation. Finally, androgenic signaling activation was evaluated through AR-dependent marker mRNA expression, after DHEA and T stimulation. This study confirmed that the human vagina is an androgen-target organ with the ability to synthesize androgens, thus providing support for the use of androgens for local symptoms of genitourinary syndrome in menopause.

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AEP862

Disorders of steroid metabolism in women of reproductive age with polycystic ovary syndrome

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Background of study
PCOS is a heterogeneous disease characterized by endocrine, metabolic and reproductive disorders. PCOS plays an essential role among the causes of chronic anovulation, menstrual irregularities, hirsutism and anovulatory infertility. Diagnostic problems appear to be extremely urgent due to the wide range of clinical and laboratory manifestations. The study of urine steroid profile by gas chromatography-mass spectrometry will improve the assessment of steroid metabolomics, and will allow for the increase in the percentage of PCOS detection, particularly at the early stages of the disease, to provide prompt treatment.
Aims of study
To study the metabolomics of androgens, progestinsand glucocorticoids by gas chromatography-mass spectrometry in obese and non-obese women with polycystic ovary syndrome
Study design, materials, and methods
53 women of reproductive age with PCOS were examined. The first group included 30 women aged 22 to 29 years with normal body weight. The second group comprised 23 obese patients aged 25 to 33 years with an average body mass index (BMI). Steroid urine profiles (SPM) were studied by means of gas chromatography-mass spectrometry (GC-MS) with optimization of the sample preparation schedule. 69 steroids were identify by this method.
Results
In women with PCOS and obesity, urinary excretion of androsterone and dehydroepiandrosterone metabolites (16-oxo-androstenediol and androstenediol-17β) was increased. In patients of normal body weight with PCOS an increase in urinary excretion of androstenedione metabolites, dehydroepiandrosterone and its metabolites, 17-hydroxypregnanolone and pregnanolone, 5-en-pregnenes was revealed. In addition, the reduction in the ratio of cortisoltetrahydro derivatives combined with cortisone to 11-oxo-pregnanthriol, pregnanthriol and 17-hydroxypregnanolone was detected, which is associated with21-hydroxylase enzyme and 3β-hydroxysteroid dehydrogenasedeficiency, which is indicative of hyperandrogenism mixed genesis. An increase in urinary excretion of 5α-tetrahydrocortisone and cortolones, the signs of decreased activity of 11β-hydroxysteroid dehydrogenase type 1 were found out in PCOS patients regardless of body mass index, which indicates functional hypercortisolism.
Conclusion
Determining simultaneously the number of androstenedione and DHEA metabolites, progestins, α- and β-glucocorticoid metabolites in the study of SPM by GC-MS method suggests new opportunities for the diagnosis and differential diagnosis of various presentations in PCOS.

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AEP863

Predictive factors of final height in children with congenital growth hormone deficiency in Tunisian children

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Introduction
Growth hormone deficiency (GHD) is a rare cause of statural retardation in children. The diagnosis is evoked in front of a bundle of anamnestic, clinical and radiological arguments. Treatment consists of substitution by recombinant GH with the aim of restoring normal size. There is interindividual variability in the response to treatment. We therefore proposed to study the response to treatment as well as the predictive factors of this response in the Tunisian population.
Methods
This is a retrospective study including 34 patients who were followed at the National Institute of Nutrition in Tunis for congenital GH deficiency and who completed their treatment.
Results
The assessment of statural response was based on total statural gain at the end of treatment and final height, thus investigating factors predictive of good response to treatment for each of these two parameters. The mean total statural gain was 31.62 ±19 cm with extremes ranging from 3 to 75 cm corresponding to a mean statural gain of 1.17 ±0.8DS. Age of discovery was negatively correlated with total statural gain (r = –0.64; P <0.001).Total statural gain was 28.6±19.6 cm for boys versus 36.66±19.96 cm for girls with no significant difference (P = 0.150). Height, BMI at baseline (P = 0.04; P <0.001 respectively) were correlated with total statural gain, and baseline IGF1 (SD) and thyroid insufficiency were correlated with statural gain (P = 0.025; P = 0.017 respectively). Bone age at baseline was negatively correlated with statural gain(cm)(r = –0.67, P <0.001). For the standard deviation (SD) assessment of statural gain, only general disease history was correlated with this parameter(P = 0.005). Final height was 158.3±7.09 cm in boys and 144.79±14 cm in girls with a significant difference (P = 0.001). The parameters correlated to the final height were: general disease history(P = 0.002), combined deficit (0.015), existence of corticotropic insufficiency(P = 0.027), thyroid insufficiency (P = 0.048), number of deficits greater than 1(P = 0.027) and pathological aspect on hypothalamic-pituitary MRI (P = 0.01).
Discussion/Conclusion
The response to treatment in our population was close to the results of the literature series. Factors predictive of a good response to treatment vary from one individual to another and from one population to another. These factors can be integrated into a true predictive model allowing for an adaptation of treatment.

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AEP864

Are there a gender difference in growth hormone (GH)-deficiency in Tunisian Children?

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Introduction
Congenital GH deficiency is more common in boys than in girls. Several differences have been noted between the 2 genders. We proposed to study these differences for epidemiological, auxological and anthropometric characteristics.
Methods
This is a retrospective study including 75 patients followed for congenital GH deficiency in the endocrinology department at the National Institute of Nutrition in Tunis.
Results
In our population, 46 patients (63%) were male. The average age of discovery was 112 ± 54 months or 9 ± 4.5 years for males and 93 ± 45 months or 7 ± 3 years for females (P = 0.137). The delay of diagnosis was on average 32 ± 32 months for males and 12 ± 19 months for females but without significant difference (P = 0.243). The mean target height of our patients was 165.45 ± 9.89 cm, 170.6±5.07 cm for boys and 156.09±9.78 cm for girls (P <0.0001). The mean weight at diagnosis was 19.72 kg ± 8.38 with a mean height of 114.56 ± 20.09 cm. The most frequent initial height in girls (41%) was less than - 4 DS versus (30%) in boys for a height between –2 and –3 DS. Initial height in DS was on average –2.33 ±1.2 DS for girls and –2.58 ±0.5 DS for boys with a significant difference (P = 0.043). The mean weight at diagnosis was 19.72 ± 8.38 kg. Underweight less than –2SD was noted in 20% of cases. There was no significant difference between the two sexes for BMI in SD (P = 0.168).
Discussion/Conclusion
This difference between the 2 genders has also been found in the literature. This is interesting to know especially for a better knowledge of the characteristics of these children which leads to a better management.

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AEP865

Steroid Cell Tumor of the Ovary - A case presenting with hirsutismus

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Introduction
Steroid cell tumors (SCTs) are a rare subgroup of sex-cord tumors of the ovary that account for less than 0.1% of all ovarian tumors. They are classified into three categories based on the cell origin: stromal luteoma, Leydig-cell tumor, and not otherwise specified (NOS). NOS tumors are the most common subtype and comprise the largest proportion of cases (60%).The clinical presentations are not specific, including abdominal pain, distention and bloating. However, the more significant presentations are those associated with the hormonal activity and virilizing properties of the tumor. The cornerstone of SCT-NOS treatment is surgery.
Case
A 55-year-old female came to our hospital in November 2020 with months' history of increasing facial and truncal hair. She also had hypertension and diabetes mellitus. In the medical history of the patient, she had been operated for papillary thyroid cancer, sleeve gastrectomy, total abdominal hysterectomy and left salpingo-oophorectomy 30 years ago. Physical examination revealed obesity (body mass index, 37.3 kg/m^2).She had a Ferriman–Gallwey score of 24. Abdominal ultrasound identified a 40 × 20 mm solid, right ovarian mass.Biochemical data shows the levels of folicle stimulating hormone and luteinising hormone were as high as 52.1 U/l and 33.3 U/l, respectively. Serum adrenocorticotropic hormone, cortisol, estradiol, serum prolactin, dihydroepiandosterone sulfate were found within reference intervals.Total and free serum testosterone levels were found to be as high as 450 ng/dl (normal 7–49 ng/dl) and 19.99 (normal<4.2 pg/ml), respectively. Magnetic resonance imaging with contrast confirmed the ultrasound findings and detected no adrenal gland enlargement or tumor.The right salpingo-oophorectomy was done, and the specimen was sent to our department for histopathological examination. On surgical staging laparotomy, it was found that there was an enlarged (3×3×2 cm) right ovary with both solid and cystic component and normal ovarian contour.Microscopically, mitotic activity 2–3/10, mild atypia, and no significant necrosis. Immunohistochemistry revealed a result of MelanA(+), ER (+), CD56(+), Calretinin (+), Inhibin-α (+), ki-67 (5–6%+). Histological features were consistent with SCTs-NOS type.At post-operative follow-up, her total serum testosterone and serum free testosterone level had gone down to 13 ng/dl and 0.73 pg/ml, respectively.
Conclusion
SCTs, NOS, are rare ovarian tumors which can be difficult to diagnose. Careful history and physical examination, in addition to laboratory values and imaging studies, are helpful in making the diagnosis.They are usually benign, unilateral and are characterized by hyperandrogenism and virilization. SCTs should be considered in differential diagnosis among women presenting with symptoms of virilization.

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AEP866

Effectiveness of iodine supplementation during pregnancy in western Poland – a single center study

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Introduction
Twenty-four years after implementing the national salt iodization programme in Poland in 1997, the country is considered as adequate iodine supply. However, most reports do not take into consideration pregnant or lactating females. Additional intake of 150–200 µg KI per day, independently on levothyroxine (LT4) treatment, is a recommended dose for pregnancy and lactation due to Polish endocrinological guidelines. The study aim was to evaluate iodine supply in the group of pregnancies and relate the results to maternal thyroid parameters.
Material & methods
95 mother-child pairs (healthy, hypothyroid and euthyroid with autoimmune thyroiditis with or without LT4 treatment) were recruited at planned admission to the obstetric ward of tertiary reference gynaecological hospital. The venous blood serum was obtained from mothers before delivery, where thyrotropin (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) and antibodies against thyroid peroxidase (a-TPO) and thyroglobulin (a-Tg) were measured by ECLIA. A single random urine sample was obtained from mothers to measure ioduria (UIC) by a validated ion-pair HPLC-UV method. Additionally, urine creatinine was measured by ELISA and iodine/creatinine ratio (UIC/Cr) was calculated.
Results
71% declared iodine supplementation intake in dose 150–200 mg/daily. The median UIC was 105 µg/l (Q25-Q75, 69–171). According to WHO 68% were iodine-deficient < 150 µg/l (including 10% with deficits < 50 µg/l), 22% were adequately supplied (150–249 µg/l), 9% had more than adequate supplies (250–499 µg/l) and 1 patient had excessive supply (> 500 µg/l) on concomitant high-dose LT4 treatment. The median UIC/Cr ratio was borderline adequate 151 µg/g (Q25-Q75, 64–282), but the higher percentage of patients (41%) had results < 100 g/l and 25% between 100 and 200 g/l. Additionally, in the group not-treated with LT4, women who supplemented iodine had higher fT3 (4.3 vs 3.7, $P = 0.03$) pmol/l.
Conclusions
Despite recommendations one-third of recruited women did not supplement iodine during pregnancy. Most females were iodine-deficient independently from iodine supplementation. Iodine intake may improve maternal thyroid function. During the construction of future guidelines, an increase of the recommended dose of iodine supplementation in pregnancy should be considered, taking into consideration concomitant LT4 treatment.

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AEP867

17-β Hydroxysteroid Dehydrogenase Type 3 Deficiency with Novel Mutation in Iranian Family

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Introduction
Deficiency of 17- beta hydroxysteroid dehydrogenase 3 (17-HSD 3) is a rare autosomal recessive disorder which causes sexual ambiguity in fetuses with 46XY karyotype. Pathogenic mutations in the 17βHSD-3 gene (MIM# 264300) are associated with impaired sexual development of the 46, XY fetus. Here, we describe the clinical and genetic findings of a large family with several 46xy cases with a new mutation in 17-β-HSD3 gene in Qazvtn,Iran.
Case reports
Proposita was a 11-year-old girl who was referred for examination due to the infertility of her aunts. The external genitalia were completely female and had a short vaginal pouch. The testicles were not found on examination. She had palpable gonads in her inguinal area and at the age of two underwent bilateral orchiectomy. Other physical examinations were normal. In pelvic sonography, uterine and ovarian were not seen. Her peripheral blood karyotype was 46xy. Three of the patient's aunts and the patient's mother's aunt also had had similar findings (Fig.1)

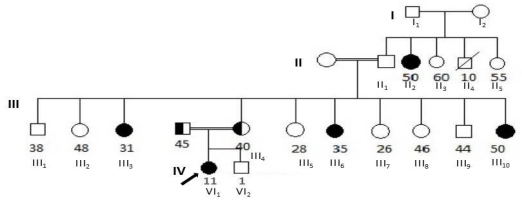

Figure 1: Pedigree

Method and Material
To determine the molecular etiology, whole-exome sequencing (WES) was performed.
Results
We identified a novel homozygous missense variation (c.731T>A, p. Ile244Lys) in HSD17B3 gene. This alteration changes Isoleucine to Lysine in exon 10. This variation – which has not been reported before – is predicted to be a variant of unknown significance (VUS) based on computational analysis.
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AEP868

Case report of complete androgen insensibility syndrome in an adult female

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Introduction
Complete androgen insensibility syndrome (CAIS) is an androgen receptor defect disorder associated with vaginal and uterine agenesis in women with a 46,XY karyotype. The syndrome affects sexual development before birth and during puberty. The major clinical issues surrounding this syndrome include timing of gonadectomy, hormone replacement, vaginal dilation, and attention to psychological issues.
Case presentation
A 25-year-old woman presented in February 2021 in the Endocrinology Clinic with primary amenorrhea. She had no significant past medical history or family history. Clinical evaluation found absent axillary hair and pubic hair, normal external genital organs and normal development of breasts. Biochemical and hormonal evaluation found normal levels of potassium and sodium and the hormonal evaluation found an elevated testosterone of 679.68 ng/dl (15 to 70 ng/dl), estradiol 32 pg/ml (45.4–854), progesterone 0.42 ng/ml (0.18 – 2.84), LH 9.9 mUI/ml (1–11), FSH 0.27 mUi/ml (1.7–7.7), prolactin 7.8 ng/ml (4.7–23.3), normal thyroid and cortisol function. Gynecological examination and ultrasound were performed identifying normal external genitalia and normal length but blind-ended vagina, absence of uterus and suggestion of the presence of gonads located in the pelvis of 21/15 mm. A pelvic magnetic resonance imaging (MRI) exam was performed to plan a laparoscopic gonadectomy and showed two soft tissue structures suggestive for gonadal tissue located in the right along the external iliac artery and along the left external iliac artery. A pericentimetric cyst was found adjacent to each gonad. Apart from the vagina, no development of Müllerian duct structures was observed. Surgery was planned for removal of gonadal tissue, as this condition is associated with an increased risk of testicular germ cell tumor. A complete psychological evaluation was performed before surgery. Hormonal treatment by progesterone will be introduced after surgery.
Conclusion
Complete androgen insensitivity syndrome is a rare genetic disease. Patients with complete AIS should undergo post pubertal gonadectomy and lifelong hormone replacement therapy is advised. Attention to psychological considerations in such patients is important to maximize long-term success.

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AEP869

Frequency of euthyroid sick syndrome before and after renal transplantation in patients with end stage renal disease and its association with oxidative stress

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Aim
Euthyroid Sick Syndrome (ESS) is a thyroid disease appeared in critical and noncritical illnesses. ESS can be seen in patients with end stage renal disease (ESRD). In this study, we aimed to evaluate the frequency of ESS before and after renal transplantation in patients with ESRD, and its association with oxidative stress by evaluating thiol-disulphide levels.
Material and Method
In this study, free triiodothyronine (fT3), free thyroxine (fT4) and thyroid stimulating hormone (TSH) levels were recorded before and after renal transplantation in patients with ESRD. ESS was diagnosed in patients with unresponsive TSH to low fT3 and/ or fT4 levels, Thiol and disulphide parameters of patients before and after transplantation were also recorded.
Results
One- hundred twenty one patients were included in the study. Of these, 69 (57%) were males and 52 (43%) were females. The mean age was 45±12.61 years. ESS was detected in 39 (32%) of 121 patients. Of 39 patients, 24 (61%) had ESS before transplantation and 15 (39%) after transplantation. Frequency of ESS was 19.8% in patients followed with ESRD. Sixteen of 24 (66.7%) patients with ESS before transplantation reached to normal thyroid functions after transplantation. After transplantation, patients with ESS had significantly higher urea and creatinine (respectively, P = 0.025 and P = 0.009), and lower fT4, fT3, total protein, and albumin (P = <0.001; for all parameters) compared to patients without ESS. Patients with ESS before transplantation had also significantly higher creatinine levels compared to patients without ESS (P = 0.034). Free T4 and fT3 levels were significantly low (P <0.001 for both). Thiol- disulphide levels of 20 patients with ESS at any time compared with 68 patients without ESS. We found that native thiol and total thiol were low significantly in patients with ESS (respectively, P = 0.025 and P = 0.044).
Conclusion
Our study is the initial study evaluating the oxidative stress and antioxidation status in etiology of ESS in patients with renal transplantation. Presence of markedly low level of antioxidation in these patients supports the possible role of oxidative stress in etiology of ESS.

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AEP870

Comparative analysis of five different ultrasonographical risk-stratification systems in the preoperative diagnosis of malignant and benign thyroid nodules

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Background
Our aim was to compare the effectiveness of five different risk-stratification systems using the ultrasonographical features of thyroid nodules in determining malignant histopathology.
Methods
The preoperative ultrasonography (US) features of 6925 nodules of 3030 patients who underwent thyroidectomy between 2007 and 2014 were analyzed retrospectively. The nodules were classified according to Kwak-TIRADS (Thyroid imaging reporting and data system), European Thyroid Association-TIRADS (EU-TIRADS), Korea-TIRADS, American Society of Clinical Endocrinologists (AACE), American Thyroid Association (ATA).1362 nodules (1042 patients) that could be scored in all of these systems were included. Malignancy rate, specificity, sensitivity, positive predictive value (PPV) and negative predictive value were calculated.
Results
In the nodules with high risk scored,malignant histopathology rate were 50%, 27.7%, 32.2%, 29.9%, 31.9% in Kwak-TIRADS, EU_TIRADS, Kore-TIRADS, AACE, ATA, respectively (Table 1). Area under curve (AUC) was higher than 0.5 for all systems (P <0.001,Table 2). When determining optimal cut-off for each system, sensitivity, specificity, PPV, and NPV were about 60%, 75%, 27–30% and 92%, respectively (Table 2). EU-TIRADS had significantly lower AUC (corrected P<0.05). AUC of Korea-TIRADS was lower than that of ATA (corrected-P<0.001). AUCs of Kwak-TIRADS, AACE, and ATA were similar and significantly higher than the others (Table 2).
Conclusion
Risk-stratification systems have variable efficiency in predicting malignancy risk since they are operator dependent and require experience in that field. The sensitivity was found to be lower than the previous studies which might be due to retrospective evaluation of US reports rather than real time risk scoring.

Table-1.Distribution of benign and malignant nodules according to risk-stratification systems

	Benign (n = 1179) n (%[1]/%[2])	Malignant (n = 183) n (%[1]/%[2])
Kwak-TIRADS		
Possibly benign	137 (97.9/11.6)	3 (2.1/1.6)
Low	774 (91.8/65.7)	69 (8.2/37.7)
Intermediate	61 (82.4/5.2)	13 (17.6/7.1)
Moderate	195 (69.4/16.5)	86 (30.6/47.0)
High	12 (50.0/1.0)	12 (50.0/6.6)
EU-TIRADS		
Benign	97 (95.1/8.2)	5 (4.9/2.7)
Low	729 (91.8/61.9)	65 (8.2/35.5)
Intermediate	58 (100.0/4.9)	0 (0.0/0.0)
High	295 (72.3/25.0)	113 (27.7/61.8)
Kore-TIRADS		
Benign	129 (94.9/10.9)	7 (5.1/3.8)
Low	787 (92.4/66.8)	65 (7.6/35.5)
Intermediate	57 (81.4/4.8)	13 (18.6/7.1)
High	206 (67.8/17.5)	98 (32.2/53.6)
AACE		
Low	187 (96.4/15.9)	7 (3.6/3.8)
Intermediate	729 (91.9/61.8)	64 (8.1/35.0)
High	263 (70.1/22.3)	112 (29.9/61.2)
ATA		
Bening	129 (94.9/10.9)	7 (5.1/3.8)
Very low	58 (100.0/4.9)	0 (0.0/0.0)
Low	729 (91.8/61.9)	65 (8.2/35.5)
Intermediate	54 (80.6/4.6)	13 (19.4/7.1)
High	209 (68.1/17.7)	98 (31.9/53.6)

[1]Row percentage;
[2]Column percentage.

Table-2. ROC curve analysis results

	Cut-off	Specificity	Sensitivity	PPV	NPV	AUC	95% CI
Kwak-TIRADS	intermadiate	60.7%	77.3%	29.3%	92.7	0.717	0.680–0.754
EU-TIRADS	high	61.7%	75.0%	27.7%	92.7	0.680	0.641–0.719
Kore-TIRADS	intermadiate	60.7%	77.7%	29.7%	92.7	0.705	0.666–0.744
AACE	high	61.2%	77.7%	29.9%	92.8	0.710	0.674–0.747
ATA	intermadiate	60.7%	77.7%	29.7%	92.7	0.713	0.675–0.751

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AEP871

Relapsed Differentiated Thyroid Cancer, clinical presentation, treatment, and prognostic factors (ERUDIT Study)

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Advanced differentiated thyroid carcinoma (aDTC), herein defined as locally unresectable and/or metastatic, is one of the most common late-stage endocrine neoplasias. However, available data about its natural history are limited. ERUDIT is a multicenter, observational, retrospective study of patients diagnosed with aDTC in Spain and Portugal. The study describes its natural history from the initial diagnosis until the advanced stages, focusing on specific characteristics of this subpopulation, its treatment, response patterns, and medical specialties involved in its management. The objective of this communication is to describe the diagnostic demographics and clinical characteristics of relapsing DTC patients, the efficacy of rescue therapies used, and the prognostic factors associated to disease evolution. Clinical records from patients ≥18 y-o diagnosed with aDTC (including poorly differentiated DTC) with first evidence of advanced disease documented between January 2007 and August 2017, were retrospectively reviewed until death or lost to follow-up. 213 aDTC patients were identified in 23 sites with median age at initial DTC diagnosis 63 y-o and 59% being females. Of these, 46% progressed or relapsed to aDTC (87% metastatic, being lung in 41% of cases) after receiving initial treatment (surgery ± 131radioiodine [RAI]) for their early DTC (eDTC). Median (95% CI) relapse/progression-free survival [(RP)FS] and overall survival (OS) from the initial treatment were 2.3 (1.8–2.9) years and 10.4 (8.1–16.0) years, respectively. Notably, significant OS differences (log-rank P<0.0001) were seen according to surgical outcome, favouring R0/R1 resections compared to R2. Post-relapse rescue therapies, when indicated, were mainly RAI (57%) and surgery (13%). Specifically, 23% of the patients treated with RAI received up to 3 courses with median dose of 150 mCi each and cumulative dose of 620mCi. Persistent structural disease was frequently reported after RAI (average 15% after three doses). Initial R2 surgical outcome, receiving <600 mCi, not receiving any RAI or requiring stimulation with hrTSH, and resulting in incomplete biochemical/structural response to it, were all negative prognostic factors for eDTC to relapse to aDTC. Endocrinology was the leading medical specialty responsible for patient monitoring (63%), while two thirds of the patients were evaluated by multidisciplinary committees. Almost half of this cohort become aDTC tumours after relapsing from previously treated eDTC with median [(RP)FS] of 2.3 years while 57% being still RAI-treatable. From this group, yet 15% showed persistent disease after three RAI doses among other poor prognostic factors. This suggests identifying early unfavorable course in some DTC patients is maybe possible from initial stages.

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AEP872

A rare cause of malignant pleural effusion: Poorly differentiated thyroid carcinoma

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Purpose
Poorly differentiated thyroid carcinoma (PDTC); is a rare type of thyroid cancer with a high risk of recurrence, metastasis, and death. Pleural effusion due to thyroid cancer has seldom been reported. In this report, we present a case with PDTC related malignant pleural effusion.
Case
A 66-year-old male patient presented with neck swelling and shortness of breath. At another center, thyroid ultrasonography revealed a multinodular goiter and an irregularly circumscribed lymphadenopathy on the left level IV. He had multiple lung metastases in thorax computed tomography (CT). Positron emission tomography/computed tomography (PET-CT) detected "hypermetabolism in malignant nodules in the thyroid, multiple metastatic lymph nodes in the neck and bilateral metastatic lung nodules." Cytology of lymph nodes at the right level 3,4,6–2a junction was malignant. The patient underwent bilateral total thyroidectomy, bilateral central lymph node dissection, and right modified radical neck dissection with a final pathologic diagnosis of "poorly differentiated thyroid carcinoma, right lateral and central tumor positive lymph node." Upon persistence of dyspnea, thoracentesis was performed for a left-sided pleural effusion, which in the end had exudative characteristics. [blood thyroglobulin (Tg): 23960 ng/ml, Tg with pleural fluid dilution > 30000 ng/ml]. Cytology confirmed carcinoma infiltration. In the follow-up, mediastinal, lung, and pleural metastases in addition to effusion in the left hemithorax persisted. We performed pleurodesis after the initial tube thoracostomy. During follow-up pleural fluid cell-block was performed due to continued pleural effusion and reported as carcinoma metastasis. 200 mCi RAI treatment was given after preparation with recombinant thyroid stimulating hormone (TSH). After the comparative PET-CT revealed progression, transthoracic lung biopsy performed and reported as carcinoma metastasis. After these results tyrosine kinase inhibitör (sorafenib) was initiated to the patient.
Conclusion
The most common sites of distant metastasis of PDTC are the lungs and bones. It constitutes about 85% of deaths related to the disease. Less than 1% of malignant pleural effusions are associated with thyroid cancers. Pleural fluid thyroglobulin level and immunohistochemical staining may enhance the diagnostic process.

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AEP873

Changes in thyroid hormones and free triiodothyronine-to-free thyroxine ratio in euthyroid patients with obesity in terms of different glucose metabolism statuses

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Purpose
Thyroid hormones are known to have an essential role in the regulation of energy homeostasis and glucose metabolism. Considering to literature data, variations of thyroid hormones within normal ranges change in obesity and type 2 diabetes mellitus (T2DM) in opposite ways. This study aims to evaluate thyroid hormone levels and fT3/fT4 ratio in different glucose metabolism statuses of euthyroid patients with obesity.
Methods
This retrospective observational study evaluated thyroid hormones and fT3/fT4 ratio of 209 patients with obesity grouped according to their glucose metabolism status.
Results
131 (62.7%), 41 (19.6%), and 37 (17.7%) patients had normal glucose tolerance (NGT), prediabetes, and T2DM, respectively. Serum fT4 level was higher in patients with T2DM compared to patients with NGT (P =0.009), although no difference was observed in TSH and fT3 levels among groups. Baseline characteristics, laboratory test results, and thyroid hormone levels of the subjects are presented in Table 1. FT3/fT4 ratio was determined to be lower in patients with T2DM than patients with NGT (P = 0.012). HbA1c was independently and positively associated with fT4 (β= 0.345, r^2=0.119, P = 0.003) and negatively associated with fT3/fT4 ratio (β= –0.371, r^2=0.138, P = 0.001).
Discussion
Serum fT4 level increased and fT3/fT4 ratio decreased in patients with T2DM independently of obesity. The interaction of T2DM with thyroid hormones may overcome obesity-related changes in thyroid functions in our cohort.

Table 1. Baseline characteristics, laboratory parameters, and thyroid hormones of the subjects

	Patients with NGT (n = 131)	Patients with prediabetes (n = 41)	Patients with DM (n = 37)	P value NGT vs DM	P value NGT vs prediabetes	P value Prediabetes vs DM
Age, years	34 (27–44)	39 (31–46)	48 (38–53)	<0.001	0.045*	0.005
Gender, female, n (%)	105 (80.2)	26 (63.4)	26 (70.3)	0.202	0.029*	0.524
BMI, kg/m²	40 (34–44)	40.4 (33–47)	41.2 (32–49)	0.869	0.676	0.886
FPG, mg/dl	89 (79–95)	104 (98–112)	136 (120–148)	<0.001	<0.001	<0.001
HbA1c,%	5.6 (5.4–5.6)	6.2 (6–6.3)	7.3 (6.8–8.2)	<0.001	<0.001	<0.001
TSH, mIU/l (RR: 0.38–5.33)	2 (1.3–3.1)	2.2 (1.2–3.4)	1.75 (1.3–2.9)	0.398	0.826	0.722
FT4, ng/dl (RR: 0.58–1.6)	0.87 (0.81–0.97)	0.86 (0.81–0.96)	0.94 (0.89–1.1)	0.009	0.769	0.018*
FT3, ng/dl (RR: 2.66–4.37)	3.5 (3.1–3.9)	3.4 (3.2–3.6)	3.4 (3–3.7)	0.054	0.446	0.344
FT3/fT4 ratio	4 (3.5–4.4)	4 (3.4–4.5)	3.6 (2.9–4.3)	0.012	0.967	0.028*

Categorical data were demonstrated with numbers and percentages (%). Other variables were presented as medians (interquartile ranges 25–75).
NGT normal glucose tolerance, DM diabetes mellitus, BMI body mass index, FPG fasting plasma glucose, TSH thyroid-stimulating hormone, fT4 free thyroxine, fT3 free triiodothyronine.
* The P value did not maintain significantly after adjusting according to Bonferroni correction.

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AEP874

Nodular goiter (NOD) observed pre- and post-nuclear powerplant accident (NPP) – Experience in a single institution close to the NPP site

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Background
An increase of pediatric thyroid cancer has been reported in Fukushima area. While there is no adult survey to date except NPP workers. Our institute is located 40 km from the NPP and has been playing a major medical role in this area (population 340,000). We analyzed patients with NOD whether there is any difference in cytological findings between pre- and post-NPP accident. Patients and methods:1,065 new patients (2005–2020) with NOD were examined; pre(A), 780 patients (46%) and post (B), 907patients. Cytological diagnosis was made 1,802 times. Ultra-sonogram (US) and hormonal assay were performed in each patient. Follow-up study was performed in 316 patients (28%).
Results
1) Yearly assay number: 318 FNAB was performed between 2007 and 2008 (a peak) then decreased to 154 between 2015 to 2016 (4 years after NPP accident, lowest). 2) Age: Period A, 59±15 years; B, 61±14 (P <0.004). 3) Gender: Proportion of female, A, 637 (82%) B, 739 (82) (NS). 4) Level of serum thyroglobulin (Tg): A, 708±3,109 (median 98) ng/ml, B, 400±1.178 (median 95) (P<0.01). 3. Size (diameter): A, 25±73mm (median 20). B, 23±13.3 mm (median 21) (NS). 5) Tg/size: A, 21.4±68 (Med 5.2) B, 15.6±40,2 (Med 4.8). (NS). 6) Cytological classification: Class 2, A, 454 (46%), B, 544 (55%); class 3, A, 27 (42%), B, 38 (59%); class 4, A 5 (42%), B, 7 (58%); class 5, A, 46 (70%), B, 20 (30%) (Kai2< 0.004). 7) Cytological diagnosis: Papillary carcinoma, A, 45 (65%), B, 24 (35%); Cellular atypia, A, 15 (32%), B, 32 (68%); Follicular neoplasm, A, 23 (49%), B, 34 (60%); Adenomatous goiter (AG), A, 152 (37%), B, 271 (63%); Benign goiter A, 197 (50%), B, 106 (50%); Cyst, A, 166 (57%), B, 124 (43%); Chronic thyroiditis, A, 46 (63%), B, 27 (37%) (Kai2, P <0.0001).
Discussion
There was no increase of NOD patients nor carcinoma diagnosis after NPP accident. Although AG was more frequently diagnosed in period B, the increase started early years of period A. Tg level decreased in period B corresponding to lesser size, possibly due to early detection by widespread US.
Conclusion
There was no apparent effect of NPP accident in adult NOD around our institution.

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AEP875

Management of thyrotoxicosis induced by PD1 or PD-L1 blockade

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Background
Thyrotoxicosis is a common immune-related adverse event in patients treated with PD1 or PD-L1 blockade. A detailed endocrinological assessment, including thyroid ultrasound and scintigraphy is missing, as are data on response to treatment and follow-up. Aim of the study was to better characterize the thyrotoxicosis secondary to immune checkpoint inhibitors, gaining insights into pathogenesis and informing management.
Methods
We conducted a retrospective study of 20 consecutive patients who had normal thyroid function before starting immunotherapy and then experienced thyrotoxicosis upon PD1 or PD-L1 blockade. Clinical assessment was combined with thyroid ultrasound, scintigraphy, and longitudinal thyroid function tests.
Results
Five patients had normal scintigraphic uptake (Sci+), no serum antibodies against the TSH receptor, and remained hyperthyroid throughout follow-up. The other 15 patients had no scintigraphic uptake (Sci-) and experienced destructive thyrotoxicosis followed by hypothyroidism (n=9) or euthyroidism (n =6). Hypothyroidism was more readily seen in those with normal thyroid volume than in those with goiter (P = 0.04). Among Sci- subjects, a larger thyroid volume was associated to a longer time to remission (P <0.05). Methimazole (MMI) was effective only in Sci+ subjects (P<0.05).
Conclusion
Administration of PD1 or PD-L1 blocking antibodies may induce two different forms of thyrotoxicosis that appear similar in clinical severity at onset: a type 1 characterized by persistent hyperthyroidism that requires treatment with MMI, and a type 2 characterized by destructive and transient thyrotoxicosis that evolves to hypo- or euthyroidism. Thyroid scintigraphy and ultrasound help differentiating and managing these two forms of iatrogenic thyrotoxicosis.

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AEP876

Influence of bitter taste gene TAS2R38 on endocrinometabolic and anthropometric parameters in a sample with thyroid disease

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Background and objectives
TAS2R38 is a bitter taste gene that can influence food consumption depending on its single nucleotide polymorphisms (SNPs) leading to aminoacid substitutions in the receptor protein P49A (proline/alanine), A262V (alanine/valine) e V296I (valine/isoleucine). Subjects with at least one PAV (proline-alanine-valine) copy are bitter tasters, while AVI homozygotes are non-tasters. Other variants have intermediate bitter tasting: AAV<AAI<PAI. TAS2R38 is expressed in thyroid and other organs. This study evaluates TAS2R38 gene polymorphisms influence in thyroid function, metabolism and body composition.
Methods
DNA of 167 individuals (79% female) 24.6% eutrophic, 43.7% overweight and 31.7% obese was genotyped by *endpoint analysis*. From these, 79 had thyroid functional disease (hypothyroidism n = 41) compared with 88 controls. Anthropometric parameters BMI (kg/m^2), fat mass (%), total fat mass (kg), total lean mass (kg) determined by DEXA; metabolic/hormonal parameters by standard methods: triglyceridaemia (mg/dl), HDL (mg/dl), LDL (mg/dl), glycaemia (mg/dl), TSH (mcUI/ml), T3 (ng/dl), T4 (ng/dl), FT4 (ng/dl). Leptin (ng/ml) by ELISA. Statistics: ñ and ANOVA, significance for P <0.05.
Results
There were differences (p<0.001) in the distribution of diplotypes between subgroups being respectively for hypothyroidism-hyperthyroidism-controls (%): PVV/AVI (65.4; 64.3; 0); AVV/AVV (19.2; 10.7; 0); PVI/PVI (7.7; 7.1; 31.6); PVV/AVV (3.8; 7.1; 0); AAV/AAV (3.8; 0; 15.8); PVV/AAI (0; 0; 46.1); PVV/PAI (0; 0; 5.3); AVV/AVI (0; 3.6; 0); PAV/AAV (0; 0; 1.3); PVV/PV (0; 7.1;0). Diplotypes were associated with fat mass (P = 0.025); leptin (P = 0.019) and triglyceridaemia (P = 0.048). For PVV/AVI and PVV/AAI diplotypes, average values were respectively: fat mass 37.45±6.67 and 34.45±7; leptin: 56.80±37.32 and 50.85±54.16; triglyceridaemia: 99.64±49.76 and 94.52±55.97. Significant association between the SNP A262V and hyper/hypothyroidism (P <0.001); total lean mass (P = 0.012) and fat mass (P = 0.03), triglyceridaemia (P = 0.05) and TSH (P = 0.025). The SNP V296I was associated with total lean mass (P = 0.014). Metabolic and anthropometric variables associated with hyper/hypothyroidism: total fat mass (P = 0.02); BMI (P = 0.002), glycaemia (P = 0.035), triglyceridaemia (P = 0.05), TSH (P = 0.008), FT4 (P = 0.027). No significant differences for other parameters.
Conclusions
The distribution of TAS2R38 diplotypes differed between the control and hyperthyroidism or hypothyroidism samples. The haplotype AVI (SNP A262V) associated with metabolic and body composition parameters and with less bitter sensitivity may be a clue for dysfunctional thyroid. This could be due to exogenous factors such as higher ingestion of bitter goitrogenic compounds inducing hypothyroidism or, on the other hand, predisposition to hyperthyroidism via higher resistance to antithyroid effects of unknown endogenous factors in individuals with the AVI variant. In conclusion, TAS2R38 gene influences thyroid function witch modulates metabolism and body composition.

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AEP877

Papillary thyroid microcarcinomas that metastasize to lymph nodes

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Background
We aimed to determine clinicopathological features that can predict lymph node metastasis (LNM) in papillary thyroid microcarcinomas (PTMC).
Methods
Medical records of 872 patients with papillary thyroid cancer >1 cm (PTC >1 cm) and 1184 patients with papillary thyroid microcancer (PTMC) (£1 cm) were reviewed retrospectively. Demographical, clinical and histopathological features of (PTC >1 cm) and PTMC were compared. Association between clinicopathological features and LNM in PTMC was investigated.
Results
The median age of patients with PTMC was significantly higher than patients with PTC>1 cm (49 vs 46 years old, P <0.001). Multifocality, capsular invasion, vascular invasion, extrathyroidal extension (ETE) and LNM were more frequent in patients with PTC>1cm compared to patients with PMTC (P <0.001 for each). In PTMC group, those with LNM had significantly higher proportion of multifocality, capsular invasion, vascular invasion and ETE compared to those without LNM (P = 0.007, <0.001, P = 0.011 and P <0.001, respectively). Multifocality and ETE were significant factors for LNM with logistic regression analysis. Multifocality increased the risk of LNM by 1.737 times (95% CI: 1.079–2.979) and ETE increased the risk by 3.528 times (95%: 1.914–6.503). Primary tumor diameter □5.75 mm was predictive for LNM with a sensitivity of 0.782 and a specificity of 0.517 in PTMC.
Conclusion
LNM should be investigated more carefully in patients with PTMC in the presence of tumor diameter□5.75 mm, multifocality or ETE.

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AEP878

Serum endocan level and its correlation with clinicopathologic features in patients with Papillary Thyroid Cancer

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Background
Papillary thyroid cancer (PTC), has a slow progression and good prognosis and is often treatable, but may show recurrence and metastasis. Age, sex, histopathologic variants of PTC, lymphatic or vascular invasion, lymph node involvement are among the factors affecting the occurrence of metastasis. Endocan is produced in vascular endothelial cells, epithelial cells lining the distal tubules of the kidney, submucosal glands of bronchus and lungs. In recent studies, the role of endocan in many cancers has been identified. Serum endocan levels can be used in the early diagnosis of cancers because of the aforementioned characteristics. In addition, many studies have suggested that it can be a molecule of prognostic importance in various cancers. The aim of this study was to compare preoperative serum endocan levels of patients diagnosed with PTC by thyroid FNAB and endocan levels of patients with no malignancy after thyroid FNAB.
Materials and Methods
This study included 48 patients with PTC who underwent total thyroidectomy and 40 age- and sex-matched healthy controls between November 2018 and May 2019. Serum samples were obtained from the patients before surgery. Serum endocan levels of the patients and controls were measured and the results were compared. The relationship between endocan levels and clinicopathological factors was investigated
Results
PTC patients had higher mean serum endocan level than control subjects (45.1 ± 9.6 vs 37.7 ± 8.3 pg/ml, P < 0.001) (Table 1). In PTC patients, there was no relationship between serum endocan levels and histopathologic variant, lymphatic or vascular invasion, surrounding thyroid tissue invasion, lymph node metastasis, surgical margin status, TNM stage and ATA risk stratification group, age and tumor size.
Conclusions
PTC patients had higher mean serum endocan level than control subjects. In PTC patients, there was no relationship between serum endocan levels and

histopathologic variant, lymphatic or vascular invasion, surrounding thyroid tissue invasion, lymph node metastasis, surgical margin status, TNM stage and ATA risk stratification group, age and tumor size. This study suggests that serum endocan level can be used as an adjunct test in the diagnosis of PTC in patients with thyroid nodules.

Table 1. Comparison of demographic and laboratory findings of patients and controls

Parameter	Patient group	Control group	*P*
Gender (M / F)	38/10	36/4	0.167
Age	48.5±14.1	48.7±15.8	0.932
Weight (kg)	70.7±9.6	72.5±8.9	0.372
Height (cm)	164.8±6.8	165.5±6.5	0.622
BMI (kg/m^2)	25.9±2.6	26.3±2.2	0.426
TSH (IU/ml)	2.1±1.3	2.2±1.3	0.846
Endocan (pg/ml)	45.1±9.6	37.7±8.3	<0.001

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AEP879

Association of thiol/disulfide homeostasis with Bethesda classification of thyroid nodules and thyroid cancer

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Background
Ultrasonography and fine needle aspiration biopsy are frequently used in the diagnosis of thyroid cancer. However, supportive data might be required in case of diagnostic difficulty. In this study, we investigated whether there is a relationship between thiol/disulfide homeostasis and cytological and histopathological diagnosis of thyroid nodules.
Materials and methods
A total of 119 participants were included in the study (81 euthyroid nodular goiter patients and 28 age and body mass index matched healthy volunteers). The patient group consisted of individuals scheduled for thyroidectomy. Thyroidectomy indications were giant nodule, cytological diagnosis and patient preference. Patients with diseases that would affect thiol/disulfide homeostasis were excluded. Cytological findings, histopathology results were evaluated. Native thiol, total thiol, and disulfide concentrations were measured, and disulfide/native thiol, disulfide/total thiol and native thiol/total thiol ratios were calculated. Thiol/disulfide levels were analyzed with automated spectrophotometric method.
Results
There was no significant difference in oxidative stress parameters between different Bethesda categories. However, the increasing Bethesda categories were weakly positively correlated with the disulfide/native thiol (r: 0.241, p: 0.030) and disulfide/total thiol (r: 0.250 p: 0.024). The disulfide concentration was 16.07±9.28 µmol/l in histopathologically benign, 19.85±11.28 µmol/l in malignant, and 14.87±7.62 µmol/l in the control group (P<0.001, f=11.724). Disulfide/native thiol was calculated as 3.58±2.0 in the benign group, 5.50±2.85 in the malignant group, and 3.41±1.70 in the control group (P <0.001, f=8.415). Disulfide/total thiol was significantly higher in the malignant compared to benign and control groups (4.96±2.24, 3.27±1.80 and 4.96±2.24, respectively, P <0.001, f=9.49).
Conclusion
Oxidative stress parameters were significantly higher in thyroid cancer. A weak positive correlation was detected between Bethesda categories and the disulfide/native thiol ratio and the disulfide/total thiol ratio. In case of diagnostic difficulties, additional benefit can be obtained from thiol/disulfide measurement.

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AEP880

Subacute thyroiditis at the time of SARS-CoV-2 pandemic

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Background
Subacute thyroiditis (SAT) has been related to acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We evaluated the incidence and the severity of SAT due to SARS-CoV-2.
Methods
A cross-sectional, retrospective study was conducted at the Endocrinology Unit of University-Hospital of Pisa, Italy. All patients experiencing SAT arisen within a period of 15 days earlier and yet untreated, assessed from January 2016 to December 2020, were included in the study. SAT cases from 2016 to 2019 (n = 152) were defined as "pre-SARS-CoV-2", while 2020 SAT patients were classified as "pos-SARS-CoV-2" (n = 13) or "neg-SARS-CoV-2" (n = 24) according to positive or negative test for SARS-CoV-2 at SAT onset or within a period of 45 days earlier.
Results
While in the years 2016–2019 most SAT cases were observed in the 3rd quarter, in 2020 there were two peaks, in the 2nd and in the 4th quarters, superimposable to the two main outbreaks of SARS-CoV-2. Compared to the same quarters of the years 2016–2019, in the 2nd and the 4th quarters of 2020 we observed higher levels of free thyroxine (FT4), C-reactive protein (CRP) and thyroglobulin (Tg). Compared to pre-SARS-CoV-2, pos-SARS-CoV-2 had higher FT4 (28·1 vs 24·1 nmol/l), CRP (8·0 vs 3·6 mg/l) and Tg (155 vs 60 µg/l) (P<0·05 for all) and resulted more frequently in hypothyroidism at 3 months (9/10 vs 30/152) (P <0·001). Neg-SARS-CoV-2 patients showed a clinical picture intermediate between pre-SARS-CoV-2 and pos-SARS-CoV-2 patients.
Interpretation
Most SAT cases in 2020 were associated with SARS-CoV-2 infection and were more severe than those previously observed.
Funding
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AEP881

Follicular thyroid carcinoma in a developing country : A retrospective study of 10 years

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Introduction
The most common endocrine tumor is thyroid cancer. Follicular Thyroid Carcinoma (FTC) accounts for 5%–10% of all thyroid cancers. Patients with FTC frequently present with more advanced stage diseases and a higher occurrence of distant metastases because of the propensity of vascular invasion. FTC are mainly treated with surgery while radioactive iodine therapy (RAI) is main adjuvant therapy as per ATA guidelines. In many developing countries surgical facilities and RAI are in short supply therefore understanding the trends of FTC may help developing countries to plan and use resources more effectively.
Methodology
It was a retrospective observational study of FTC patients of age 18 years and above conducted at Aga Khan University Hospital, Karachi from 1st January 2010 to 31st December 2019.
Results
There were total of 404 patients of thyroid carcinoma out of which forty (10.1%) were FTC. 50% of the patients were in age group of 41–60 years and female to male ratio was 1.5 : 1. 60% presented with complain of neck swelling followed by bony, lung metastasis (20%) and compressive symptoms (20%). The pre-operative thyroglobulin level was done in six out of eight metastatic patients (75%) in which it was elevated. This emphasizes

the importance of checking thyroglobulin level in unusual presentation (bone pain, fractures) of patient having neck swelling also. On FNAC, 50% (20 patients) had Bethesda category III-IV nodules while 10% (4 patients) had Bethesda category II. In sixteen patients FNAC was not done as they presented with compressive symptoms or metastasis. Fifty percent had total thyroidectomy and 50% had subtotal followed by completion thyroidectomy plus ten patients had lymph node dissection out of which seven had histopathological lymph node involvement. On histopathology twenty three patients (57.5%) had minimally invasive while seventeen (42.5%) had widely invasive FTC. In our study 65% of the patients had clinical stage 1 disease while 25% had stage 2 and 10% had clinical stage 4. Seventeen patients (42.5%) had received RAI 30–100 mCi while ten patients (25%) received more than 100 mCi.
Conclusion
FTC demographic and clinicopathological presentation are same in Pakistan as compared to other countries. Surgery followed by RAI are the main stay of treatment. Thus understanding the trend of FTC and proper planning and utilization of the resources will help the developing countries in effectively treating the FTC.

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AEP882

Clinical and pathological features of thyroid cancer in adolescents and young adults

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Introduction
Thyroid cancer is the most common endocrine malignancy and its overall incidence has increased significantly in the last 30 years. Cancer in adolescents and young adults (AYA) is defined by the National Cancer Institute as diagnoses occurring among those aged 15 to 39 years. Thyroid cancer is the second most common cancer in the AYA population. In this study, we aimed to compare clinical, ultrasonographical, cytological and histopathological features of thyroid carcinoma in patients AYA with older counterparts.
Materials and methods
The medical records of patients who underwent thyroidectomy between December 2006 and September 2016 and were diagnosed with thyroid cancer histopathologically were retrospectively reviewed. Patients were subdivided into two age groups: 15–39 (Group1) and ≥ 40 years old (Group 2). Thyroid functions, ultrasonographic features of malignant nodules, cytological and histopathological findings were compared in patients with AYA patients and ≥ 40 years.
Results
The study included 229 (22.6%) AYA patients and 784 (77.4%) patients aged ≥ 40 years. Thyroid functions, thyroid autoantibody positivity and thyroidectomy indications were similar. There were 305 (21.4%) and 1121 (78.6%) malignant foci in Group 1 and 2, respectively. Preoperative US features were similar in the two groups. Cytological results were distributed similarly in two groups (P = 0.512). Of all cancer types, 93.1% in Group 1 and 93.5% in Group 2 were papillary thyroid cancer (P = 0.772). Follicular cancer was found in 2.6% of Group 1 and 2.1% of Group 2 (P = 0.544). Medullary cancer constituted 1% of Group 1 and 1.1% of Group 2 (P = 0.895). Anaplastic cancer was found in 0.4% of Group 1 and 0.4% of Group 2 (P = 0.940). Lymph node metastasis was detected in 9.2% of group 1 and 7.4% of group 2 (P = 0.246). Distant metastasis was not detected in group 1, and it was found in 3 (0.4%) patients in group 2 (P = 0.366). There was not any significant difference in capsular and vascular invasion and extracapsular extension between groups.
Conclusion
Previous studies have found that although AYA patients are more likely to be diagnosed with locoregional lymph node involvement compared to older patients, they are less likely to be diagnosed with distant metastases. In our study, the rate of diagnosis of lymph node metastasis was higher and the rate of distant metastasis was lower, but the difference was not statistically significant.

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AEP883

Transient thyrotoxicosis induced by bone metastasis from differentiated thyroid cancer : a case report

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Introduction
Thyrotoxicosis due to functioning metastases in differentiated thyroid cancer (DTC) is exceedingly rare. The mechanism remains unknown despite several hypotheses. We report on a case of transient thyrotoxicosis due to functioning bone metastasis of follicular thyroid carcinoma.
Case report
We present a case of female patient of 68-years-old diagnosed with follicular thyroid carcinoma revealed by a lytic lesion of the right iliac bone. She had undergone total thyroidectomy followed by treatment with 100 mCi of iodine 131.The post-therapeutic whole-body scan showed intense uptake in the right iliac bone and residual thyroid gland uptake. Bone scintigraphy and SPECT/CT fusion images showed focal, intense uptake in the right iliac bone. Thoracic computed tomography and skeletal scintigraphy revealed bilateral multiple nodules in her lungs. Initially, TSH levels after 4 weeks of stopping levothyroxine treatment in preparation for treatment with I-131were high (> 60 mU/l; normal range, 0.25–5 mU/ml). The patient had undergone partial surgical resection of approximately 50% of the volume of the right iliac tumor mass.The bone metastasis was much too extensive and hypervascular to permit complete resection. After surgical management, the patient complained of symptoms of hyperthyroidism. The hyperthyroidism was confirmed by laboratory tests. Thyroid stimulating hormone (TSH) remained suppressed and free T4 remained elevated after I-131 therapy without thyroid hormone supplementation. The levothyroxine remained discontinued. TSH returned to adequate levels 8 months after surgery. TSH levels increased to 128 mU/l. Levothyroxine treatment was restarted at a suppressive dose of 175 µg/ml.
Conclusion
Thyrotoxicosis caused by thyroid follicular metastases is principally the consequence of multiple metastatic localizations, with a large tumoral volume. It must be evoked when there is no increase of the TSH after a thyroidectomy, or during the period of interruption of the suppressive treatment.

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AEP884

A tru-cut biopsy proven rare thyroid neoplasia in a giant nodule with a benign fine needle aspiration cytology

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Introduction
Extramedullary plasmacytoma (EMP) is a plasma cell neoplasm of extraosseous tissues. Less than 5% of all plasma cell neoplasms develop extramedullary. EMP is most common in the upper respiratory tract and oral cavity. The thyroid gland is one of the extremely rare regions. It is more common in men and the average age at diagnosis is 55. Primary thyroid plasmacytoma is one of the rare thyroid neoplasms. It often manifests as a rapidly growing mass in the neck and cause symptoms due to mass pressure. Pathological evaluation is particularly important. At the diagnosis of thyroid plasmacytoma, multiple myeloma must be ruled out. Here we present our case of thyroid plasmacytoma diagnosed by tru-cut biopsy.
Case
A 71-year-old female patient, with hypothyroidism and multinodular goiter since 2014, presented with a 6-month history of dyspnea and neck swelling. She had type 2 diabetes mellitus, hypertension, and coronary artery disease. Thyroid gland was grade 3, fixed nodules were bilateral palpable. Thyroid function tests were euthyroid on levothyroxine treatment and thyroid autoantibodies were positive. An ultrasound scan of the thyroid revealed an enlarged thyroid with thyroid nodules on the right and left lobes, extending to the isthmus with a significant increase in size compared to previous controls. Fine needle aspiration cytology was benign. Due to suspicion of

thyroid lymphoma, tru-cut biopsy was performed which suggested plasma cell neoplasia and plasmacytoma. Hematology consultation was made, as a result of the tests, multiple myeloma and other plasma cell disorders were excluded. The patient was evaluated as extramedullary plasmacytoma. In the council of endocrinology and metabolism, hematology, general surgery, nuclear medicine and radiation oncology departments operation was preferred. Bilateral total thyroidectomy was performed, histopathology reported as plasma cell neoplasm. Radiotherapy was not considered to be given to the patient as she had no residue in the examinations performed in the postoperative period. The patient has been followed in remission for one year.
Conclusion
Primary thyroid plasmacytoma is a rare thyroid neoplasm. Clinical examination and imaging methods are usually not determinative in diagnosis, pathological evaluation is at the forefront of diagnosis. Even if fine needle aspiration biopsy is benign, patients should be evaluated for tru-cut biopsy in case of clinical suspicion. In the begining, multiple myeloma must be ruled out. Regular follow-up of the patient is necessary, as conversion to multiple myeloma may occur rarely.

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AEP885

Thyro-cutaneous fistula a rare presentation of thyroid lymphoma

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Background
Primary thyroid lymphoma (PTL) is defined as a lymphoma involving only the thyroid gland or the thyroid gland and adjacent (regional) neck lymph nodes. Primary lymphomas of the thyroid are uncommon tumours, representing approximately 5% of the thyroid neoplasms and 2% of extranodal lymphomas. The most characteristic presentation is that of a rapidly enlarging neck mass often associated with dysphagia [5]. The majority of patients are euthyroid and one third of patients have compressive symptoms. The mass is usually fixed to surrounding tissues and half the patients have unilateral or bilateral cervical lymph node enlargement. Abscess formation in the background of thyroid lymphoma with thyro-cutaneous fistula is further rare. Reaching the final diagnosis can be delayed if insufficient biopsy material is obtained and ıt may be difficult to distinguish thyroid lymphoma from anaplastic carcinoma and thyroiditis. The present study describes the case of a patient who was presentad with Abscess formation suggesting the possibility of anaplastic carcinoma and finaly diagnosd by diffuse large B-cell lymphoma.
Case
A 73-year-old female presented with anterior neck pain, hoarseness and rapidly expanding mass with Abscess formation on here neck. the patient was admitted to our clinic for preoperative thyroid surgery suggesting the possibility of anaplastic carcinoma due to fine needle aspiration cytology of suspicious for malignancy. Her serum TSH was *elevated to* 47 mU/l and anti TPO was very high. Here neck ultrasound showed a significantly enlarged, diffuse parenchymal inhomogeneity and ill defined border of the thyroid gland. We performed Tru-cut biopsy and histological diagnosis was Diffuse large B-cell lymphoma of the thyroid gland. After 18FDG-positron emission tomography/computed tomography (PET/CT) scanning the patient reseaved 6 regimen of chemotherapy R-CHOP (rituximab, cyclophosphamide, doxorubicin [hydroxydoxorubicin], vincristine [Oncovin], prednisone with antibioticsand she has a good physical condition.
Discussion
Thyroid abscess is a rare clinical situation. It is most commonly associated with pyriform sinus fistula. Abscess formation in the background of thyroid cancer with thyro-cutaneous fistula is further rare. PTL is an uncommon malignancy of the thyroid. PTL occur most commonly in elderly women and are commonly of B- cell origin. Fine needle aspiration has become the procedure of choice for the initial pathological diagnosis of thyroid nodule. However, studies have also shown inconsistent results in the diagnosis of lymphoma of the thyroid. But clinical and radiological suspicion and cytomorphological features can help reaching the correct diagnosis in such cases.

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AEP886

Hematological changes before and after radioactive iodine therapy

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Objective
Radioactive iodine (RAI) therapy is widely used in both diagnosis and treatment of benign and malignant thyroid diseases. It is generally a well tolerated therapy. Bone marrow suppression is often a temporary side effect with a decrease in white blood cells and platelets up to 6–10 weeks. In this study, we aimed to examine hematological changes in patients who received RAI treatment for benign or malignant diseases of the thyroid.
Methods
The records of patients who applied to our endocrinology clinic between January 2016 and January 2019 and received RAI treatment for benign or malignant etiologies were evaluated retrospectively. The demographic data of the patients and data on thyroid disease, additional diseases, and the drugs used were recorded, the patients were grouped according to the etiology and the RAI dose they received. Blood count parameters measured before RAI treatment within 7 days, after RAI treatment and at the last control of the patient were recorded and compared in these patients.
Results
In the study, data of total 202 patients, including 158 women (77.5%) and 44 men (21.6%), were evaluated. 168 of these patients (82.4%) had received RAI treatment due to malign, and 34 benign (16.7%) etiologies. The median age they received RAI was 45 (20–84), while the median dose of RAI was 75 mCi (10–200). Pre-treatment and first control interval was median 44 (18–93) days, and the median time between pre-treatment and last control was 35 (4–56) months. In comparison of hematological parameters before and after treatment, the median leukocyte count was 7.72 (3.89–19.93) × 10^9/l before treatment, while it was significantly reduced 6.27 (0.86–14.5) × 10^9/l at the first control after treatment and 6.78 (3.58–10.8) × 10^9/l at the last control. Similarly, a decrease in neutrophil and lymphocyte counts was detected after treatment. While the median hemoglobin value was 13.95 (8.8–17.2) g/dl before RAI treatment, it was 13.5 (7.8–17.3) g/dl and 13.5 (6.7–17.6) g/dl at the first and last control after treatment, respectively. The median platelet count was 283 (149–563) × 10^9/l, and it was 250.5 (134–507) × 10^9/l at the first post-treatment control and 266.5 (116–539) × 10^9/l at the last control. While the median value of mean platelet volume(MPV) was 10.8 (8.5–13.8) fL before treatment, it was 10.15 (7.6–13.1) fL and 8.2 (6.6–11.1)fL, respectively, in controls.
Conclusion
In our study, a significant decrease was found in the leukocyte, neutrophil, lymphocyte, platelet counts, hemoglobin levels and mean platelet volumes in the post RAI treatment period. According to these findings, it can be thought that the decrease in hematological parameters continues not only in the acute period but also in the chronic period after RAI.

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AEP887

Effect of iodine 131 in the treatment of Graves' disease on thyroid mass and clinical signs of hyperthyroidism

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Introduction
Radioiodine I-131 (RAI) therapy of Graves' Disease (GD) affects biological thyroid function, clinical signs of hyperthyroidism (SCH), but also the mass of the thyroid (MT). The aim of our study is to assess the effect of RAI on GD and TM according to biological thyroid function after 6 and 12 months.
Methods
This is a prospective study of 86 patients (mean age 43 ± 11, sex ratio 2.07) referred for RAI therapy of GD. The biological thyroid function was assessed after 6 months and one year of RAI. The patient's weight, heart rate and thyroid mass were evaluated at 6 months and 12 months. According to the biological thyroid function at 6 and 12 months, the patients are divided into two subgroups: the subgroup of patients who persist in hyperthyroidism

(GI) and the patients who achieved remission (eu- or hypo-thyroidism) (GII). We compared the change in weight, heart rate, and thyroid mass after RAI between the two subgroups.
Results
Follow-up after RAI was possible in 66 patients at 6 months and 63 after a year. Hyperthyroidism persists or recurs in 29% of patients at 6 months and 20% at 12 months. We noted weight gain ($p < 0.0001$ at 6 and 12 months), reduction in heart rate ($P = 0.003$ at 6 months and $P < 0.0001$ at 12 months) and reduction in TM ($P < 0.0001$ at 6 and 12 months) for all patients. Weight gain was significant for both subgroups at 6 and 12 months, but less significant for GI ($P = 0.001$ vs $P < 0.0001$ at 6 months and $P = 0.047$ vs $P < 0.0001$ at 12 months). At 6 months, the reduction in heart rate was significant for GII ($P = 0.002$) but not significant for GI ($P = 0.47$). At 12 months, the reduction in heart rate was significant for both subgroups, but less significant for GI ($P = 0.008$ vs $P = 0.005$). The reduction in MT was significant for both subgroups at 6 and 12 months, but less significant for GI ($P = 0.001$ vs $P < 0.0001$ at 6 months and $P = 0.007$ vs $P = 0.0001$ at 12 months).
Conclusion
RAI therapy improves SCH and reduces thyroid mass even for the subgroup of patients with persistent hyperthyroidism, but less significantly than the subgroup of patients who achieved remission at 6 and 12 months.

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AEP888

Thyroid diseases and mastopathy in normally cycling women

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Objective
To evaluate the combined pathology of the thyroid and mammary glands in normally cycling women
Materials and Methods
We have examined normally cycling 265 women aged 18 to 56 years. The modeling was performed using the SPSS 17.0 statistical software package.
Results
the combined pathology of the thyroid and mammary glands was detected in 149 women (56.2%) of the number of examined women. Isolated pathology of the thyroid gland in the age group from 18 to 35 years old was defined in 29 people (23.0%); isolated breast pathology - in 36 (28.6%); combined pathology of the thyroid and mammary glands - in 49 women (38.9%). In the group from 36 to 44 years old, isolated thyroid pathology was diagnosed in 14 women (14.9%); isolated pathology of the mammary gland - in 13 (13.8%), combined pathology of the thyroid and mammary glands - in 63 women (67%). In the group of 45 years and older, isolated pathology of the thyroid gland was diagnosed in 5 women (11.1%); isolated breast pathology - in 1 (2.2%); combined pathology of the thyroid and mammary glands - in 37 women (82.2%). The incidence of combined pathology of the thyroid and mammary glands in all age groups is higher than the isolated pathology of the thyroid gland (group 1 - $\chi^2 = 7.43$; $P < 0.05$; group 2 - $\chi^2 = 52.06$; $P < 0.001$; group 3 - $\chi^2 = 44.72$; $P < 0.001$). The incidence of combined pathology in groups from 36 to 44 years old and 45 years and older is higher than isolated breast pathology (group 2 – $\chi^2 = 54.45$; $P < 0.001$; group 3 – $\chi^2 = 57.76$; $P < 0.001$). The incidence of concomitant pathology is significantly higher in group 3 (compared with women in group 1 - ($\chi^2 = 10.17$; $P = 0.001$).
Conclusions
The incidence of combined pathology of the thyroid and mammary glands in all age groups is higher than the isolated pathology of the thyroid gland.

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AEP889

Emergency total thyroidectomy in a COVID 19 patient with Graves' disease and pancreatitis induced by methimazole

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Introduction
The use of antithyroid drugs is associated rarely with severe hepatotoxicity. Recently, due to several cases reported in the literature, acute pancreatitis was added as a severe potential adverse effect induced by methimazole. The physiopathology of methimazole induced pancreatitis is not fully understood (intrinsic toxicity or idiosyncratic drug reaction were proposed as possible mechanisms). If adverse effects occur and no other treatment options are available (other antithyroid agent, radioiodine therapy), the rapid correction of hyperthyroidism can be obtained by surgery (thyroidectomy).
Case presentation
A 69-year-old woman was diagnosed with Graves' disease in January 2021, with severe thyrotoxicosis, without ophthalmic involvement. The patient started methimazole treatment with high doses (30 mg/day) gradually tapered over the following weeks. Three weeks later she presented to the Emergency Department with severe abdominal pain, nausea, vomiting, inappetence, palpitations, and sweating. She had no fever and was negative for coronavirus (RT-PCR test). She reported no history of hypertriglyceridemia, alcohol or other medication. The laboratory tests confirmed acute pancreatitis (serum lipase was elevated 6 times the upper limit of normal) and liver dysfunction (transaminases were elevated 10 times the upper limit). Alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and total bilirubin were significantly increased. All the imagistic investigations (abdominal ultrasound, computed tomography, echoendoscopy) confirmed the diagnosis of acute pancreatitis, without signs of gallstones or tumors. Thyroid ultrasound revealed normal thyroid volume (15 ml), marked hypoechoic parenchyma, increased vascularization. The hormonal data showed a very suppressed TSH associated with normal FT3 and slightly increased FT4. Methimazole was interrupted and Propranolol was administered in high doses (80 mg/day). After i.v. fluids, pain medication and proton pump inhibitor administration, patient's condition improved. After five days, transaminases, lipase, ALP and GGT levels decreased significantly. On the sixth day, the repeated RT-PCR for COVID 19 was positive. She was transferred to the special COVID 19 Department, where she was evaluated (thoracic CT showed only minor lesions, with "ground-glass" appearance affecting less than 10% of the lungs) and treated with i.v. perfusions, pain medication, anti-inflammatory drugs, heparine and propranolol. Radioactive iodine therapy was unavailable. On the same day she underwent emergency total thyroidectomy, without any complications. She was discharged after 6 days, on oral anticoagulants and levothyroxine.
Conclusion
As severe thyrotoxicosis may be associated with more serious complications from COVID-19, urgent thyroidectomy is a valid option in patients with severe adverse effects to antithyroid drugs (pancreatitis).

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AEP890

Radiofrequency ablation for benign thyroid nodules: 600 patients - five years follow-up single center experience

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Purpose
The objective of this study was to evaluate the efficacy and safety of ultrasound (US)-guided radiofrequency ablation (RFA) for treating of benign thyroid nodules of long-term follow-up.
Material and methods
The retrospective analysis included the results of treatment of 600 patients with benign tumors of the thyroid gland in the Samara Oncology Center. 108 (18%) patients had autonomously functioning thyroid nodules and 492 (82%) had symptomatic ones. The mean volume of nodule was 33.1 (1.5–179.5) ml.
Results
RFA reduced nodular volume by 68% after 6 months, 85% after 60 months and it was an effective method for treating nodule-related clinical problems and hot nodules. 54 (9%) patients with nodule volume more than 75 ml underwent 2–10 sessions of RFA. Cosmetic results were excellent in 95% of patients. No serious complications such as thyroiditis, voice change, and hematomas were observed.
Conclusion
Long-term follow-up showed that RFA was effective and safe for treating benign thyroid nodules.

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AEP891

SARS-Cov-2 related subacute thyroiditis in Belarusian patients with the previous autoimmune thyroiditis

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Introduction & Background
A COVID-19 pandemic smashed the world not only by it`s severity, but also by the tremendous amount of comorbidities, many of them having autoimmune basis. Thyrotoxicosis as one of the above - could result either from SARS-CoV-2 directly infecting the thyroid gland, as described in other viral infections, or can develop due to immune overactivation during the severe viral load. Subacute thyroiditis (SAT) is a self-limiting inflammatory disease of viral or post-viral origin, characterized by general symptoms, neck pain and thyroid dysfunction, lasting for a period of weeks or months—followed by hypothyroidism with subsequent restoration of euthyroidism. The pathogenesis of SAT started after SARS-Cov-2 infection is thought to be similar to the association with the other viral conditions.
Aim
In our study we aimed to analyze the variety of clinical, laboratory and ultrasonic data in the observed cases of subacute thyroiditis associated with SARS-Cov-2 infection.
Materials and methods
We have analyzed 8 cases of late-onset subacute thyroiditis in 6 Belarusian female and two male patients. All our patients have had a history of mild to severe SARS-Cov-2 infection, that required admission to the clinic. In a short period (from 2 to 7 weeks) after the discharge from the hospital they returned to an out-patient department with complaints for a tachycardia and a pain on the frontal area of the neck.
Discussion
The pathogenesis of subacute thyroiditis emerging in a short time after SARS-Cov-2 infection is thought to be similar to the association with the other viral-induced thyroid conditions. The viral etiology is supported by the onset of SAT after an upper respiratory infection and its occurrence during viral outbreaks. In our observed cases – only two of the females (2/6) had the diagnosis of autoimmune thyroiditis before the pandemic period, in other cases – ultrasound features of autoimmune thyroiditis and slightly decreased fT4 and fT3 levels were revealed during the exams.
Conclusion
An analysis of more cases is definitely needed to answer the question "Does antecedent autoimmune thyroiditis lead to a higher risk of SARS-Cov-2-associated subacute thyroiditis?" Current recommendation remains as a proposal of more thorough observation of thyroid out-patients with all forms of autoimmune disorders in case of reported SARS-Cov-2 reconvalescence.

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AEP892

Evaluating the role of circulating dendritic cells in methimazole-treated pediatric Graves' disease patients

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Graves' disease (GD) is hyperthyroidism associated with organ-specific autoimmune 14 inflammation. GD occurs more frequently in adults than in children, however, pediatric patients are 15 a therapeutic challenge due to cycles of remissions and relapses requiring constant monitoring at 16 every stage of treatment administered. Dendritic cells (DCs) are considered a link between innate 17 and adaptive immunity. DCs as antigen-presenting cells (APCs) are involved in antigen 18 presentation to T lymphocytes, thereby, initiate shift towards effector cells. In accordance, DCs 19 participates also in the modulation of tolerance to specific antigens. To date, the data on DC role in 20 Graves' pathological processes are scarce. Therefore, here we evaluated frequencies and role of 21 circulating DCs in GD pediatric patients treated with methimazole. Flow cytometric analysis was 22 implemented to evaluate mDC1, mDC2 and pDC cells and their correlation with clinical GD-related 23 parameters. We found significantly higher levels of DC subsets in patients at admission. 24 Furthermore, methimazole treatment seemed to effectively reduce subsets of DCs which, in 25 addition, were found to differentialy correlate with thyroid function. Our study shed a new light on 26 DCs role in pediatric GD pathomechanism. Further studies are required for mechanistic assessment 27 of DCs exact role in disease progression and influence on thyroid function.

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AEP893

Two cases of rare thyroid cancer• Hyalinizing trabecular tumor and Warthin like papillary carcinoma.

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Background
Following the 4th edition of WHO classification of thyroid tumors several pathologic entities were reclassified, mainly as a means of de-escalating addressed therapy. We herein present two rare types of thyroid cancer, hyalinizing trabecular tumor (HTT) and Warthin-like papillary carcinoma (WL-PTC).
Cases presentation
A 64-year-old female patient presented with an ultrasonographic 1.92 × 1.11 cm isoechoic thyroid nodule with intranodular vascularity. Fine–needle aspiration (FNA) cytology showed atypia of undetermined significance (TBS III). Three years later FNA was repeated due to nodule enlargement and the cytology was reported as suspicious of malignancy (TBS V). A total thyroidectomy was performed and the pathology report revealed HTT. Substitution levothyroxine therapy was started. Three months postoperatively the patient was in an excellent condition with undetectable thyroglobulin levels and negative antithyroglobulin antibodies. The second patient, a 54-year-old woman with a known history of Hashimotos' disease, presented with an ultrasonographic 13 mm-thyroid nodule, with irregular margins and microcalcifications. The subsequent FNA cytology showed papillary thyroid carcinoma (PTC), probably a tall cell variant (TSB VI). The patient underwent a total thyroidectomy and the pathology revealed a WL-PTC. Ablation radioiodine treatment was offered and suppression levothyroxine treatment was started.
Discussion
Both variants have a female preponderance with a middle-aged occurence and are usually associated with lymphocytic thyroiditis. HTT incidence is not known, but it is considered to be a rare thyroid neoplasm with a characteristic trabecular growth pattern and hyalinization. In FNA thyroid samples HTT shares nuclear features of PTC, so that it is usually diagnosed only after thyroidectomy. Cell membrane and cytoplasmic positivity for Ki67 and somatic GLIS rearrangement, especially PAX8-GLIS3, are characteristic of HTT. The majority of these tumors is noninvasive and considered to be benign, nevertheless distant metastases have been reported. WL-PTC is a rare histological variant of papillary carcinoma with a similar prognosis to the classical PTC. Histopathologically it resembles the Warthin tumor of salivary glands. While at first it was considered a subtype of the oncocytic variant of PTC, it is now reclassified as a separate PTC variant.
Conclusion
Despite their rareness, both HTT and WL-PTC might be clinically encountered. They are generally considered to have a benign clinical behavior. More information regarding long-term courses is needed, in order to properly treat such patients and avoid unnecessary therapies

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AEP894

Radioactive iodine therapy with recombinant human TSH (rhTSH) for well-differentiated thyroid cancer had no difference in GO outcome; case report

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Background
The risk of cancer is relatively higher in Graves' patients presenting simultaneously with thyroid nodules. Radioiodine (RAI) therapy recommended in intermediate-high risk differentiated thyroid carcinoma may be associated with worsening of a pre-existing Graves' orbitopathy (GO) or developing a new onset. The impact of RAI therapy in patients with differentiated thyroid cancer on the course of a pre-exisiting GO has not been specifically investigated. we report a sever GO patient treated by recombinant Tsh (RhTSH) for intermediate-risk of papillary thyroid cancers (PTC).
Case
A 47-year-old man, presented to our center with exophthalmos and ptosis of eyes. His thyroid function tests and thyroid autoantibodies were as follows: TSH; 0.01 (0.4–4 uIU/ml), FT3; 5.41 (1.6–4.9 pg/ml), FT4; 1.74 (0.78–1.76 ng/dl); anti TPO was positive TSH-R Ab; 1.249. On the ultrasonographic examination of the thyroid gland the paranchyme was heterogeneous and in the right lobe 11.2 × 8.9 mm heterogeneous, iso-hyporechogenic nodule and pathologic lymphadenopathy were detected in levels 4 of neck. US-guided fine-needle aspiration biopsy was performed and the cytological examination were suspicious for papillary thyroid cance of the nodule and malign sitology of the lymph node. Computed tomography scan of orbita demostrated bilateral anterior bulging of bulbus oculi clearly and bilateral enlargement of medial, inferior and superior rectus muscles and also swelling of the optic nerve. In addition to antithyroid and beta blocker, for severe ophthalmopathy intravenous pulse therapy with high doses of methylprednisolone as 500 mg tapered in 24 weeks duration, followed by 250 mg for 24 weeks. He underwent thyroidectomy and a dissection of the santral and right lateral lymph nodules was conducted. The diagnosis were PTC with < 5% of hobnail variant and mestatic lymph nodules was confirmed. Once stabilized of GO under oral methylprednisolone and became euthyroid he reseved 150 mCi RAI with rhTSH with no changes in GO after One month observation.
Discussion
The risk of cancer is relatively higher in Graves' patients in the presence of an accompanying nodular disease. Moreover, some authors reported that thyroid cancer associated with GD seemed to be more aggressive. RAI therapy is recommended in high-risk differentiated thyroid carcinoma, but it might worsen or induce a new onset of GO. Glucocorticoid treatment should be given especially in patients who will receive high doses of RAI. RAI with rhTSH had no difference in GO outcome at first month.

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AEP895

Are the outcomes that matter most to persons with thyroid dysfunction in Malaysia the same as in other populations in developed countries?

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Background
The burden of disease in thyroid dysfunction (TD) is modifiable. Social domain of quality-of-life is a vital aspect of the biopsychosocial approach to management. Treatment decisions are increasingly guided by quality-of-life issues, creating a need to monitor the quality-of-life within clinical practice. Thyroid-specific patients reported outcomes scale/tool (ThyPro) was developed and used predominantly in populations in developed countries. Whether this tool can capture the important social domains of quality-of-life in patients with chronic multi-morbid TD in diverse cultures, e.g., South-east Asia, is uncertain. We aimed to compare the findings from our quality-of-life qualitative research project of persons with TD in Malaysia to those in the ThyPro tool study.
Methods
The questionnaires of a Malay language version of the semi-structured qualitative survey in Malaysia, part of the larger research: A CORE OUTCOME SET FOR THYROID DYSFUNCTION[1], were developed from interactive discussions with patients who have thyroid dysfunction. A mixed-method approach was used to collect the data: face-to-face in-depth interviews in the endocrine clinic and online survey using the same set of questionnaires. The responses were analyzed using Braun and Clark's thematic analysis[2] framework guided by the question: What are the perceptions and experiences of thyroid care that matter most to patients with TD? The findings were then compared with the items in the ThyPro scale.
Findings
There was no significant difference in the baseline demographic characteristic of our subjects in comparison to the ThyPro cohort (Table 1). The only marked difference is that our study participants have TD of prolonged duration compared with the recent onset in the ThyPro cohort. Major themes that emerged from our analysis are emotional security, functional ability, self-care (including psychosocial and socioeconomic well-being), and quality of physician-patient relationships (Details in Table 2). Symptoms of hyperthyroidism and hypothyroidism impacted upon all the above themes. All the items in the ThyPro scale are present in our cohort. However, health-service factors emerged as an important parameter in our population and are absent from the ThyPro scale.
Conclusion
Our study can capture all the items in patients with recent and chronic TD, unlike the ThyPro scale that captures only outcomes in patients with recent TD. Further robust research is required to determine whether the additional important patient-reported outcomes in populations with varying duration of TD and diverse cultures impact the development of core outcome set for thyroid dysfunction.

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ePosters

Adrenal and Cardiovascular Endocrinology

EP1

A case report of metastatic adrenocortical carcinoma

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Introduction
Adrenocortical carcinoma is a rare neoplasm with local development, rarely metastatic in the spine. We report a case of metastatic dorsal spinal cord compression due to adrenocortical carcinoma.
Observation
A 38-year-old lady with no notable medical history, complained of generalised weakness, severe abdominal pain and spasms. Abdominal computed tomography showed a large right adrenal renal mass measuring 127 * 118 mm infiltrating the tendon center of the diaphragmatic pillar pushing back up the liver and down the kidney with loss of the fatty border. She did not have any signs of hypercortisolism or virilisation. Serum potassium level, oestradiol, testosterone, serum cortisol and 24 h urinary metanephrine were within normal limits. Per operatively, the tumour was free from the kidney and entire adrenal mass was removed with adequate resection margin. Histological examination made the diagnosis of malignant adrenocortical carcinoma. Three days after surgery, she complained of rapidly progressive and continuous back pain, and a sudden heaviness in both limbs. Physical examination revealed proximal paraplegia of the two lower limbs, pyramidal syndrome and hypoaesthesia with a T3 sensory level. A spinal magnetic resonance imaging was performed in emergency visualizing a progressive spinal cord compression secondary to the epidural component of the T3-T4 mass. Decompressive laminectomy and resection of endoluminal tumor material were performed urgently. Histological examination was in favor of spinal metastasis from adrenocortical carcinoma.
Conclusion
Spinal metastasis of adrenocortical carcinoma is exceedingly rare with only few cases having been reported previously. This case highlights the rapid and agressive nature of non-secreting adrenocortical carcinoma causing metastatic dorsal spinal cord compression.

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EP2

Screening for subclinical Cushing's Syndrome in Malaysians with metabolic syndrome: A single center, cross-sectional study

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Background
Patients with Subclinical Cushing's Syndrome (SCS) share many similarities with those of metabolic syndrome. Several studies have shown variable prevalence of SCS in patients with diabetes and obesity of up to 9% suggesting that it may be more common in these patients. Our study aims to explore the prevalence of SCS in Malaysians with metabolic syndrome and examine any possible predicting factors.
Methods
This is a cross-sectional single center study at a tertiary referral hospital of 147 patients in outpatient diabetes and obesity clinics who fulfil the criteria for metabolic syndrome and do not have any discriminatory features of Cushing's syndrome (facial plethora, easy bruising, proximal myopathy and reddish or purple striae measuring > 1 cm). Patients were screened with the 1 mg overnight dexamethasone test (ODST), followed by the 48-h 2 mg low dose dexamethasone test (LDDST), using cut-offs of 50 nmol/l for both tests.
Results
Six patients had a non-suppressed ODST result and only 1 patient had both non-suppressed ODST and LDDST. Hence, the prevalence of SCS was 0.7% in this study. There were no statistically significant differences between suppressors and non-suppressors on ODST testing.
Conclusion
Based on the results of this study we do not recommend routine screening for SCS in patients with metabolic syndrome in absence of clinical suspicion.

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EP3

Bilateral primary adrenal lymphoma: a case report

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Introduction
Primary adrenal lymphoma (PAL) are rare extranodal lymphomas and account for<1% of all non-Hodgkin lymphomas, with characteristic clinical features including high incidence of bilateral involvement, predominantly diffuse large B-cell histology, and low incidence of extra-adrenal disease at diagnosis. We report a case of 50-year-old patient affected by bilateral B-cell adrenal lymphoma.
Case presentation
A 50-year-old woman was admitted for exploration of suspicious bilateral adrenal incidentalomas. History of the disease dates back to February 2020, marked by the onset of recurrent urinary tract infection. Abdominal ultrasound showed two right and left adrenal masses measuring respectively 9 and 10 cm. There were no hyperpigmentation, no touchable lymph nodes, no abdominal mass, untouchable liver and spleen and no breast nodule at physical examination. Computed Tomography (CT) showed oval hypodense right and left adrenal masses, with limited contours measuring respectively 66 * 90 mm and 100 * 81 mm, with average spontaneous density of 43UH and 42UH, and absolute washout at 33% and 27%, slightly enhanced after injection of contrast product, heterogeneous with necrosis and without calcifications. Biology revealed microcytic hypochromic anemia with normal ferritinemia, elevated levels of erythrocyte sedimentation rate at 80 mm (reference: 25 mm/h), C-reactive-protein (CRP) at 51 mg/l (reference<6) and lactate dehydrogenase (LDH) at 400 UI/l (0–247). Morning plasma cortisol was low at 133 nmol/l (185–624 nmol/l), Adrenocorticotropin (ACTH) was increased at 470 pg/ml (reference<46 pg/ml). The patient was treated with hydrocortisone. Serum catecholamines, plasma renin activity, aldosterone, testosterone and dehydroepiandrosteone sulfate (DHEA-S) were normal. β-microglobulin was slightly elevated at 3.51 mg/l (1.42–3.21 mg/l). Serum tumor markers were normal. Thoraco-abdomino-pelvic CT showed right thyroid nodule with no other lesions especially no lymphadenopathy. Biopsy of left adrenal mass revealed a diffuse lymphomatous proliferation partially necrotic. Cells are large with a rounded or ovoid nucleus strongly nucleolated. Immunohistochemestry showed that cells were CD20(+), Pax5(+), CD3(−) and CK(−). Cell proliferation index (Ki67) was 90%. The diagnosis of diffuse large B-cell lymphoma was made. The patient presented an acute adrenal decompensation related to macrophage activation syndrome. Broad-spectrum antibiotics and dexamethasone were administrated with a good clinical course. After chemotherapy, the patient presented a tumor lysis syndrome with septic shock and acute respiratory distress syndrome and she died.
Conclusion
PAL is rare and prognosis is generally poor. More studies are needed in the future to identify the predictors of good clinical and radiological response to therapy.

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EP4

Successful spontaneous pregnancy and successful delivery in a patient with severe 11-beta hydroxylase deficiency

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Objective
11-Beta Hydroxylase deficiency (11ß0HD) is a rare form of congenital adrenal hyperplasia, resulting in glucocorticoid deficiency, virilization and hypertension. In the literature, there are rare case reports of successful pregnancy in a patient with genetically confirmed classic 11ß0HD.
Case
Our patient, now age 31, was diagnosed at birth with ambiguous genitalia. There was no family history of any intersex disorder. Deafness was detected when she was 8 months. She was commenced on hydrocortisone. She had a homozygous CYP11B1 gene mutation [NM_000497.3, p.L299P (c.896T>C)]. She underwent surgery, when she was four and 24. She has

had hypertension for 19 years. She has used spironolactone intermittently. She had a spontaneous pregnancy four years ago. She was commenced methylprednisolone 4 mg in morning and dexamethasone 0.5 mg in evening in the first six months of her pregnancy. In the last 3 months, she used hydrocortisone 30 mg/day. Laboratory results are shown in Table 1. During the pregnancy her blood pressure was normal and ultrasound showed a female foetus. Elective caesarean section was performed at 34 weeks of gestation. She delivered a healthy female baby, with a birth weight of 2.750 g and with normal external genital. Her blood pressure was 160/100 mmHg six months after delivery and amiloride treatment was given. In the genetic examination of the family, the mother, father, two brothers and daughter were heterozygous positive for 11-Beta Hydroxylase deficiency, and her husband was normal. Now, she is taking hydrocortisone 20 mg/day.

Conclusion

There is limited knowledge in current literature regarding pregnancies in patient with 11ßOHD. Information on the disease is limited to case reports only.Our patient is the first report of a spontaneous successful pregnancy and successful delivery with 11ßOHD in Turkey.

Table 1

Laboratory Results				
	Before pregnancy	6th months of pregnancy	4 months after birth	Reference range
17-OHP (ng/ml)	6.09	2.7	2.1	0.19–0.71
ACTH (pg/ml)		5.76	138	9–46
Aldosterone (pg/ml)	8.01	172	32	14.6–174
Plazma Renin Activity (ng//ml per hour)	1.02		0.7	<2.01

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EP5

Acquired hypoaldosteronism as classified by circulating aldosterone levels: characteristics

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Acquired Hypoaldosteronism may be caused by low circulating aldosterone levels (AD), resistance to mineralocorticoid action (MR), or a combination of both (CB). We describe the clinical/biochemical characteristics of these three types of hypoaldosteronism.

Methods

Retrospective review of a series of 177 patients with acquired hypoaldosteronism assessed by the Endocrinology Department of a tertiary teaching hospital from 2012 to 2019. We analyzed serum and urine markers of cases in which serum aldosterone (PAC) and direct renin concentration (PRC) levels were available coinciding with hyperkalemia: serum Potassium (SK) ≥5 mmol/l. Cases were classified as follows: AD: PAC <90, MR: PAC >200, or CB: PAC 90–200. PAC, PRC by Radioimmunoassay, in pg/ml. Serum/urine electrolytes in mmol/l. Mean ± S.D.

Results

51 cases analyzed, 27 (52.9%) male, age 73 ± 12 years. 30/51 were hypovolemic, 25 of whom (83.3%) presented hyponatremia. 30/51 were hyponatremic, 25/30 presenting hypovolemia. Hypovolemia was associated to hyponatremia (P<0.001). 17/32 in whom acid-base status was evaluated presented hyperchloremic metabolic acidosis (HMA). Results by group given in Table 1. No correlations were found between PAC and SK or trans-tubular-potassium gradient (TTKG) in any group, nor when all patients were grouped together (ALL). In ALL, there was a negative correlation between TTKG and urine sodium (UNa) (r= **–0.333,** P=**0.041**), TTKG and UNa/urine potassium (UK) ratio (r= **–0.725**, P<**0.001**), PAC and UNa (r= **–386**, P=**0.007**), PAC and Serum sodium (SNa) (r= **–346,** P=**0.013**), and PAC and UNa/UK ratio (r= **–0.355,** P=**0.014**).

Conclusions

In our series of patients, most hypovolemic patients presented hyponatremia. In the absence of concomitant measurement of circulating aldosterone levels, discerning the pathogenesis of hypoaldosteronism is difficult. However, higher UNa and UNa/UK levels were observed in cases of aldosterone deficit. Furthermore, marked hyponatremia may suggest mineralocorticoid resistance.

Table 1. Clinical/Biochemical characteristics of the types of acquired hypoaldosteronism.

	AD (n=28)(54.9%)	MR (n=9)(17.6%)	CB (n=14)(27.5%)	P
Hypovolemia	14 (50)	8 (88.9)	8 (57.1)	0.087
Hyponatremia	14 (50)	8 (88.9)	8 (57.1)	0.087
Hypovolemic hyponatremia	10 (35.7)	7 (77.8)	8 (57.1)	0.07
HMA	8/17 (47.1)	4/7 (57.1)	5/8 (62.5)	0.747
SK	5.4 ± 0.5	5.4 ± 0.3	5.3 ± 0.3	0.580
SNa	134 ± 7	130 ± 5	135 ± 4	0.155
Serum Creatinine, mg/dl	1.2 ± 0.6	1.3 ± 0.4	1.1 ± 0.5	0.544
HCO3, mmol/l	23.1 ± 3.8	23.3 ± 3.3	22.3 ± 3.6	0.828
UNa	87 ± 3	38 ± 15	68 ± 30	0.003
UK	30 ± 13	28 ± 15	33 ± 14	0.615
UNa/UK ratio	3.24 ± 1.62	1.5 ± 0.62	2.27 ± 1.17	0.009
SK/SU ratio	0.21 ± 0.08	0.22 ± 0.09	0.19 ± 0.08	0.594
TTKG	3.6 ± 1.3	4.8 ± 1.5	4.5 ± 1.2	0.099
PAC	43 [IQR:32–67]	317 [IQR:256–610]	128 [IQR:97–155]	<0.001
PRC	2.7 [IQR:1.2–10.4]	14.4 [IQR:1.3–26.9]	5.3 [IQR:2.8–12]	0.279

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EP6

Acute respiratory distress syndrome in a patient with new onset Addison's disease

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Primary adrenal insufficiency, Addison's disease, is a rare endocrine disorder. Early diagnosis is often difficult and the presentation is commonly only recognised after a life threatening adrenal crisis. Fortunately, with appropriate early treatment further complications are uncommon in the acute setting. This case concerns a 19-year-old man who presented with lethargy, dyspnoea on exertion and a one month history of hyperpigmentation. He had a history of nocturnal enuresis for which he was taking desmopressin. On examination he had tanned skin, buccal pigmentation and borderline hypotension. Admission bloods revealed hyponatraemia and hyperkalaemia. After establishing a working diagnosis of first presentation with Addison's disease, treatment was started including fluid resuscitation and intravenous hydrocortisone. The diagnosis of primary adrenal insufficiency was supported by inadequate response on short synacthen test and positive adrenal cortex antibodies. Two days after admission he developed sudden onset respiratory distress and hypoxia. Bi-basal crepitations were present. CTPA reported bilateral predominantly central ground glass and confluent opacities with no evidence of pulmonary embolus. Of note there was CT evidence of right heart strain. An echocardiogram showed good systolic function with estimated ejection fraction 60–65%. Pulmonary artery pressures were elevated. COVID-19 throat swab was negative. Troponin was mildly elevated though ECG showed sinus tachycardia with no ischaemic changes. He rapidly improved with CPAP for several days. Further endocrine investigations confirmed the diagnosis of primary adrenal failure (0900 h ACTH levels 688 ng/l (reference range <30 ng/l), aldosterone levels <60 pmol/l (reference range 90–700 pmol/l), grossly atrophic adrenals on CT). He was successfully converted to oral therapy prior to discharge. The reason he developed acute respiratory distress syndrome (ARDS) following treatment of adrenal insufficiency remains unknown. A literature review conducted to identify links between cases of Addison's disease and ARDS reports few cases. One (1) presented a very similar, though more severe, history and course of

illness. For our patient, previous desmopressin use may have been a contributor, exacerbating the rapid changes in fluid balance as steroid deficiency was corrected. This case highlights a rare, though potentially life-threatening, complication of acute adrenal crisis and the necessity for increased awareness of such cases among treating physicians.

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EP7

Addison's disease and type 2 diabetes

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Introduction
Recent studies in patients with Addison's disease (AD) have shown that this condition, even if treated, is fraught with significant morbidity. In this context, we report a retrospective study which concerned 32 patients with AD in order to determine the deleterious effects of long-term glucocorticoid substitution, mainly on the occurrence of type 2 diabetes.
Results
In the 32 patients followed during this study, the average fasting blood sugar level at the discovery of the disease was 4.8 mmol/l. After an average of 17 years of follow-up (range 5 and 38 years) 25% of the patients had developed type 2 diabetes. At the last consultation, almost half of the patients (42.8%) were on insulin with a dose average of 0.66 IU/kg per day. Diabetes was unbalanced in 85.7% of cases with an average fasting glucose of 9.22 mmol/l and an average HBA1c of 10.01%. The impact assessment showed retinopathy and diabetic nephropathy in 25% of patients for each.
Discussion
In the literature, a higher risk of glucose intolerance or even diabetes has been noted during treated AD. This is because patients treated with hydrocortisone have higher cortisol concentrations than physiologically, especially in the afternoon. This reduces glucose tolerance, insulin sensitivity and secretion in these patients. This effect is proportional to the dose of hydrocortisone without correlation with the duration of the disease.
Conclusion
Adjustment of replacement therapy during Addison's disease is an issue in view of the morbidity and mortality associated with overdose. Regular monitoring and a personalized therapeutic approach are necessary to improve the prognosis of his patients.

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EP8

Very large adrenal nodule and Cushing syndrome – when histology differs from the clinical suspicion

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Introduction
The malignancy risk of an adrenal nodule is based on clinical symptoms (rapid onset of hypercortisolism and hyperandrogenism; mass symptoms) and imaging characteristics. These suspicious criteria include boundary irregularities, heterogeneity, dimension>6 cm and density>20 HU (CT). However, these are not absolute criteria.
Case report
We report the case of a 43 years-old female patient with a history of alopecia, decrease in muscular strength, secondary amenorrhea, and easy bruising with 4 years of evolution. Arterial hypertension, diabetes *mellitus* and dyslipidemia were diagnosed 1 year after. A 20 kg weight gain during the previous 6 months and the appearance of abscessed skin lesions 2 months ago were also refered. Physical examination showed exuberant hypercortisolism. Analytical study revealed the presence of an ACTH-independent Cushing Syndrome: morning and midnight ACTH levels <5 pg/ml (9–52); morning and midnight serum cortisol of 19 and 18 µg/dl (5–25); urine-free cortisol of 841 µg/24 h (10–80); salivary midnight cortisol of 1.7 µg/dl (<0.1); and cortisol of 19 µg/dl after low-dose dexamethasone suppression test. The patient performed an adrenal CT that revealed, in the left adrenal gland, the presence of an 8.3×6.3 heterogeneous nodule with cystic areas, calcifications, without cleavage plan with stomach and spleen and without infiltrative aspects. Based on the high suspicion of adrenal carcinoma, the patient started therapy with ketoconazole 400 mg a day and was referred to adrenalectomy. Histological exam showed a 9 cm adrenal cortex neoplasm with score 1 in modified Weiss criteria (necrosis, reticulin pattern, and Ki<5%). This was compatible with a benign tumour. The patient maintains follow-up under replacement therapy with hydrocortisone, anti-hypertensive and anti-hyperglicemic drugs in progressive reduction. The patient also presents significant improvements in her morphotype, with a relevant weight loss of 27 kg in 5 months.
Conclusion
Imaging results (dimension> 8 cm, heterogeneity and calcifications) raised the suspicion of carcinoma. ACTH independency was also suggestive, as cortisol is the most frequent hormonal secretion associated with malignancy, as well as the age and female sex. However, the slow progression of the disease was a factor that disfavour this hypothesis. Although these imaging signs are more often associated with an aggressive behaviour, only histological results define the exact type of the lesion.

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EP9

Pheochromocytoma of urinary bladder: a case report

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Background
Paraganglioma of the urinary bladder is rarely encountered. Its clinical signs and symptoms are usually nonspecific.
Case presentation
We report a case of a 48-year-old woman who presented with recurrent hematuria for last 2 months with a recently detected hypertension. Computed tomography (CT) revealed a lobulated mass arising from the posterior wall of the urinary bladder and protruding into the vesical lumen measuring 3 cm with inhomogeneous postcontrast enhancement. Transurethral resection of the mass has instantly produced a hypertensive peak (200/110 mmHg) leading to an interruption of operation. Pathology of the specimen found a pheochromocytoma. Our patient denied a history of dizziness, sweating, and palpitations during micturition. Hormonal evaluation showed a normal level of both plasmatic and urinary metanephrine and normetanephrine. Metastatic workup was negative. Both adrenal glands were normal at CT. MIBG scan showed an increased localized activity in the bladder. After preoperative stabilization of hypertension and medical preparation, a complete transurethral resection of the tumor was performed. This case was discussed at a tumor board meeting and surveillance was decided. The patient has been disease-free for 9 months.
Conclusion
In patients with unusual, striking symptoms and an increase in blood pressure with micturition, diagnosis of pheochromocytoma of the urinary bladder must be considered. Imaging will help in confirming the diagnosis and localizing the tumor. Surgical removal is the treatment of choice.

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EP10

Adrenal tumors and mixed secretions

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Introduction
Adrenal tumors represent an increasingly common problem in modern endocrine practice. The diagnostic approach can be challenging and occasionally reveals surprising features like mixed hormonal secretion: aldosterone-and-cortisol producing adenoma. This rare situation can also impact on the therapy and the post-operative management. In this context, we report 5 patients who are followed in the Endocrinology department in Hedi Chaker hospital, sfax, Tunisia for adrenal mixed tumors.

Purpose
The aim of our study was to describe the clinical and data of these patients and monitor their evolution after appropriate treatment.
Methods
A retrospective study of patients who have cortico and or medullary mixed tumors.
Results
We objected Aldosterone- and cortisol-co-secreting tumors in four cases and corticomedullary mixed tumors in one case. All patients were female aged between 42 and 76 years old, and the average age was 59 years old. No particular family medical history was found. All patients had hypertension and type 2 diabetes. Obesity was described in one case and overweight in the others. Two patients were referred to our departement for adrenal incidentaloma, 2 for recent and resistant hypertension and 1 for hypokaliema. Medical examination revealed high blood pressure in one patient and cushing manifestation in one patient. No neuromuscular signs nor paroxysmal seizures were noted. Laboratory finding revealed hypercortisolism in all patients associated to hyperaldosteronism in 4 cases and catacholamine excess in one case. Adrenalectomy was performed to all patients without incidents. Histopathological study revealed 1 case of corticomedullary adenoma, 3 cases of mixed adrenocortical adenoma and one case of myelolipoma associated with mixed adrenocortical adenoma. After a follow up of 7 years, patient with corticomedullary adenoma showed multiple cardiovascular incidents. These incidents were myocardial infarction, ischemic stroke and peripheral arterial occlusive disease. An Uncontrolled diabetes was also noted during her monitoring. In the other patients with co-secetion cortisol and aldosterone, 3 patients had steady evolution after 1.5 years of follow up. However, one patient developed contralateral adrenal adenoma.
Conclusion
Mixed adrenal adenoma are rare. The clinical suspicion of cortisol co-secretion by an APA and corticomedullary adenoma can be confirmed bay hormones tests. In addition, a more detailed histological and molecular work-up of such lesions may inform us on additional ways of development of adrenal autonomy.

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EP11

A 14 cm nonfunctioning left adrenocortical carcinoma in an adult man: a case report

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Background
Adrenocortical carcinoma is a rare endocrine malignancy, with an unfavorable prognosis. Radical adrenalectomy is the gold standard for localized disease.
Case presentation
We report a case of a 47-year-old male with left abdominal pain and sensation of discomfort. Our patient didn't present classical tumor symptoms, such as cachexia or night sweats. Computed tomography revealed a left heterogeneous retroperitoneal enhancing adrenal mass measuring 17 cm, with high density (30 Hounsfield units), smooth margins, and a wash-out <60%. Hormonal evaluation was negative, with normal ACTH and cortisol level. Suppression test was negative. Measurement of plasma renin activity and serum aldosterone levels showed no abnormalities. Plasmatic metanephrine and normetanephrine was also normal, excluding a pheochromocytoma. Open left adrenalectomy was performed by sub-costal approach. Pathology confirmed the diagnosis of adrenocortical carcinoma with positive microscopic surgical margins. Metastatic workup was negative. This case was discussed at a tumor board meeting. Adjuvant treatment by mitotane was not recommended. The patient has undergone a regular follow-up and has been disease-free for 6 months.
Conclusion
Adrenocortical carcinoma is a diagnosis challenge. Surgery remains the main treatment. A multidisciplinary management should be offered in those cases.

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EP12

Clinical, imaging and laboratory features of patients with adrenal incidentaloma referred to a tertiary medical center in recent years and a comparison with a historical institutional cohort

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Background
The term adrenal incidentaloma (AI) refers to the existence of an asymptomatic adrenal mass that was detected at random in an imaging test performed not in order to evaluate the adrenal glands. In recent years, the use of imaging tests has increased, and the resolution of the imaging studies has been improved. This trend may affect the characteristics of AIs at the time of diagnosis.
Objective
Investigating the demographic, clinical, imaging and laboratory characteristics of patients with AI who were referred to the Endocrine Institute at the Rabin Medical Center in the recent years and comparing the findings with data collected from consecutive patients referred to the same institute between 1995 and 2005.
Research Methods
The research was conducted at the Endocrine Institute at Rabin Medical Center. The study's design is retrospective-comparative. Demographic, clinical, imaging and laboratory features of 191 consecutive patients who were referred to the Endocrine Institute with AI over the years 2005–2016 years were retrieved from the computerized files, analyzed and compared with 100 patients referred for investigation between 1995 and 2005.
Results
The patients' average age at diagnosis was 61.6 (median 62), and female patients constituted 62.3% of the cohort (119/191). The average size of the mass at presentation was 23 ± 12.2 mm (mean 20). Most patients (169/191, 88.5%) underwent an additional imaging test during a follow-up of 4.5 ± 3.3 years. In 52 patients (27.2%), a change in the diameter of the mass at the end of the follow-up period was reported. The Incidence of left AIs was higher more than twice than right adrenal masses (59.1% vs. 28.3%) and bilateral masses were demonstrated in 12.5%. The rate of functional tumors was 14.6% and most of them (25/28, 89%) were cortisol-secreting. A known diagnosis of a malignancy at time of the detection of AI was present in 29.3% of the patients, diabetes in 35.6%, hypertension in 59.1% and obesity in 30.9%. Adrenalectomy was performed in 17 patients (8.9%) of whom a primary adrenal malignancy was diagnosed in two. In comparison to the results from the previous study on patients diagnosed with AI during the years 1995–2005, we did not find differences in the age of the patients and their underlying conditions or the characteristics of the adrenal mass.
Conclusion
The clinical features of patients diagnosed with AI and the imaging characteristics of the adrenal mass have not been changed significantly in recent years.

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EP13

Pheochromocytoma in pregnancy: the need for a multidisciplinary approach

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Introduction
Pheochromocytoma(PHEO) occurs in pregnancy with an estimated incidence of 0.007%. Its rarity and overlapping presentation with other pregnancy-related hypertensive disorders make the diagnosis really challenging. If left unrecognized, may result in increased maternal and fetal mortality. There are no guidelines on approaching PHEO during pregnancy. This case highlights the difficulties encountered in managing this condition in pregnancy.

Clinical case
A 33-year-old previously healthy female(G3P2) with clinical features of pulsatile headache and palpitations triggered by physical efforts, without hypertension, starting 4 months before conception, treated with antidepressants. She had a gestational diabetes *mellitus* history since the 11th week of gestation (WG) which was managed with diet and metformin. Until the 2nd trimester of pregnancy she was normotensive, however, her headaches worsened at 24thWG and related hypertensive peaks were reported (180/100 mmHg) from this time. Methyldopa was initiated at a starting dose of 250 mg, twice daily with a necessary increase to three times daily. Nevertheless, the clinical picture's worsening prompted further investigation at 36thWG. Laboratory data revealed elevated plasma metanephrine of 201 pg/m(<65) and normetanephrine of 1735 pg/ml (<196); elevated total urinary metanephrine of 10 605 µg/24 h(<785). MRI showed a right adrenal solid mass of 4.6×5.5 cm. She was admitted to the hospital and treated with phenoxybenzamine (increasing doses, 20 mg/day) followed by propranolol(40 mg/day) and nifedipine(10 mg, SOS). Methyldopa was suspended. Maternal dyspnea, chest pain, orthostatic hypotension accompanied by fetal distress emerged. On the sixth day of adrenergic blockade, at 38thWG, she went into spontaneous labour. A multidisciplinary decision (Endocrinology, Internal Medicine, Obstetrics, Anaesthesia, Surgery and Neonatology) was made to perform a caesarean section. Hypertensive peak (220/120 mmHg) was controlled with boluses of IV isosorbide-dinitrate. The newborn had an Apgar score of 10/10 (1`/5`) and was transferred to the intensive care unit (ICU) for surveillance. He was discharged 3 days after birth, without complications. Twenty days after delivery, the patient underwent an uncomplicated laparoscopic adrenalectomy. In the postoperative period she remained in the ICU for 11 days due to difficult to manage hypertensive peaks. Histopathology examination confirmed PHEO.
Conclusions
PHEO should be considered in pregnant patients presenting atypical/resistant hypertension despite treatment. Moreover, methyldopa may cause false high values in urine metanephrine levels, hampering the diagnosis. There are few reports in literature describing the antepartum difficulties in the management of these patients. We emphasize hypotension, decisions concerning timing/method of delivery and the appropriate surgical timing. A multidisciplinary team's commitment is of utmost importance.

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EP14

Severe adrenal hemorrhage in a hypertensive patient, with high plasma aldosterone and metanephrines

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Introduction
Severe hemorrhage is a rare and potentially lethal manifestation of adrenal gland nor usually associated with primary aldosteronism.
Material and methods
Review of the patient's clinical record and of the relevant literature.
Case report
A 47-year-old male with personal history of asthma, untreated stage II hypertension, obesity, dysphagia associated with diffuse esophageal spasm and head trauma with subdural hematoma (several years ago) came to the Emergency Room of our Hospital with sudden periumbilical pain radiating to the left renal fossa, after a strenuous exercise. He showed malaise, peripheral hypoperfusion, diaphoresis and high blood pressure. His renal function was previously normal but plasma creatinine in the ER was 1.6 mg/dl and the estimated glomerular filtration rate was 46.5 ml/min/1.73 m^2. The abdominal CT scan revealed a large (8 × 12 × 19 cm) retroperitoneal hematoma apparently flowing from the left adrenal which showed active bleeding, with a possible underlying lesion. The patient suffered anemization requiring successive blood transfusions plus continuous perfusion with solinitrine and urapidil to control blood pressure. The physical examination showed the persistence of high blood pressure and a painful left hemiabdomen with a rigid left flank. In the context of hemorrhagic shock, the lab tests showed: plasma aldosterone 657 pg/ml (PRA not available), potassium 3.48 mEq/l, metanephrine 165 pg/ml and normetanephrine 619 pg/ml. After hemodynamic stabilization aldosterone was 130 pg/ml, PRA 0.4 ng/ml/min and ARR 32.5; metanephrine 26 pg/ml and normetanephrine 76 pg/ml, with normal ionogram, TSH 4.18 µUI/ml and cortisol 16 µg/dl. A PET-CT scan ruled out adrenal malignancy. The patient developed hypertensive encephalopathy with hypertensive retinopathy, and persistence of the renal insufficiency associated to nephroangiosclerosis. He is presently being treated with carvedilol, doxazosin and amlodipine, with acceptable blood pressure control. A follow-up abdominal MRI showed partial persistence of the hematoma, and absence of an underlying adrenal lesion. Primary aldosteronism has not been ruled out, and a confirmation test after carvedilol withdrawal is scheduled.
Conclusion
Adrenal hemorrhage is infrequent, and has not usually been reported as a complication of primary aldosteronism. The rapid normalization of the plasma aldosterone and metanephrines after haemodynamic stabilization is also noteworthy, and reminds us that the diagnostic workup of primary aldosteronism and pheochromocytoma/paraganglioma must wait until the patient is stable.

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EP15

Hiding in plain sight – a case of adrenal Cushing

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Bariatric surgery is increasingly deployed world-wide in patients with significant weight excess in order to mitigate the deleterious effects of associated metabolic and cardiovascular comorbidities. Pre-operative evaluation systematically investigates for possible causes of secondary obesity due to endocrine pathologies. In our hospital a standard blood test panel comprising the anterior hypophysis, the adrenal and the thyroid is requested as well as an endocrinological evaluation thereafter. We report the case of a 39-year old male patient with morbid obesity and relatively new-onset diabetes and hypertension. At the time of presentation (October 2020), he weighed 128 kg at a height of 173 cm, BMI 42.7 kg/m^2. The patient reported a weight gain of 37 kg during first half of 2020. The same year he was diagnosed with hypertension and a worsening of his diabetes. The hormonal profile revealed a cortisol in the normal range (212 nmol/l), a suppressed ACTH (1.7 ng/l), all other hormonal axes were in the normal range. A redo analysis confirmed the initial findings and at that moment the patient remembered being investigated several years ago for an adrenal mass, with unclear hormonal profile at the time but labelled as incidentaloma, hence probably hormonally inactive. An abdominal CT-scan in December 2020 demonstrated a mass in the left adrenal gland. Furthermore, both the low dose and the high dose dexamethasone suppression test showed no effect on the morning cortisol level (311 nmol/l and 375 nmol/l, respectively). A diagnosis of adrenal Cushing was established and the patient was referred for surgery. The mass was laparoscopically removed and the histological examination demonstrated a benign adenoma. Post-surgery a substitutive therapy with hydrocortisone adapted for the weight was instituted and an endocrinological follow-up was organized. No data concerning the weight curve at the time of writing this abstract was available. The current case emphasizes the importance of screening all candidates for weight-loss surgery for endocrinological cases of obesity as the therapeutic approach radically changes and missing a curable endocrinological cause may complicates the evolution post-surgery and hinders the results in terms of weight loss. The particularity of this case is the fact that the existence of the adrenal mass was already known but somehow flew under the radar all the while the predisposition to progress to a secretory state is well described in the medical literature.

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EP16

Functional retroperitoneal paragangliomas: a case report

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Introduction
Paragangliomas (PGs) are rare tumors arising from sympathetic and para-sympathetic paraganglia with an incidence of 15–20%. We report a case of a pre-operative diagnosis of retroperitoneal PGs evoked on anatomic imaging confirmed by biochemical evaluation.

Observation
A 55-year-old female was referred to the endocrinology department for investigation of a paroxistic hypertension. For her personal medical history, she had a 15-year history of hypertension with hypertrophic obstructive cardiomyopathy (HCM). She was treated with calcium channel blockers, and angiotensin 2 receptor blockers but her hypertension was never controlled. She was receiving high doses of propranolol for her HCM. An abdominal computed tomographic (CT) scan done 3 years ago for abdominal pain revealed retroperitoneal mass; lymphoma was suspected and a biopsy was indicated but the patient was lost to follow-up. There was no significant family history. The patient complained of paroxysms of headache, sweating and palpitations associated with abdominal pain for over 15 years. On examination, she had a blood pressure of 220/120 mmHg with orthostatic hypotension. 24-h blood pressure measurement has confirmed the presence of paroxism up to 270/140 mmHg. Biochemical testing revealed an elevated plasma normetanephrines with normal metanephrines level. The abdominal CT examination revealed two left hypervascular retroperitoneal masses (43 mm and 65 mm) with left adrenal gland and abdominal aorta contact, consistent with PGs. MIBG scintigraphy revealed an uptake in the retroperitoneal space corresponding to the location of the masses. On the basis of all findings, the diagnosis of functional retroperitoneal non-metastatic PGs is made. Surgery is postponed after septal alcoholization for HCM.
Conclusion
Our case highlights the importance of including extra-adrenal PGs in the differential diagnosis of retroperitoneal tumors, despite their rarity. Definitive diagnosis requires a histopathological assessment and genetic testing as PGs were detected before the age of 50 years.

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EP17

Biopsy in the diagnosis of bilateral pheochromocytoma

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Pheochromocytoma is a rare neuroendocrine tumour usually formed in the adrenal medulla. Percutaneous biopsy has been associated with life-threatening haemorrhage, hypertensive crisis, capsular disruption with tumour implantation and death. We present a case of a 63 years old woman with non-specific clinical signs which included high blood pressure, headache, tachycardia and abdominal pain. She was treated for rheumatoid arthritis. Bilateral expansion of adrenal gland with delayed wash-out, on the right site 45 × 20 × 40 mm with cystic necrosis and 25 mm on the left site. In the liver there were unclear foci, not typical for a cyst or haemangioma. The radiological diagnosis was not clear. Therefore for fear of malignancy percutaneous biopsy under ultrasonic control was performed before the knowledge of metanephrine levels. Plasma metanephrines were available later. The level of metanephrine level was 0.45 nmol/l (normal range 0.06–0.31) and of normetanephrine was 4.64 nmol/l (normal range 0.1–0.61), respectively. Other screening tests done to exclude the other tumours that are connected to the inherited syndrome were negative. No mutation in RET proto-oncogene was found. Bilateral laparoscopic adrenalectomy was performed after pre-treatment with alpha-1 blocker Doxazosin. In this case, fortunately, complications related to the biopsy of pheochromocytoma did not occur. However, tumours suspected to be a pheochromocytoma or paraganglioma should not have a biopsy, unless it is absolutely necessary to confirm a diagnosis.

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EP18

Clinical and endocrinological characteristics of adrenal incidentaloma in Algiers Center

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Adrenal incidentaloma (AI) is an adrenal mass discovered accidentally during abdominal or chest imaging techniques not aimed to adrenal gland assessment. Guidelines suggested confirming the benignity of AI radiologically and excluding hormonal dysfunctions. This study was designed to evaluate the clinical, endocrinological and histological characteristics of adrenal incidentalomas (AI).
Methods
Retrospective study of patient addressed to the endocrinology department at Algiers Hospital (Bologhine) for assessment of an incidentaloma from 2014 to 2018. In all, sixty patients were followed, involving 45 females and 15 males.
Results
Means age of population is 52 ± 30 years. Endocrinological evaluations demonstrated that 45% of total AI were non-functioning adenomas, 18% are cortisol production adenoma, including 13% with subclinical Cushing's syndrome. 15% as pheochromocytomas, and 1.66% as aldosterone-producing adenomas. The mean nodule size of AI based on computed tomography was 3.7 cm. 60% of the nodules are size under 4 cm, 11% size between 4 and 6 cm, and 28% upper 6 cm. it is noted that 88% of pheochromocytomas and 100% of adrenal carcinoma have a size of more than 4 cm. When to Compared to non-functioning adenomas (NFAs), tumor diameters were significantly larger in adrenocortical carcinomas (ACCs), pheochromocytomas, cortisol-producing adenomas (CPAs), myelolipomas, cysts,($P < 0.01$).
Conclusion
The occurrence of incidentally discovered adrenocortical carcinomas and pheochromocytomas is not rare. These data shows that an endocrine evaluation should be performed in all adrenal incidentalomas and Evaluation of the mass size and CT characteristics are asimple and effective methods to differentiate malignant lesions.

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EP19

Correction of androgen deficiency in a woman with primary adrenal insufficiency. Clinical case

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Introduction
There is no consensus about the necessity of dehydroepiandrosterone (DHEA) replacement in women with adrenal insufficiency (AI).
Methods
The woman aged 44 with medical compensation of autoimmune 1-AI, 1-hypogonadism, osteoporosis took DHEA (tablets of 50 mg in every morning) during 4 months. Concomitant therapy: hydrocortisone, fludrocortisone, drospirenone+estradiol, colecalciferol, calcium carbonate.
Results

	Units	Baseline	Day		Month	
			1st	14th	4	7 (3 months after the end of therapy)
DHEA-S	µmol/l	0.003	5.04	5.72	5.74	0.003
SHBG	nmol/l	102.5	–		108.1	102.2
Total testosterone		0.17			0.975	0.17
Free testosterone	pmol/l	1.6			7.7	1.6
Estradiol		415.7			396.57	423.6
Osteocalcin	ng/ml	26.18			21.18	18.29
β-Cross laps		0.64			0.33	0.36
Colecalciferol		24.3			28.3	22.6
AMH		1.10			1.17	1.48
Inhibin B	pg/ml	59			52	60.7
LH	U/l	27.6			14.4	23.9
FSH		31.5			15.6	32.3
Glucose	mmol/l	4.64			4.04	4.34
Cholesterol		5.68			5.03	5.06
Insulin	µU/ml	4.18			6.51	5.3

HbA1c	%	5.5		5.5	5.8
Hair growth –axillary –pubic (Tanner scale)		 No V		 Yes V	 No V
Ultrasound of the pelvic, mammary glands		*n*		*n*	
Cytological examination of smears					
Side effects		–		Slight greasiness of the face	
Golombok-Rust Inventory of Sexual Satisfaction-Female					
Frequency		5	–	5	
Incommunicability		2		3	2
Dissatisfaction		4			4
Avoidance		2		0	
Anorgasmia		3			
Vaginismus		0			
Touch				4	0
Hospital Anxiety and Depression Scale					
Anxiety		7	–	4	6
Depression		3		2	1
Symptom checklist-90-revised					
Somatization		0.75	–	0.5	0.67
Obsessive-Compulsive		0.5		0.8	0.8
Interpersonal Sensitivity		0.11		0.22	0.11
Depression		0.31		0.23	0.31
Anxiety		0.5		0.3	0.4
Hostility		0.33		0.17	0.5
Phobic Anxiety		0		0	
Paranoid Ideation					
Psychoticism					
Positive Symptom Total		28		26	27
Global Severity Index		0.32		0.29	0.34
Positive Symptom Distress Index		1.04		1.00	1.15
SF-36 health status survey					
Physical health		43.33	–	51.24	46.42
Physical Functioning		70		80	70
Role-Physical Functioning		0		50	
Bodily pain		100		100	
General Health		52		70	47
Mental health		45.93		51.93	45.22
Vitality		55		60	
Social Functioning		75		75	62.5
Role-Emotional		100		100	66.67
Mental Health		52		76	68
Wechsler Memory Scale					
Visual Reproduction		7	–	10	6
Paired Associates		12		15	14
Digits –forward –backward		 6 5		 6 5	 7 4

Conclusion
DHEA-S reached normal values within a day after taking the drug. A positive effect on the quality of life, mood, sexual function, some types of memory, bone metabolism was found. An inverse negative relationship between DHEA-S and gonadotropins is assumed. No significant side effects were observed.

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EP20

Aldosterone antagonist responsive hypokalaemia, hypercortisolism and colonic pseudo-obstruction

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Hypokalemia is a common and potentially fatal electrolyte disturbance, especially in hospitalised patients. Therefore, prompt assessment and management is vital to avoid serious complications. We report a case of 77 Year old gentleman with a background of Alzheimer's presenting with abdominal distension, intermittent diarrhoea and shortness of breath. He had normal blood pressure with no signs of Cushing syndrome but was found to have hypokalaemia. Plain imaging revealed dilated markedly distended bowel loops. CT pulmonary angiogram found bilateral pulmonary embolism, which was treated with apixaban. CT imaging also revealed colonic pseudo-obstruction and fat rich left adrenal nodule. Due to Type 1 respiratory failure, he required three days of intubation and ventilation. Hypokalaemia worsened requiring intravenous potassium replacement. His breathing and diarrhoea improved, but he had persistent hypokalaemia despite oral and intravenous potassium replacement. Flexi-sigmoidoscopy and partial thickness colonic biopsy was unremarkable. He was deemed unfit for colectomy due to his comorbidities. Endocrine biochemistry revealed raised 24 h urinary cortisol, non-suppressed cortisol after overnight dexamethasone suppression test and low renin and aldosterone. He had inappropriately normal 24 h urinary potassium, normal serum bicarbonate and magnesium. Addition of spironolactone and eplerenone normalised potassium levels. He has clinically improved and further testing is being performed to establish an endocrine diagnosis. The cause of hypokalemia in this case is unclear. The differentials include gastrointestinal or renal loss and the latter could be due to possible hypercortisolism. Irrespective of the cause, clinicians should consider treating hypokalaemia before a cause could be established in situations where hypokalaemia could be contributing to a potentially life threatening condition. It is also important to emphasize that patients have physiological hypercortisolism during periods of illness and hence endocrine testing must be repeated when the stress of illness is over.

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EP21

Recurrence of ACTH-secreting bronchial carcinoid: a therapeutic challenge

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A man presented at age 32 with clinical features of Cushing's syndrome and biochemical investigations were consistent with ectopic ACTH. The only potential source on imaging was a 5 mm right lung nodule on chest CT but which was too small to biopsy. Medical therapy was not successful at controlling his Cushing's features so he was referred for thoracotomy. Following lobectomy, the lung nodule was found to be a carcinoid tumour. Post operatively, the patient's symptoms improved. He remained well for many years. 11 years later he represented with similar symptoms and recurrence of ACTH-dependent Cushing's syndrome was confirmed. A CT thorax, abdomen and pelvis revealed no abnormality but an octreotide scan suggested recurrence of disease a right infrahilar lymph node. He underwent lobectomy with lymphadenectomy for recurrent typical carcinoid in his mediastinal glands. Postoperatively, his symptoms improved. To date he has not shown any signs of recurrence and is doing very well. This case highlights the major diagnostic and therapeutic challenges associated with ectopic ACTH-secreting lesions. In addition, it points out the importance of long-term follow-up even after surgical resection and apparent cure of this condition.

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Calcium and Bone

EP22

Deficiency or insufficiency of vitamin D and the frequency of hypocalcemia episodes and the circadian rhythm of serum calcium level

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Introduction
Vitamin D deficiency is considered as a major public health concern. Due to vitamin D's crucial role in the intestinal calcium absorption, its deficiency may result in hypocalcemia and in a spectrum of associated clinical manifestations.
Aim
To assess the effect of 25(OH) vitamin D level (25(OH)D) on the frequency of hypocalcemia episodes and the daily profile of serum calcium and 24-h urinary calcium levels.
Methods
The interventional, prospective, comparative study of 10 healthy volunteers (women/men – 9/1) was performed. We have analyzed the daily profiles of serum calcium (total (Ca_{total}) and albumin-corrected calcium (Ca_{corr})) and 24-h urinary Ca levels. The descriptive statistics are represented by medians and the first and third quartiles in Me (Q1; Q3) and by absolute and relative frequencies.
Results
Episodes of hypocalcemia were registered in patients with low vitamin D levels: in 3.33% for Ca_{total} and in 5.8% for Ca_{corr}. No clinical symptoms was observed. The frequency of hypocalcemia decreased to 0% for Ca_{total} and to 2.5% for Ca_{corr} after vitamin D supplementation, while we did not detect any difference in Me serum Ca and 24-h urinary Ca levels. However, the summary number of reference calcium values increased as 25(OH)D level was reached more than 30 ng/ml: from 90.8 to 100% for Ca_{total} and from 94.2 to 97.5% for Ca_{corr}. Analysis of Ca_{total} and Ca_{corr} deviations during the day showed a less variability of the calcium profile after vitamin D treatment. This study also revealed circadian character of daily serum calcium profile with the presence of maximum (0940–1740) and minimum (2340–0740) values during the day.
Conclusion
Target 25(OH)D levels more than 30 ng/ml are needed for effective calcium absorption. We confirmed the decreased frequency of hypocalcemia and the less variability of serum calcium levels during the day, as well as an increased number of reference calcium values after vitamin D supplementation.

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EP23

Severe hypercalcemia due to vitamin D intoxication in patients with chronic hypoparathyroidism: Five cases report

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Introduction
Current standard treatment of primary hypoparathyroidism is based on calcium and activated vitamin D supplementation. Iatrogenic severe hypercalcemia due to vitamin D intoxication is an uncommon complication rarely described in literature. Herein we report 5 cases of severe hypercalcemia secondary to vitamin D intoxication.
Observations
Three men and two women with chronic hypoparathyroidism were included in this study. Their mean age was 56 years with extremes of 18 and 76 years. All patients were admitted in our department for a severe hypercalcemia secondary to vitamin D intoxication. Calcium bicarbonate was prescribed at the dose of 1500 mg per day in all of them. One patient was overdosed in active vitamin D, while the other patients presented dosing error in this drug. Four patients had abdominal pain and asthenia. However, one patient had confusion and agitation. The five patients had dehydration signs with acute renal failure. Electrical changes of hypercalcemia were present in three of them. The mean calcium level was 156 mg/l with extremes of 130 and 182 mg/l. Hemodialysis was indicated in one patient who had neurological symptoms. His calcium level decreased from 182 mg/l to 134 mg/l. All of patients received normal saline rehydration with a duration of 2–3 days and an infusion of 3 l/24 h. The mean of calcemia declined from 147 mg/l to 113 mg/l and reached normal levels in three patients after rehydration. Intravenous corticosteroids were prescribed in two patients and helped to normalize calcium level. Bisphosphonates were not prescribed in any patient.
Conclusion
Iatrogenic hypercalcemia due to vitamin D intoxication can present a life-threatening condition indicating urgent and appropriate management. Intravenous saline rehydration, intravenous corticosteroids and eventually hemodialysis should be considered in this situation. Furthermore, education of patients with chronic hypoparathyroidism on their doses of vitamin D as well as symptoms of hypercalcemia is the cornerstone of severe hypercalcemia prevention.

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EP24

Primary Hyperparathyroidism with SVT and hypertensive crises; to proceed or not to proceed with surgery?

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57 year old lady was admitted in hospital with hypertensive urgency (BP 205/107 mmHg) as first presentation of hypertension. There was no other past medical history. During admission, her BP was controlled over 24 h with combination therapy of amlodipine (10 mg OD) and doxazocin (2 mg OD). Routine blood tests revealed raised serum calcium (levels) and PTH (levels) consistent with diagnosis of primary hyperparathyroidism (PHPTH). Her hypercalcaemia was treated with IV fluids and IV pamidronate infusion. All subsequent investigations confirmed the final diagnosis of primary hyperparathyroidism (Corrected Calcium=2.97 mmol/l, PTH=30 pmol/l, urinary calcium=4.39 mmol/l, Vitamin D=55 nmol/l). Parathyroid imaging (US parathyroid and SESTAMIBI) revealed bilateral parathyroid adenomas. Whilst awaiting elective parathyroidectomy she required she had another hospital admission with supraventricular tachycardia (SVT). ECG revealed sinus tachycardia (heart rate 142 bpm) which resolved without use of rate control medical therapy after a period of observation, use of vagal manoeuvres and IV fluids. Due to two admissions with hypertensive urgency, supraventricular tachyarrhythmia (SVT) and multiple glandular parathyroid adenomas, a possibility of underlying genetic cause for PHPTH was raised. One of the worries with episodic tachyarrhythmia and hypertensive crises is possibility of pheochromocytoma associated with multiple endocrine neoplasia (MEN). There was no family history of note but for perioperative safety she was screened for pheochromocytoma. Multiple screening tests for pheochromocytoma were reported as borderline positive with the conclusion of inability to exclude pheochromocytoma.

Plasma metanephrine (results)		
Plasma Metadrenaline	**656** pmol/l	(80–510)
Plasma Normetadrenaline	**2582** pmol/l	(120–1180)
Plasma 3-methoxytyramine	<120 pmol/l	(<120)
Urinary metanephrine:		
Normetanephrine	**4.56** umol/day	(<3.7)
Metanephrine	**1.55** umol/day	(<1.3)
24 h Urine 3-methoxytyramine	0.82 umol/day	(<2.6)
30 min supine plasma metanephrine		
Plasma Metadrenaline	375 pmol/l	(80–510)
Plasma Normetadrenaline	**2100** pmol/l	(120–1180)
Plasma 3-methoxytyramine	<120 pmol/l	< 120

A pituitary hormonal profile and MRI pituitary was requested revealing eupituitary hormonal status with an incidental finding of 4 mm microadenoma. The case was discussed in local MDT and the outcome was to continue conservative management of PHPTH with cinacalcet until pheochromocytoma has been ruled out completely. Both MEN-1 and MEN-2 are associated with PHPTH. If a patient is having episodic adrenergic crises with inconclusive metanephrines analysis then excluding pheochromocytoma is important for perioperative safety. This case highlights the diagnostic work up in such cases.

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EP25

Fahr's syndrome secondary to hypoparathyroidism revealed by generalized pustulosis (about 2 cases)

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Introduction
Amicrobial skin pustulosis is one of the exceptional manifestations of hypoparathyroidism. We report 2 observations of a Fahr syndrome secondary to hypoparathyroidism revealed by generalized pustulosis.
Observations 1
24 year old woman, with no history of thyroid surgery, The patient was admitted for generalized covering more than 90% of the body surface. Biology objected to hypocalcemia at 57 mg/l, hyperphosphatemia at 66 mg/l and parathyroid hormone at 2.9 pg/ml. Fahr's syndrome was confirmed on a brain tomodensitometry conveyed bilateral calcifications of the central gray nucleus. The ophthalmologic examination revealed a bilateral posterior subcapsular cataract.
Observations 2
A 47-year-old woman, without the notion of thyroidectomy. The patient was admitted for a diffuse pustular rash. Biology objected : hypocalcemia at 39 mg/l, hyperphosphatemia at 69 mg/l and parathyroid hormone at 3 pg/ml. The brain tomodensitometry conveyed bilateral calcifications of the central gray nucleus. The diagnosis of Fahr syndrome on hypoparathyroidism was retained. The two patients were treated with intravenous calcium 8 g/d and with alfacacidol 3 µg/d magnesium 600 mg/d orally. The evolution of the 2 patients was marked by the disappearance of more than 95% of the lesions, concomitant with the correction of calcium levels.
Conclusion
The dermatological expression of Fahr syndrome secondary to hypoparathyroidism has been rarely reported in the literature, which should be considered in the presence of any skin pustulosis.

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EP26

Challenges in diagnosis and treatment of Parathyroid Carcinoma – case report

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Introduction
Parathyroid carcinoma (CaPa) is an extremely rare cause of primary hyperparathyroidism. Patients with CaPa usually present severe hypercalcemia with abrupt bone and renal diseases, neurologic manifestations and gastrointestinal symptoms. However, sometimes the presentation is insidious with nonspecific symptoms and mild hypercalcemia. Surgery is the only curative treatment and after surgery close monitoring of calcium levels are necessary due to high risk of severe hypocalcemia by 'hungry bone syndrome'. Progressive disease is common with local recurrence and distant metastases.
Case Report
A 63-year-old woman with nonspecific bone pain for 7 years and progressive serum calcium elevation went to the hospital with an acute back pain without any sings of traumatic injury. Personal and family history was unremarkable. Laboratory investigations showed serum total calcium level of 4.24 mmol/l (NR 2.2–2.5 mmol/l), parathormone levels (PTH) 1387 pg/ml (NR 15–68.3 pg/ml), phosphate 0.51 mmol/l (NR 0.81–1.55 mmol/l), magnesium 0.61 mmol/l (NR 0.66–1.07 mmol/l), 25-hydroxyvitamin D 25 ng/ml (n>29). Ultrasonography of the neck showed a nodular lesion, with 25 mm at the lower pole of the left thyroid lobe with Tc-99m sestamibi scintigraphy confirming increased uptake in the same location. Genetic tests were negative for MEN1 and HRPT2/CDC73. She underwent surgical resection. The histologic examination confirmed the diagnosis of parathyroid carcinoma with capsular invasion and thyroid tissue involvement. Despite the efforts to prevent 'hungry bone syndrome', a severe hypocalcaemia was observed in the immediate postoperative period indicating the need to prolong medical treatment. Three months after surgery there was evidence of local recurrence and left thyroid lobectomy was completed. New local recurrence was observed two years after, and the patient underwent resection of the lesion. However, a progressive increase in PTH and calcium levels were observed six months after the last surgery, despite imaging investigations not revealing any evidence of residual or metastatic disease. It was decided to keep the patient under surveillance, as the patient is asymptomatic under calcimimetic therapy (cinacalcet 90 mg), with stabilization of the serum total calcium level.
Conclusion
Parathyroid carcinoma is an extremely rare tumour with challenges in diagnosis and treatment that are often difficult. All these are associated with delayed diagnosis, ineffective treatments, and consequently with poor prognosis. In the presence of hypercalcemia and elevated PTH level, parathyroid carcinoma, although a rare condition, should be considered.

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EP27

Surgical difficulties during parathyroid surgery

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Introduction
Parathyroid surgery is indicated essentially in primary and secondary hyperparathyroidism. This surgery may present some difficulties even in experienced hands. Our aim is to describe the difficulties that can occur during parathyroid surgery.
Material and methods
A retrospective study including 81 cases of hyperparathyroidism, operated between 2001 and 2018.
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 done in these 5 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 oesophagus (1 case).
Conclusion
Preoperative imaging has an important role in the guidance of the surgical procedure. Nevertheless, a good knowledge of the surgical anatomy of the parathyroid and thyroid glands is essential to overcome the difficulties that can occur during parathyroid surgery.

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EP28

Giant maxillary tumor as initial presentation of primary hyperparathyroidism: a case report

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Case
Male, 44 y.o., with rigth maxillary tumor of progressive growth for 1 year with local and low back pain. Imaging exams: CT/MRI skull and face: right axial expansive lesion (62×52×46 mm), heterogeneous, multiloculated with bulging of the right orbit inferomedial wall, with a neoplastic aspect. CT pelvis: bone lesions with soft tissue densities in pelvis, heterogeneous L4, with height reduction. Biopsy of the lesion suggesting a brown tumor. Investigation continued with PTH: 998 pg/ml and calcium: 10.4 mg/dl (8.5–10.5 mg/dl), scintigraphy: parathyroid-hyperfunctioning left lower parathyroid and bone-hypercapture, with emphasis on the skull, right scapula, some costal arches, T8, L4, sacroiliac regions, iliac crystals, left pubic branch, left ischium, trochanter of the right femur, proximal third of the left tibia and medial and malleoli right side, DXA Z-score RD -8.0DP. The patient was admitted with severe hypercalcemia (calcium: 14.6 mg/dl), phosphorus 2.4 mgdl, without neurological symptoms. Parathyroidectomy was performed with histological result of adenoma and a significant reduction in PTH levels (29.9 pg/ml) in the immediate postoperative period. In the

6 months of follow-up, he has normalization of calcemia and PTH, significant pain improvement, and gradual reduction of the tumor.
Discussion
Brown tumor appears in hyperparathyroidism, due to the action of PTH, leading to a replacement of bone tissue by dense connective tissue well vascularized, with fusiform and giant cells, areas of hemorrhage with a large amount of hemosiderin pigments and bone trabeculae, forming a very demineralized and fragile area, with a higher risk of fracture. In the initial evaluation of a lesion suggestive of a brown tumor, it is essential to measure the levels of calcium and PTH. Majority of cases of HPT are caused by adenomas (80 to 85%) and the minority due to hyperplasia of the four glands (15%), with 2 to 4% of multiple adenomas and less than 0.5% caused by carcinoma. Differentiation of adenoma and carcinoma by histological/immunohistochemical study takes into account degree of lesion invasion, number of mitoses, trabecular pattern and evaluation of a panel of markers (parafibromine, galactin-3, PGP9.5 and Ki67).
Final comments
It is necessary to emphasize the importance of screening methods and early diagnosis of a systemic disease such as hyperparathyroidism, which can evolve with serious complications, increasing morbidity and mortality.

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EP29

Atypical parathyroid adenoma : a case report

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Introduction
The atypical parathyroid adenoma is a histological diagnosis. It is a parathyroid tumor with atypical histological features different from an adenoma and not similar enough to be considered as a carcinoma.It has an uncertain malignant potential.
Observation
We report the case of a 55 year-old woman, referred to us by her rhumatologist after discovering a severe hypercalcemia when exploring her for osteoporosis. The biology found a high level of calcium 3.68 mmol/l, and a very important level of parathormone PTH 1325.62 pg/ml (20 fold the normal level), confirming the diagnosis of primary hyperparathyroidism. The cervical ultra sound revealed a left hyperechoic, heterogeneous parathyroid mass, measuring 2.05 × 3.97 × 3.18 cm in diameter and a normal thyroid gland, and the Sestamibi-scintigraphy showed a large left inferior parathyroid adenoma. In front of this large mass, the severe hypercalcemia and the very high level of PTH, the malignancy was suspected and we completed the exploration by dosing two biomarkers of malignancy,the alkaline phosphatase (ALP) which was at 420 U/l (3 fold normal level) and the BHCG was high at 4.09 mUI/ml. Before referring the patient to surgery, she received an intravenous bipohosphonate therapy to control the hypercalcemia, then she underwent a parathyroidectomy and a lobo-isthmectomy with no post operative complications and the level of calcium normalized to 2.25 mmol/l and the PTH level dropped to 152 pg/ml. On the examination of the removed tissue, the histo-pathological exam concluded to an atypical parathyroid adenoma.
Conclusion
The atypical parathyroid adenoma is a very rare tumor, and the diagnosis is still a challenge, the outcome of patients is not well known yet, there for the surveillance is important and must be regularly.

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EP30

Sporadic multiple parathyroid gland disease in young woman with primary hyperparathyroidism

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Background
Most cases of primary hyperparathyroidism (PHPT) is caused by a single benign adenoma, multiple parathyroid neoplasms (MPN) occur less often in 10–15%, parathyroid carcinoma accounts for <3%. MPN can be sporadic or develop due to inherited genetic syndromes (most commonly multiple endocrine neoplasia syndrome type 1 (MEN-1) that usually manifest at a young age. The preoperative examination of patients with MPN is important for achieving acceptable cure rates.
Aim
To describe the young patient with severe sporadic PHPT and giant parathyroid neoplasms.
Clinical case
34-year old woman presented with tooth damage, permanent neck ache, pains in lower extremities and general weakness. She had an episode of renal colic and previous fracture of metatarsal bone. There were no other diseases and no family history of endocrinopathies. Lab tests revealed severe PHPT: albumin-adjusted calcium level 3.0 mmol/l (reference range 2.15–2.55), PTH 403.7 pg/ml (16–65), 24-h urinary calcium 11.0 mmol (2.5–8). Other estimated parameters were osteocalcin 100.9 ng/ml (11–43), b-CTx 1.31 ng/ml (0.01–0.69), GFR 120 ml/min/1.73 m^2. We detected a significant decrease in bone mineral density (BMD) in all areas, maximal in Radius (−4.9 s.d., *Z*-score). CT scans confirmed the osteitis fibrosa cystica, Th12-vertebral fracture, as well as bilateral nephrolithiasis. Ultrasound and SPECT/CT showed multiple tumors in right (6.6×4×16 mm) and both left parathyroid glands (27×22×59 mm and 15×12×39.3 mm). The tumor of the left lower parathyroid gland covered the carotid artery. Clinical data allowed to suspect MEN-1 or the parathyroid cancer. Diffusion-weighted MRI was additionally completed (ADC 1.6–1.7×10^{-3} mm^2/s). Genetic testing excluded *CDKN*, *CDC73*, *MEN1* mutations. The patient underwent the removal of three identified tumors. Morphological examination diagnosed benign adenoma of the both left and hyperplasia of the right parathyroid glands. Post-surgery hypocalcemia (serum calcium 1.67 mmol/l, PTH 57 pg/ml) and severe hungry bone syndrome were managed with alfacalcidol, calcium carbonate and cholecalciferol. The follow-up one year after surgery revealed increased PTH (80.25 pg/ml) with normocalcemia (2.4 mmol/l) and adequate 25(OH) D level, but 7-day stimulation test with alfacalcidol confirmed the PHPT persistence (serum calcium 2.57 mmol/l, PTH 113 pg/ml). The ultrasound showed the residual tissue between brachiocephalic and left carotid arteries (14 × 19 × 20 mm). Given the patient's refusal to reoperate and significant improvement of target organs, we decided to continue the active observation and cholecalciferol treatment.
Conclusion
MPN remains a quite difficult condition with high rate of recurrent or persistence PHPT. It requires extensive preoperative diagnostics and explorative surgery. The long-term follow-up is mandatory in such patients.

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EP31

Recurrent and persistent primary hyperparathyroidism due to secondary parathyromatosis

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Introduction
Parathyromatosis is a potential cause of recurrent hyperparathyroidism, of rare etiology, described as multiple nodules of hyperfunctioning benign parathyroid tissue, it constitutes less than 1% of the cases of recurrent hyperparathyroidism and since its description in 1975, less than 40 cases have been reported Worldwide. The presentation in primary hyperparathyroidism is extremely rare, with around 20 cases reported in the English literature. In the databases reviewed, no cases published in Cuba or in the rest of Latin America were found.
Case report
43-year-old female patient, with 18-years history of recurrent and persistent primary hyperparathyroidism due to secondary parathyromatosis that debuted with a brown cell tumor; currently with multiple spontaneous fractures, bone deformations and the onset of of stage II chronic kidney disease secondary to bilateral nephrolithiasis and moderate right hydronephrosis. Parathyroidectomy of 6 glands was performed prior to the identification of the lesions by imaging studies, at four surgical times in a period of 18 years, associated with right hemithyroidectomy due to incidental finding of papillary thyroid carcinoma. In the last admission with serum parathyroid hormone of 1000 pg/ml, serum calcium of 3.9 mmol/l, serum phosphorus of 0.73 mmol/l. A radioguided left lower parathyroidectomy was performed, obtaining a 4.8 × 2.7 cm gland. The pathological study reported parathyroid tissue with proliferation of oxyphilic cells with lesion limited to the

capsule. After the intervention, parathyroid hormone levels decreased by 40% (610 pg/ml) but remained high, with normalization of serum calcium and phosphorus. He continues to be monitored for external consultation.
Conclusion
The treatment of choice is cytoreduction of all identifiable parathyroid tissue remains, while treatment aimed at removing all disseminated nodules is rarely successful, patients are initially controlled with subtotal parathyroidectomy, however reintervention is often necessary, as noted in this case, cinacalcet is a medical option. Parathyromatosis is a rare cause of recurrent and persistent hyperparathyroidism. Preoperative diagnosis continues to be a challenge even with the advent of new technologies, even after 40 years of being described. Its pathophysiology continues to be studied and discussed. Lack of knowledge about this entity can result in unsuccessful attempts to control and eradicate the disease. It is important that it be considered especially in patients with persistent hyperparathyroidism.

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EP32

Secondary hyperparathyroidism associated with exostosis in a 10-year-old girl: a case report

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Background
Secondary hyperparathyroidism is a condition that can occur as a result of low vitamin D level. Parathyroid hormone (PTH) has the role of stimulating bone resorption by two mechanisms: direct activation of osteoblasts and indirect stimulation of osteoclast. Exostosis or bone spur is a benign tumor that consists in overgrowth of a pre-existing bone. Exostoses can affect any bone, however they are most commonly located on the bones of the joints such as: the ribs, hips, knees, ankles, shoulders and elbows. Their exact cause is not known, however, they appear mostly during the active growth stages and as a result of bone lesion. They can cause chronic pain or can be asymptomatic and discovered incidentally.
Case presentation
We herein report the case of a 10-year-old Caucasian girl who presented to the orthopaedic ward complaining of leg pain during walking. The radiologic investigation showed a lateral exostosis above the right knee. The patient's family physician referred her to our endocrinology clinic. Her pubertal stage was Tanner IV for breast growth and Tanner IV for pubic hair development. Biochemical investigations showed elevated PTH level 91.4 pg/ml (normal range, 15–68 pg/ml), low vitamin D level 23.5 ng/dl (normal range, >30 ng/ml), normal calcemia, urinary calcium/creatinine ratio <0.2 mg/dl (normal range, <0.14 mg/dl) and normal thyroid hormone levels. The diagnosis established was secondary hyperparathyroidism due to vitamin D insufficiency. The patient received replacement therapy with cholecalciferol (2000 IU) under which the levels of PTH turned within normal range.
Conclusion
This case illustrates the unusual association of exostosis located above the knee in a patient with secondary hyperparathyroidism caused by low vitamin D level. Although there is only the possibility of a casual association, this case is noteworthy to report because of its interesting features. We highlight the importance of vitamin D replacement in childhood, for it can prevent secondary hyperthyroidism along with its consequences.

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EP33

Hyperparathyroidism complicating a pre-existing diagnosis of Familial Hypocalciuric Hypercalcemia (FHH)

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Familial hypocalciuric hypercalcemia is a rare clinical condition of persistently elevated serum calcium and reduced urinary calcium levels with an autosomal dominance inheritance pattern to the three out of four large types of this condition known. This rare condition goes largely undiagnosed as patients are largely asymptomatic and where symptoms are present, other causes of hypercalcaemia are considered first. Hyperparathyroidism, superimposing on FHH, is an even rarer occurrence. We present the case of an adult male with an initial provisional assessment of FHH, which was later confirmed with a genetic study. He went on to develop hyperparathyroidism (with evident parathyroid hypertrophy on Sestamibi parathyroid scan done). This occurred on his pre-existing familial hypocalciuric hypercalcemia and surgical consideration (subtotal parathyroidectomy) was offered. It remains to be established if this is an incidental occurrence or if there is a causal relationship between FHH and an onward development of parathyroid hypertrophy or adenoma(ta).

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EP34

Severe hyperinsulinemia and osteoporosis in a lean patient with Jacobsen syndrome

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Introduction
Jacobsen syndrome (JS) is a rare gene disorder caused by a terminal deletion of the long arm of chromosome 11. The estimated prevalence of Jacobsen syndrome is 1/100.000 births. It is most commonly presented with psychomotor and physical growth retardation, dysmorphic facial features, thrombocytopenia or pancytopenia. It is also characterized by congenital heart defects, and kidney, gastrointestinal tract, genitalia, CNS and skeletal deformities.
Case presentation
We herein report an unusual case of a 19-year-old male, non-smoker, with a medical history of moderate cognitive disorder, facial deformities, lower limb skeletal malformation and hearing impairment, who was referred to the outpatient clinic due to severe osteoporosis and hyperinsulinemia. His BMI was 21.5 kg/m^2. The OGTT showed glucose levels within normal range and increased insulin levels, 46.4 pmol/l and 238.8 pmol/l at time 0' and 30', respectively. Spine (L1–L4) and total body mass density were measured 0.875 g/cm^2 and 0.877 g/cm^2 with *Z*-score of –2.7 and –2.0, respectively, finding which documented the presence of severe osteoporosis. Thyroid and adrenal function tests, vitamin D and PTH levels, liver function tests, autoantibodies specific for celiac disease and 24-h urine calcium were within normal limits. A genetic analysis was performed and revealed a de novo deletion in 11q24.1-qter, compatible with JS. The patient was placed on bisphosphonates along with calcium and cholecalciferol supplementation as a treatment for his severe osteoporosis.
Conclusion
We present this case to alert the medical community on the possible association of Jacobsen syndrome with severe osteoporosis and hyperinsulinemia in a young male.

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EP35

Coexistence of multiple cystic parathyroid adenomas and thyroid carcinoma

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Background
Cystic parathyroid adenoma is a rare entity (<0.01% of all cervical masses) that leads to primary hyperparathyroidism in 9% of cases. Parathyroid scintigraphy is essential for the diagnosis although there are pitfalls with false negative results. Parathyroidectomy is the treatment of choice but its success depends on the exact preoperative localization of the parathyroid lesions. 4D-CT is a very helpful diagnostic tool in such cases.

Case presentation
A 43-year-old man presented with a history of recurrent episodes of nephrolithiasis. Cervical ultrasound was indicative of multiple isoechoic thyroid nodules and 3 cystic hypoechoic lesions behind the middle and lower part of both thyroid lobes. The biochemical examinations indicated primary hyperparathyroidism. Thyroid function tests, calcitonin and urine metanephrines were in normal range. CBI scintigraphy showed one parathyroid adenoma behind the lower part of the left thyroid lobe. Since there was no accordance between the two diagnostic procedures, cervical MRI followed, demonstrating 7 small lesions, indicative of parathyroid adenomas or lymph nodes. A 4D-CT Scan revealed 3 mixed solid and cystic lesions ranging from 2 to 2.8 cm, posteriorly to both thyroid lobes. The patient underwent total thyroidectomy because of multinodular goiter and parathyroidectomy according to the 4D-CT. The histological examination demonstrated the coexistence of 1 right and 2 left mixed cystic parathyroid adenomas and a unifocal right lobe papillary thyroid carcinoma invading the thyroid parenchyma. There was a significant decrease in PTH levels after the excision of the adenomas.
Conclusions
Simultaneous mixed solid and cystic multiple parathyroid adenomas and papillary thyroid carcinoma is an extremely rare entity. Functional imaging has low sensitivity in displaying cystic lesions. It is worth noting that 4D-CT is a very important preoperative diagnostic tool in cases of discrepant functional (Sestamibi) and structural (ultrasonography) imaging.
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EP36

Cerebral calcifications revealing familial pseudohypoparathyroidism
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Introduction
Pseudohypoparathyroidism (PHP) is the first example of hormonal resistance observed in human pathology characterized by a great variability of clinical and genetic expression. We present a case of PHP in a Tunisian family.
Observation
The index case is a 31-year-old man. He was burn out of a consanguineous marriage (distant consanguinity) followed since the age of 15 for convulsive seizures. Three months earlier, complex partial seizures became reccurent and refractory to medication. The brain MRI revealed the presence of calcifications of the central gray nuclei. Serum biochemical analysis presented severe hypocalcemia (1.15 mmol/l), hyperphosphatemia (2.76 mmol/l) and an elevated serum parathyroid hormone level (320 pg/ml) (normal range 10–60 pg/ml). On general physical examination, there was a short stature, facial dysmorphia, android obesity, bradymetacarpia of fourth and fifth fingers bilaterally, bradymetatarsia and subcutaneous ectopic calcifications. Signs of latent tetany in the form of Chvostek's and Trousseau's sign were present. Renal function and 25 (OH) vitamin D levels were normal with no biological signs of malabsorption. The ophthalmologic examination showed a bilateral subcapsular cataract.Thyroid profile revealed normal T3, T4 levels with slightly elevated TSH levels (8.5 uIU/ml), suggestive of TSH resistance. Patient was diagnosed as PHP type 1a. He was treated with oral calcium (3 g/day) and calcitriol (1 µg/day). He responded to the treatment, and is presently asymptomatic with maintenance of normal calcium levels and no recurrent epileptic seizures. Family investigation revealed the presence of the same abnormal regulation of calcium and phosphate homeostasis in his sister and his younger brother (older brother would be unharmed), and the discovery of asymptomatic hypocalcemia in the mother and maternal uncle. The biomolecular study of the Gs protein is in progress.
Conclusion
PHP is a rare, deeply impairing disorder of calcium metabolism, characterized by end-organ resistance to the action of paratyroid hormone. This group of disorders is caused by different and complex genetic and epigenetic defects. There is an urgent need to improve knowledge on the natural history of the diseases, to better understand the bridges between these clinically heterogeneous and to develop new therapies.
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EP37

Bisphosphonate-related osteonecrosis of the jaws in persistent primary hyperparathyroidism
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Background
Primary hyperparathyroidism (PHPT) results from inappropriate overproduction of parathyroid hormone from one or more of parathyroid glands with consequent hypercalcemia. Medical therapy by bisphosphonates is indicated for patients contraindicated for surgical treatment or those with therapy failure. We report the observation of a patient receiving zoledronic acid for persistent PHPT and who developped bisphosphonate-related osteonecrosis of the jaws (BRONJ).
Case report
A 54-year-old man, who had diabetes mellitus presented with symptomatic PHPT manifested by joint pain with chondrocalcinosis, and elevation in serum PTH to 720.4 pg/ml and total calcium to 3.2 mmol/l levels. Neck ultrasonography, sestamibi scan, cervico-thoracic Magnetic Resonnance Image were negative. Exploratory cervicotomy was indicated and parathyroidectomy of 3 glands was released. The fourth parathyroid gland was not found. Histological findings revealed hyperplasia of three parathyroid glands. He was presented with reccurence after 3 years. Cervical computed tomography and sestamibi scan were negative and a second mediastinal operative procedure was planned, however, no ectopic parathyroid gland was found. Because of persistence of severe hypercalcemia associated to renal lithiasis, he was medically managed with intravenous zoledronic acid for 6 years. One day, he came with left gingival pain. He was referred to maxillofacial surgeon who noted gingival redness and swelling with pus discharge and necrotic bone exposure. Finally, he was diagnosed with BRONJ. A review of the dental history indicated that he extracted one tooth 2 months ago. Subsequent treatment consisted of antibiotic and recurretage of the extraction socket without improvement. Bisphosphonates were discontinued immediately after the diagnosis and sequestrectomy was performed. A histological reported sclerotic and necrotic bone. The patient maintained on palliative treatment consisting of local wound dressings, antibiotics, and antimicrobial rinses. Although surgery appeared to give some initial relief painful symptoms returned and the patient was proposed to hyperbaric oxygen.
Conclusion
BRONJ has been well documented in a patient with persistent primary hyperparathyroidism who received 6 years of bisphosphonates. It presents a serious adverse effect and often related to a site of previous dental treatment. Therefore, patients should be informed of an increased potential risk for osteonecrosis and the importance of conservative therapy.
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EP38

Vitamin D deficiency and primary hyperparathyroidism
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Introduction
The association between vitamin D deficiency and primary hyperparathyroidism(PHP) has clear implications. Co-existing vitamin D deficiency may cause the serum calcium level to fall into the normal range, which can lead to diagnostic uncertainty. The objective of this study is to assess the vitamin D status of patients followed for primary hyperparathyroidism.
Materials and methods
This is a retrospective study conducted at the endocrinology department of EPH Bologhine in Algiers between 2013 and 2017, involving 21 patients followed for primary hyperparathyroidism. The diagnosis of PHP was made in the presence of normal or elevated serum calcium in relation to inappropriate PTH with elimination of secondary hyperparathyroidism. The 25OHD assay was performed in 16 patients.

Results
The mean age of the patients was 56.5 years. These were 20 women and only one man diagnosed with a familial form. HPP was asymptomatic in 47.6%. The mean serum calcium was 2.98 mmol/l. The mean PTH was 475 ng/l. The mean 25OHD level was 14.42 ng/ml. 87.5% of patients had 25OHD <30 ng/ml, 81.2% had 25OHD <20 ng/ml) and 25OHD <10 ng/ml was found in 43% of patients. Osteodensitometry was performed in 13 patients, it was normal in 2 patients, osteoporosis was found in 69.2% (9 cases) and osteopenia in 15.4 cases.
Discussion
Vitamin D deficiency and insufficiency seem to be more prevalent in patients with primary hyperparathyroidism than in geographically matched populations. Regardless of the clinical severity of primary hyperparathyroidism, the disease seems to be more severe in those with concomitant vitamin D deficiency.
Conclusion
Vitamin D insufficiency is very common in patients with primary hyperparathyroidism. Vitamin D deficiency is associated with high blood calcium and high PTH levels. Recent recommendations from learned societies propose a systematic dosage of 25OHD in all patients with primary hyperparathyroidism.

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EP39

Osteoporosis, as a manifestation of multiple myeloma disease in women post menopause

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Osteoporosis is a systemic skeletal disease characterized by a decrease in bone strength and an increased risk of fractures. In the structure of osteoporosis, secondary osteoporosis is 5% in women and 20% in men. Clinicians need to exclude the secondary nature of osteoporosis, since under the 'mask' of mineral metabolism disorders, more rare and dangerous diseases can arise. A 65-years-old women presents with complaints of three low-traumatic fractures in the last year. From the anamnesis: in 2018 she consulted a traumatologist with complaints of back pain and increased fatigue. Dual-energy X-ray absorptiometry (DXA): compression fractures of the 2nd and 3rd lumbar vertebrae, a decrease in bone mineral density (BMD) in the lumbar part of vertebral column (*T*-score −2.5). A diagnosis of postmenopausal osteoporosis was made, therapy with zoledronic acid was recommended, however, due to the high cost of the drug, calcium and vitamin D therapy was chosen. In March 2020, a low-traumatic fracture of 2 ribs was developed (VIII rib on the left, IX rib on the right). In July 2020, there was a fracture of the scaphoid on the right. Due to persistent complaints, the patient consulted an endocrinologist. Physical examination: BMI-27 kg/m^2, BP-135/80 mmHg, HR-68 beats per minute, pale skin and visible mucous membranes, musculoskeletal system without visible deformation, muscle tone is normal, risk of falls on the Morse scale is high (55 points). She denies taking medications that affect BMD. DXA was performed: BMD was reduced in the lumbar part of vertebral column (*T*-score – −2.5), in the area of the femoral neck (*T*-score – −2.6). Was calculated the FRAX: the risk of major osteoporotic fracture was 22% ten-year risk of hip fracture-4.3%. Due to the presence of atypical localization fractures an additional examination to exclude secondary causes of osteoporosis was performed: primary hyperparathyroidism, vitamin D deficiency were excluded. However, anemia (hemoglobin-95 g/l) and accelerated ESR (40 mm/h) were detected, which in combination with osteoporosis can be clinical manifestations of paraproteinemia, so the patient was referred to a hematologist. After an additional examination a diagnosis of multiple myeloma was made. The patient is currently receiving chemotherapy. Differential diagnosis of osteoporosis must be carried out in the early stages of the disease in order to exclude secondary osteoporosis and identify pathologies accompanied by a violation of mineral metabolism. Identification of reliable causes of osteoporosis allows prescribing timely etiotropic therapy, which ultimately improves the prognosis of such patients.

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EP40

Shoulder pain, polyuria and lytic lesions: novel presentation of primary hyperparathyroidism or multiple myeloma?

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Traditionally, patients diagnosed with primary hyperparathyroidism present with mild hypercalcaemia and tend to be asymptomatic. Symptomatic patients tend to have severely high calcium and exhibit the classic 'bones, stones, abdominal moans and psychic groans.' We present a case of a 92-year-old Caucasian gentleman presenting with recurrent falls, postural hypotension and trauma to head and shoulder. X-ray imaging showed small non-specific lucencies in the cervical and upper thoracic vertebral bodies, clavicles and left upper humerus along with an old left clavicular fracture. He was normocalcaemic (2.52 mmol/l) on admission, had normocytic anaemia and had a mild acute kidney injury (AKI) on chronic kidney disease (CKD). The computer tomography (CT) chest, abdomen and pelvis showed multiple punched out lytic lesions within the skeleton bones and an 13 mm elongated nodule behind the right lobe of thyroid. Presence of similar lucencies in shoulder imaging from 2015 and 2016 ruled out the possibility of metastatic disease. Biochemistry revealed raised parathyroid hormone at 35.6 pmol/l (1.6–6.9) and vitamin D deficiency of 24 nmol/l. On two occasions during the admission, his calcium was found to be mildly elevated (2.73 mmol/l). Tests for myeloma screen were inconclusive. He had urinary bence jones protein (BJP), raised kappa and lambda free light chains and no immunoparesis. He was managed with vitamin D and is awaiting further tests, such as sestamibi scan. He will be followed up in endocrine clinic to discuss results. Any bone lesion detected in a patient above the age of 40 years, should have further investigations for myeloma and/or metastatic disease. The differentials in this case are primary hyperparathyroidism as suggested by long standing bone lesions, high PTH and a potential parathyroid lesion or plasma cell neoplasia as suggested by BJP in the urine with kappa light chains. Literature search suggests that lytic lesions, specifically brown tumours can be seen in patients with primary hyperparathyroidism. The diagnosis is still unclear, nevertheless a uniquely delayed presentation of potential primary hyperparathyroidism or both the conditions.

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EP41

Calcium metabolism in Latvian patients with granulomatosis with polyangiitis (GPA) at the time of diagnosis – 2013-2018 data

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Key words
GPA, granulomatosis, serum, 24 h urine, calcium.
Introduction
Granulomatosis with polyangiitis (GPA) is a very rare systemic disease of unknown etiology that is defined by the formation of granulomas in different organ systems. Due to this pathology, there may be an increase in serum and 24 h urine calcium that can have a clinical impact on the course of the disease.
Aim
The goal of this study was to assess the changes in total serum calcium and 24 h urine at the time of diagnosis in new cases of GPA from 2013 till 2018.
Materials and methods
In a retrospective study, medical records of all patients who were screened due to suspected GPA (*n*=48) in the Riga Eastern University Hospitals' 'Clinic of Tuberculosis and Lung Diseases' between the 1st of January 2013 and 31st of December 2018 were analyzed. For further analysis, only patients with first-time histologically and/or clinically confirmed diagnosis of GPA (*n*=30; 15 men and 15 women) were selected, and only the data from the first episode was evaluated. The information was obtained from patients' case files and medical records in the centralized hospital information system.
Results
On average, there were 5 (ranging from 3 to 10) new GPA cases (approximately 50% women and 50% men) per year in Latvia. Patients' age ranged from 29 to 77 years with mean age of 56 ± 13.4 years. The highest number of newly diagnosed GPA was in the age group of 50–59 years (*n*=12; 7 women and 5 men). Serum calcium level was evaluated only in 9 of 30 patients, hypercalcaemia was detected in one case (*n*=1) – 2.57 mmol/l [2.1–2.55]. 24 h urine calcium level was evaluated only in two cases (*n*=2), no hypercalciuria was found.
Conclusions
Most patients lack serum and/or 24 h urine calcium levels evaluated at the time of the diagnosis of GPA. Hypercalcaemia was observed in one case. Due to small number of cases and the lack of serum and urine calcium

evaluation at the time of diagnosis, substantial statistical analysis was not possible. Doctors should be reminded and encouraged to perform an early basic calcium metabolism screening in GPA patients.

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EP42

Impact Of Vitamin D Supplementation On Phospho-Calcium Metabolism

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Introduction
It has been estimated that prevalence of vitamin D deficit (25(OH)D) in the world is between 20 and 100%, depending on age group, ethnicity and region. In European population, the prevalence is around 40%. The Endocrine society guidelines recommend the supplementation of vitamin D when vitamin D deficiency is confirmed. The objective of this work is to evaluate the effect of 25(OH)D supplementation on phospho-calcium metabolites: calcium (Ca), phosphorus (Ph) and parathormone (PTH).
Methods
Retrospective study of 185 individuals diagnosed with 25(OH)D deficit in routine analyses and to whom supplementation was prescribed. Individuals with hyperparathyroidism (HPTP) were excluded. We analysed the age, sex, glomerular filtration rate (GFR), Ca, Ph, 25(OH)D and PTH baseline, at 6 and 12 months(M) after supplementation. Two levels of deficiency of 25(OH)D were defined: deficiency if 25(OH)D<20 ng/ml and insufficiency if 20 ng/ml≤ 25(OH)D <30 ng/ml. The various formulations of 25(OH)D were prescribed, according to the recommended dosage. Statistical analysis was performed in Excel® with significance level *P*=0.05.
Results
185 patients, 51.9% female with a mean age of 69 years and mean GFR 91.6 ml/min. In the pre-supplementation phase 74.6% had 25(OH)D deficiency and 25.2% had insufficiency. 26.5% of patients were supplemented with calcifediol and 73.5% with cholecalciferol. The mean values of analysed metabolites at 0, 6 and 12 months were respectively: 25(OH)D 16 ng/ml, 30 ng/dl and 29.95 ng/dl (*P<0.001*); Ca 9.47 mg/dl, 9.55 mg/dl and 9.57 mg/dl (*P=0.208*); Ph 3.34 mg/dl, 3.5 mg/dl and 3.22 mg/dl (*P=0.178*); PTH 88.1 pg/ml, 74.4 pg/ml and 82.4 pg/ml (*P=0.077*). We did a sub-analysis of patients with renal failure (GFR<60 and 60<GFR<90 ml/min) with similar results, without statistical significance (GFR<60 ml/min: Ca *P=0.49*; Ph *P=0.55*; PTH *P=0.19* and 60<GFR<90 ml/min: Ca *P=0.32;* Ph *P=0.28;* PTH *P=0.29).*
Conclusion
In this study it was found that vitamin D supplementation is an effective therapy in the treatment of this deficiency. After 12 months of 25(OH)D supplementation, there was no significant statistical variation in the phospho-calcic metabolites. Renal failure did not influence the results obtained in this study. These results are in line with those previously published in the literature.

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Diabetes, Obesity, Metabolism and Nutrition

EP43

Pregnancy outcomes after successful chemotherapy for choriocarcinoma in a diabetic woman: A case report

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The pregnancies conceived after chemotherapy for trophoblastic neoplasia should be followed with clinical surveillance due to higher rates of some pregnancy complications especially when associated with diabetes mellitus. We report the case of a 30-year-old nulliparous woman, obese, had been diagnosed with type 2 diabetes mellitus for 10 years,without micro or macrovascular complications, treated by conventional insulin therapy,with a history of low-risk gestational choriocarcinoma complicating a hydatidiform mole,treated with 11 sessions of Methotrexate chemotherapy in remission for four months. Pregnancy was allowed to proceed by an obstetrics–gynecology specialist after a 3-month preconception program with optimization of insulin therapy and switching to Asparte and Detemir insulin analogues, allowing a decrease in glycated hemoglobin (HbA1c) from 8.4% to 7.7%. Folic acid and iron supplementations were also carried out as well as progestin and salicylic acid. The patient was hospitalized once every three months in order to carry out the assessment of the impact of her diabetes by monitoring of glycemic control as attested by (HbA1c) and fasting blood glucose (FBG), as well as an ophthalmological examination and the search for albuminuria.In the gestational diabetes unit,the patient maintained a strict regimen of capillary blood glucose measurements six times a day weekly as well as dietary avoidance of fat.Blood glycemic control required high doses of insulin (1.2 UI/kg per day) to maintain the HbA1c and FBG levels in the range of 7% and 0.98 mg/dl, respectively.The cardiac and ophthalmologic examinations showed normal findings at each visit.No rise of albuminuria was detected.However, the patient had gained weight more than recommended (11 kg).All measurements of beta-hCG titer showed normal findings throughout pregnancy. Pregnancy progressed favorably up to a term of 27 weeks of gestation when the patient was hospitalized in a gynecology–obstetrics department because of a threat of premature delivery. The contractions were stopped and an obstetrical ultrasound showed a progressive pregnancy with fetal hypotrophy with an estimated weight of 830 g and hydramnios. After a regularly monitored pregnancy, the patient gave birth by caesarean section at 37 weeks of gestation and 2 days. The newborn weighed 4.050 g and had normal Apgar score at 1 and 5 minutes, respectively and was devoid of serious metabolic complications. No similar case has been described in the literature, hence the originality of our case.

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EP44

The second Moroccan mobile application for type 1 diabetes self-care : towards a new pedagogical dynamism in T1DM self-management

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Introduction
Mobile health technology has been highly beneficial for people with diabetes, offering a plethora of educational patterns especially during COVID-19 pandemic. Diabetes self-management education through telehealth technologies is important in promoting health practices and in reducing the risk of complications. Nevertheless, the challenge is to elaborate a digital application in light of sociocultural background and economic status.
Material and methods
We imagined and developed a new smartphone application named : 'Ana wa Soukari' in simplified Arabic, using mapped sections with pictured characters, and providing individualized blood glucose prescription chart helping the patient manage rapid insulin doses. The purpose of our study is to evaluate the clinical and biological effectiveness of the second Moroccan mobile application 'Ana wa Soukari' on type 1 diabetes mellitus self-management.
Results
Here we present our preliminary results. A total of 9 patients initially received the application 'Ana wa soukari' on their smartphones. The mean age of our patients was 12.7 years (6–20). 33% of them were male and 66% were female. The patients were diagnosed with type 1 diabetes for a mean of 3.39 years. Only one patient had diabetes for more than 5 years. 55% of the patients were initially admitted in our endocrinology diabetology department for poor glycaemic control, and 45% were admitted for a newly diagnosed diabetes mellitus. All of them had initially received therapeutic education in its usual form. None of them had a degenerative complication of diabetes. The mean HbA1c level was 8.51% (6.4%–12.4%). The mean number of hypoglycaemic events before the application was used dropped from 4.3 events per week to 2.1 per week after one week using the application.The patients thought the content was suitable for the young diabetic patients and understandable, and found that the application was perfectly complementary to therapeutic education in its classic form besides giving them the possibility of adapting their insulin doses according to each meal and physical activity.
Conclusion
Our preliminary results bring out the need for a longer study to explore the efficacy of 'Ana wa Soukari' to optimize outcomes in young people with type 1 diabetes mellitus and give a greater opportunity for computer-aided diabetes education to play a significant role in Diabetes self-management.

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EP45

Initial daily insuline dose and body mass index

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Introduction
Insulin therapy can lead to obesity which can affect the comorbidities of the type 2 diabetes. Should we consider the body mass index (BMI) before prescribing it?
Methods
Our study is prospective, randomized and comparative.We recruited patients with type 2 diabetes hospitalized for a switching to insulin in the C department of diabetology and nutrition at the National Nutrition Institute in Tunis, during 6 months.We divided the patients according to their BMI and compared the corresponding averages of the initial daily insuline dose using the Welch test.
Results
We included 50 patients with type 2 diabetes, hospitalized for a switching to insulin, 54% were men, 46% were women, with an average age of 59 years (± 11), the averge duration of diabetes was eight years (± 7), the average BMI was 29 (95% CI 27–31), the average waist size was 101 cm (95% CI 97–105), 28% of patients were normoponderal, 34% were overweight, 22% had stage 1 obesity, 6% had stage 2 obesity, 10% had morbid obesity. We measured the average of the initial daily insuline dose for each of these groups, it was 0.52 IU/kg/d (95% CI 0.4–0.6) for normoponderal patients, 0, 46 IU/kg per day (95% CI 0.4–0.5) for overweight patients, 0.34 IU/kg per day (95% CI 0.3–0.4) for those with stage 1 obesity, 0.36 IU/kg per d (95% CI 0.2–0.5) for those with stage 2 obesity, 0.36 IU/kg/d (95% CI 0.3–0.4) for those with morbid obesity.We found a statistically significant difference between these avearges only for the normoponderal group and the group with stage 1 obesity ($P = 0.041$).
Conclusion
According to this study, the initial daily insuline dose of the normoponderal patient is lower than the obese one**.**

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EP46

Diabetic ketoacidosis: role of the patient 'Expert' in the management!

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Introduction
The emergence of the concept of the expert patient has changed the paternalistic doctor–patient relationship. The 'knowing' patient is an active actor, his level of knowledge acquired during therapeutic education programs (ETP), allows him a certain autonomy in the management of his pathology. We focus through a case report of ketoacidosis on the useless intervention of an 'expert' patient to prevent it.
Case report
A 25-year-old patient, type 1 diabetic since the age of 6, having received in our departement as part of therapeutic education, a training in functional insulin therapy, which she stopped for lack of funds. She was admitted to the visceral surgery departement for surgical management of appendicitis. The postoperative course was marked on the second day by the installation of hyperglycemia at 3.3 g/l with ketosis. On biological assessment, natremia was 140 mg/l, kalaemia 4.3, alkaline reserves 12 meq/l, with good renal function and significantly improved creatinine reactive protein. We noted that the patient had been put by the healthcare team, only on rapid insulin boli since admission. In addition, she reports having unsuccessfully requested from caregivers to give her her basic insulin regimen for fear of falling into ketoacidosis. Our treatment consisted of introduction of the correction regimen and then, the return of her previous insulin regimen with good progress.
Discussion/conclusion
In the case of a chronic disease, in this case diabetes, the patient's quality of life will be 'impacted' by the therapeutic choice. In particular, compliance with this choice will be all the greater the more the patient has participated in the decision. By observing his body and his reactions to the disease, the patient-expert accumulates experiential knowledge (derived from knowledge of the disease *in vivo*) that can complement the physician's clinical knowledge and guide its decisions. The behaviour of this patient-expert does not aim to question the legitimacy of the physician, since this legitimacy is institutionalized, but raises the question of the acceptability and credibility of this legitimacy.

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EP47

Glycemic control of patients on human insulin and those on insulin analogues, is there a difference ?

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Introduction
The objective of our study was to compare the glycemic control between patients on human insulin and those on insulin analogues.
Methods
We conducted a prospective, randomized and comparative study. By recruiting patients with diabetes hospitalized in the day hospital departement at the National Nutrition Institute in Tunis during 8 months. The glycemic control of patients on human insulin and those on insulin analogues was evaluated by comparing the averages of their fasting glucose level and glycated hemoglobin.We used the *t*-test for independent samples.
Results
We included 50 patients with diabetes, 80% with type 2 diabetes and 20% with type 1 diabetes, 60% were women and 40% were men,the average age was 49 years (± 16), the average duration of diabetes was 10 years (± 7), insulin-treated for an average duration of 5 years (± 6), 74% were on human insulin and 26% were on insulin analogues, the average body mass index was 28 (95%CI26-29), the average fasting glucose level was 10 mmol per liter (95%CI9-11), the average glycated hemoglobin was 9.5%(95%CI9-10). The average of fasting glucose level for patients on human insulin was 10 mmol/l (95% CI 8.6–11.4) and for those on insulin analogs 10.4 mmol/l (95% CI 8.4–12.3), we found no statistically significant difference between these two averages (P=0.66). The average of glycated hemoglobin for patients on human insulin was 9.67% (95%CI 9.1–10.1) and for those on insulin analogues 9.2% (IC95% 8.5–10%),we found no statistically significant difference between these two averages($P = 0.34$).
Conclusion
In this study, we found no statistically significant difference between the glycemic control of patients on human insulin and those on insulin analogues. More studies are needed to validate these results.

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EP48

Relationship between vitamin D levels and visceral fat thickness, insulin resistance, inflammation and thyroid parameters in patients with obesity

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Background
Low serum vitamin D concentrations have been associated with autoimmune thyroiditis. Obesity is characterized by lower vitamin D levels and higher risk to develop autoimmune diseases. The aim of the study was to investigate the possible relation of serum vitamin D concentrations to visceral fat thickness (VFT), insulin resistance (IR), inflammation (serum monocyte chemoattractant protein-1 – MCP-1) and thyroid parameters in obese patients.
Materials and methods
A total of 45 non-diabetic, obese patients aged 20–59 years without a history of thyroid pathology were recruited. Biochemical markers, insulin, 25(OH) D, thyroid parameters (thyroid stimulating hormone – TSH, free thyroxine – fT_4, free triiodothyronine – fT_3, thyroid peroxidase antibodies – TPO-Ab, thyroglobulin antibodies – Tg-Ab) and VFT were measured. Serum MCP-1 evaluated the inflammation. A HOMA-IR cut-off value of 3.0 defined IR.
Results
Most patients had vitamin D deficiency (46.7%) and insufficiency (48.9%). Vitamin D level was negatively associated with BMI ($P = 0.038$) and VFT ($P = 0.006$). Vitamin D deficiency correlated with autoimmune thyroiditis prevalence ($P = 0.032$) and was a risk factor for its occurrence ($P = 0.023$).

At 20 ng/ml cut-off value, vitamin D was negatively correlated with MCP-1 (P = 0.007). Also, MCP-1 was positive correlated with HOMA-IR (P = 0.039), TPO-Ab levels (P = 0.015) and with autoimmune thyroiditis (P = 0.028). MCP-1 was a risk factor for vitamin D deficiency (P < 0.001). The final logistic model of a multivariate analysis, performed with autoimmune thyroiditis as the dependent variable and age, BMI category, 25(OH)D category, and TSH levels as the independent ones, showed that patients with autoimmune thyroiditis were more likely to have deficiency of 25(OH)D (P = 0.023) and higher TSH (P < 0.001) levels.
Conclusion
This investigation supports an interaction between vitamin D and systemic inflammation in obese patients. Systemic inflammation is related to the frequency of autoimmune thyroiditis. Vitamin D deficiency is the single independent factor associated with autoimmune thyroiditis in patients with obesity.

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EP49

Internet searches for diet and obesity in the COVID-19 era: a study in Greece and Lithuania

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Introduction
Internet searches mirror – to a degree – real-life behaviors and are influenced by chronic situations or abrupt events. From 2019 onwards the advent of the COVID-19 pandemic has changed profoundly daily habits, particularly during periods of protracted lockdown and following stay-at-home orders.
Aim
In this study we aimed to assess Google Trends internet searches for diet and obesity over time and vis-à-vis searches for COVID-19 in Greece (GR; a typical mediterranean country) and Lithuania (LT; a typical northern European country); both countries have comparable per capita income and Gini indexes (measuring income inequality).
Methods
We collected data on Google Trends internet searches (by means of relative search volumes; RSVs) in GR and LT regarding 'diet/obesity' and 'coronavirus/COVID-19' (in English, Lithuanian and Greek) from 2016 onwards. Statistical assessment was done with analysis of covariance, linear regression, evaluation of autocorrelation and cross correlation.
Results
A positive time trend – particularly in 2020 – was noted for RSVs regarding 'diet' both in LT and GR (in English), whereas a negative time trend was noted regarding 'dieta = diet' and 'nutukimas = obesity' (in Lithuanian). The periodicity of RSVs did not reach statistical significance. Searches regarding 'diet' and 'obesity' were positively correlated in LT and GR. Mostly negative cross-correlations regarding RSVs for 'diet/obesity' and 'coronavirus/COVID-19' were noted in both countries, with the exception for searches regarding 'nutukimas = obesity' vs 'COVID-19' in LT (r at lag 0 = +0.341, P = 0.013).
Discussion
Being locked in at home is stressful and with limited physical activity. Comfort food consumption and increased food intake were reported during lockdown for COVID-19; this may lead to weight gain. More than half of the population in GR and LT are overweight or obese. Our results show a growing interest for diets over time (that was not necessarily coupled with an interest in obesity) which was dampened to a degree by searches for COVID-19. Other factors – that were not assessed here – may also play a role: in Asia, a study has shown national Google Trends internet searches for diet and obesity to reflect the country's economic indices; this finding was subsequently not verified in GR.

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EP50

Metabolic disorders in children who are obese A study of 84 cases

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Introduction
Metabolic syndromeis the association in the same individual of a number of cardiovascular risk factors, namely abdominal obesity, dyslipidemia, high blood pressure and glucose intolerance. The objective of this study is to analyze the clinical and paraclinic characteristics of obese and overweight children in order to look for the elements of metabolic syndrome in these children
Methods
We carried out a retrospective and analytical study, we included children admitted for explorations of obesity to the department of endocrinology of the Hédi Chaker Hospital in Sfax between January 2015 and December 2019. Obesity was defined by a BMI greater than the 97th percentile according to the French reference curves. Abdominal obesity was retained if waist circumference is greater than 90° percentile depending on age and sex according to the American reference curve for children of European origin. The metabolic syndrome was defined according to the child-adapted NCEP-ATPIII.
Results
The study population consisted of 84 children, 44 boys and 40 girls. 71.4% of patients come from an urban area. Family history of obesity was recorded in 84.5% of cases. The average weight at first consultation was 72.68 kg (20–125 kg), average waist circumference was 98.7 cm (65–145 cm) and Average BMI was 31.55 kg/m^2. Obesity was primary in 96.4% of cases, 1st class in 21% of cases and 2nd class in 79% of cases. The obesity complications were cardiovascular in 4.8%, mechanical in 4.8% of cases, respiratory 7.1% of cases. and metabolic in 22% of cases. according to the criteria of NCEPATPIII adapted for the child 22.2% of patients had a metabolic syndrome. this metabolic syndrome was noted in 20.6% of boys and in 24% of girls, HTA was present in 4 patients (4.8%). Android fat distribution was present in 69 patients (82%). The mean HDL cholesterol was 1.12 mmol/l, and the mean triglycerides was 1.1 mmol/l. Twenty four percent of patients who hada family history of obesity and none of the patients without family history of obesity had a metabolic syndrome. In our series, metabolic syndrome was 6% in children under 10 years, 25% in children 10–15 years, and 36.4% in children above 15 years.
Conclusion
In our study, 22% of all children included had a metabolic syndrome. this high prevalence requires the research of this pathology in at-risk children, particularly children who are obese and aged above 10, to prevent complications in adulthood.

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EP51

Outcome of intensive treatment for obesity at our hospital

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Since 2006 at our hospital, lifestyle modification, such as diet and exercise, for obese patients has been provided through a team approach with a physician, dietician, nurse, physical therapist and psychologist. From 2016, a surgeon and anesthesiologist were added to the team for metabolic/bariatric surgery. The aims of this study are to clarify the effectiveness and problems of lifestyle modification for short-term intensive management (for 3 months) and long-term management (for over 2 years), and to clarify the characteristics of patients who transferred for surgical treatment. The diet menu is as follows: intake energy is (resting energy expenditure + exercise energy) × 0.9, and nutrients/total energy is 55–60% carbohydrates, 15–20% protein and 20–25% fat. The exercise is performed as follows: regular exercise more than 3 times per week or more than 5000 steps per day, and if possible, more than 10000 steps per day. Until now, 150 obese patients (mean age of 50 years and mean body mass index (BMI) of 36) have received medical management, and the mean BMI significantly decreased by 1.2 over 3 months. Thirty patients (20%) have transferred for surgical treatment. Seventeen patients had diabetes with a BMI of 31–48 and HbA1c 8–9% despite intensive therapy. Five with a BMI of 41–60 had bilateral knee osteoarthritis and required total knee replacement, three with a BMI of 38–51 had severe sleep apnea, and one with a BMI of 44 had infertility. The complete (HbA1c < 6% without diabetic medication) and partial (HbA1c < 6.5% with some medication) remission of diabetes was achieved in 70% and 30%, respectively. Serum C-peptide levels were significant higher in patients with the complete remission of diabetes than that in patients with the partial remission. In conclusion, diabetic patients need a lower BMI

for metabolic/bariatric surgery compared with non-diabetic patients, and baseline serum C-peptide level has a major influence on outcome in Japan.

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EP52

The association of depression with adipose tissue inflammation related to obesity

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Background and aim

Major depressive disorder (MDD) is one of the common mental disorder that affect more than 350 million subjects. MDD has been reported to be associated with systemic inflammation and obesity. However, there are no data that relate adipose tissue (AT) inflammation to MDD. The analysis of inflammatory markers in AT could pave the way to clarify the potential association between MDD and obesity. For this reason, the aim of our study was to analyze the expression of inflammatory adipokines in human and mice AT in relation with obesity and MDD.

Materials and methods

IL-6, IL-1b, ADIPOQ, TNF-a, MCP-1, ITGAM and PLAUR expression levels were measured by real-time qPCR from subcutaneous (SAT) and visceral (VAT) adipose tissue of depressive and no depressive normoweight subjects (n = 10) and depressive and no depressive morbid obese (n = 10) and from male obese mice fed a high fat diet (HFD, n = 7) and male lean mice fed a standard diet (S.D., n = 7).

Results

in this study, we observed that in both SAT and VAT the expression levels of *IL-6, IL-1b, TNF-a, MCP-1, ITGAM and PLAUR* increased significantly in no depressive normoweight and no depressive obese compared with no depressive normoweight, while *ADIPOQ* expression was lower in these groups compared with no depressive normoweight. Additionally, in obese subjects, the expression levels of IL-6 were higher in depressive subjects compared with no depressive subjects whereas ADIPOQ expression was lower in depressive subjects compared with no depressive in SAT and VAT. The expression levels of *Il-6, il-1b, Tnf-a, Mcp-1, Itgam and Plaur* increased significantly from obese mice HFD compared with lean mice S.D. in VAT and SAT while, Adipoq expression decreased with obesity.

Conclusion

Our results suggest the potential involvement of VAT and SAT inflammation in MDD, inducing complex mechanisms which are strongly linked with obesity. This work was supported by grants from the Spanish Ministry of Health (FIS), PI18/00785 and Miguel Servet II" [CPII13/00041], and co-funded by Fondo Europeo de Desarrollo Regional–FEDER, and from the Consejería de Innovación and co-funded by Fondo Europeo de Desarrollo Regional–FEDER (CTS-7895) S.L. was a recipient of a post-doctoral grant Plan Andaluz de Investigación, Desarollo e Inovación (DOC-01138) from Consejería de Economía, Conocimiento, Empresas y Universidad.

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EP53

Evaluation of the effect of lockdown order during Covid-19 pandemic on the clinical and metabolic parameters of obese patients in Turkey

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Aim

Lockdown order during COVID-19 pandemic caused a sedentary life-style and disruptions in eating and sleeps patterns of obese patients. In this study, it is planned to evaluate the clinical and metabolic effects of this period on obese patients.

Methods

This study included 44 obese patients who were followed up in Endocrinology and Metabolic Diseases Clinic of Karadeniz Technical University. In this study, metabolic parameters (fasting plasma glucose, insulin, homa-IR, lipid profile) and obesity-related problems during the lockdown (weight gain, dietary habits, exercise situations) experienced by obese patients, who were followed up in our clinic, were compared between the 6 months period before the March 11, 2020 the date of the first case of COVID-19 seen in Turkey and the period patients started to apply for the first time after the pandemic started to slow down. During the outpatient clinic applications of the patients; whether the patients followed up their weight, physical activity status, any change in their dietary habits, whether they needed to apply to the hospital and had any infection during the lockdown order was questioned and blood samples were taken for biochemical analysis.

Findings

72.7% of the study group was women. Average age of subjects was 39.89 ± 13.92 years. Subjects' average body mass index (BMI) was 36 kg/m^2 and 27.3% (n = 12) of the subjects were morbidly obese. Dietary compliance before and during COVID-19 pandemic was found as 27.3% and 13.6%, respectively (P: 0.109). The ratio of exercise at home was 29.5% before the COVID-19 pandemic and increased to 31.8% during the pandemic (P: 0.999). 68.2% of the participants stated that they tracked their weight and 52.3% stated they had an increased appetite. The behavior of not tracking the weight during the pandemic was more common in morbidly obese participants (P = 0.027). An increase was observed in weight (P<0.001) and BMI (P<0.001) measurements of participants during the lockdown order. During the pandemic; diet (P: 0.609) and exercise (P: 0.633) were not found associated with weight increase. After the lockdown order; a significant increase was found in glucose (P: 0.001), insulin (P< 0.001), homa-IR (P<0.001) and cholesterol (P<0.001) values of the participants.

Conclusion

This study shows lockdown order during COVID-19 pandemic caused weight increase and related disruptions in insulin resistance and lipid parameters regardless of dietary and exercise habits in obese patients who have not had COVID-19 infection.

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EP54

Effects of a single-centre lifestyle modification programme on anthropometric, metabolic, and cardiovascular risk factors in adults with severe obesity

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Background

Structured lifestyle modification programmes are offered as first line treatment to patients referred to bariatric specialist services. We sought to describe changes in anthropometric and metabolic characteristics in a cohort of bariatric patients following completion of an eight-week, multidisciplinary group-based lifestyle intervention focussed on diet and physical activity.

Methods

We conducted a prospective cohort study of all patients who completed the programme from 2013 to 2019. Weight, body mass index, blood pressure, HbA1c, lipid profile and functional capacity (Incremental shuttle walk test) at baseline and follow-up were compared in per-protocol analyses.

Results
Of 1122 patients enrolled in the program, 877 (78.2%) attended for follow up measures. Mean age was 47.3 ± 11.9 years and 66.9% were female. BMI decreased from 47.0 ± 7.8 to 46.2 ± 7.8 kgm^{-2} (P<0.001), weight decreased from 131.6 ± 25.5 to 129.5 ± 7.8 kg (P<0.001) and the number of patients achieving HbA1c <53 mmol/l increased from 79.4% to 83.6% (P = <0.001). There were also improvements in blood pressure, lipid profiles and functional capacity: MET (metabolic equivalents of thermogenesis) max 5.6 ± 2.1 vs 7.0 ± 2.8 (P = <0.001).
Conclusions
Adults with severe and complicated obesity referred from a hospital-based bariatric service who completed eight weeks of supervised, group-based structured lifestyle modification had improvements in anthropometric and metabolic characteristics consistent with a reduction in cardiovascular risk.

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EP55

Association of Vitamin D deficiency with obesity in middle-aged subjects with or without Type-2 diabetes in India

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Background
The prevalence of type 2 diabetes has been increasing all over the world. Various risk factors have been identified for the generation of type 2 diabetes include; ageing, family history of diabetes, general obesity, central obesity, physical inactivity, and sedentary lifestyle. Obesity, particularly central obesity is associated with insulin resistance (IR), 'beta-cell' dysfunction, partly through increased free fatty acids (FFAs) and lipotoxicity. Approximately 1 billion individuals worldwide, nearly 15% of the world's population, are vitamin D deficient or insufficient (less than 20 ng/ml or between 20 and 30 ng/ml, respectively). Vitamin D deficiency become a very common among all age groups worldwide and the highly prevalent in obese people.
Material and methods
The study was conducted in 90 control and 90 type 2 subjects with Type 2 diabetes mellitus patients of both genders aged 30–50 years. We obtained ethics approval from Institutional Ethics Committee, Symbiosis International (Deemed University), Pune, India before blood sample collection. The data regarding BMI, among control and T2DM subjects were collected. We have used WHO cut-offs to define overweight and obesity, whereas IDF cut-offs to define central obesity using different indicators such as WC and WHR. 'American Diabetes Association (ADA)' cut-offs were used for categorizing dyslipidemia Serum 25(OH)D, fasting plasma insulin (FPI), fasting plasma glucose (FPG), HbA1c, and lipid profile were measured by standard methods.
Results
In the control group, an almost equal percentage of subjects had normal BMI (41.11%) or were overweight (42.22%), while in the T2DM group majority of subjects were overweight (48.89%). Data indicated that T2DM subjects had significantly higher BMI, WC, HC, WHtR, blood pressure, TG, and VLDL-c than controls. The proportion of waist circumference WC>90cm was seen significantly higher among T2DM male subjects than control male subjects, while there was no significant difference for the proportion of WC>80 cm in female subjects. Also, among the study groups, there was no significant difference observed in the proportions of waist hip ratio WHR>0.88 in male and WHR≥0.80 in female subjects. Among lipid profile parameters there was a significant difference observed in the proportions for TG and HDL (in females) among control and T2DM groups. 'Spearman's rank-order correlation' was utilized to evaluate the correlation of '25(OH)D' with anthropometric and biochemical variables among control, T2DM, and total study subjects.
Conclusion and significance
Vitamin D could be associated with obesity and insulin resistance.
Key words
Vitamin D deficiency, Insulin resistance, Obesity, Middle-aged, Type 2 Diabetes

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EP56

Self-esteem among obese patients in Sfax, southern Tunisia

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Introduction
Self-esteem is widely viewed as a person's overall evaluation about self-worth or personal value and is considered an essential indicator for positive mental health and psychological well-being. This study sought to explore the level of self-esteem and identify the factors associated with low self-esteem in this population.
Methods
It was a cross-sectional study conducted in Sfax, Southern Tunisia from June to July 2020. We included all obese adults aged 19 to 64 years consulting at the basic health centre of Sfax and having a BMI greater than or equal to 30 kg/m^2. We excluded pregnant and nursing women and patients with severe decompensated organic disease and psychiatric disorder. We used the Rosenberg Self-Esteem Scale. Statistical analysis was performed using SPSS.24.
Results
A total of 150 obese patients were included in the study. There were 115 women giving a male to female ratio of 0.3. The mean age was 50 ± 12.5. There were 82 cases (54.7%) in stage I, 31 cases (20.7%) in stage II and 37 cases (24.7%) in stage III of obesity. Overall, 84 patients (56%) were from urban areas. History of associated illness was noted in 90 cases (60%). There were 12 current smokers (8%) and 62 patients (41.3%) were exercising physical activity. Overall, 69 patients (46%) had obesity for more than 10 years. The mean score of self-esteem was 26.9 ± 2.9. Of all patients, 139 cases (92.7%) had a low or very low self-esteem score. Prevalence of depression, anxiety, extreme self misperception, severe social phobia and bulimia were 26%, 75.3%, 29.3%, 38.7% and 10%, respectively. There was no significant association between low self-esteem and depression, anxiety, self misperception or social phobia. Besides, exercising physical activity was statistically associated with good self esteem (OR = 0.1; P = 0.01).
Conclusion
Obese patients demonstrated lower levels of self-esteem. Health-focused conversations between practitioners and obese patients about weight status and self-esteem, and appropriate follow up counseling can help improve self-esteem and mental health among obese patients.

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EP57

The association between obesity and type 1 diabetes: prevalence and complications

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Introduction
An increasing number of type 1 diabetics (T1DM) are being identified as having characteristics of metabolic syndrome and obesity. The aim of our work is to assess the prevalence of overweight and degenerative complications in a population with type 1 diabetes.
Material and methods
This is a descriptive and retrospective study concerning 377 type 1 diabetics hospitalized in the endocrinology-diabetology department over a 6-year time period.
Results
The mean age was 21.4 ± 11 years. A total of 44.6% had active diabetes for more than 5 years with an average of HbA1c 10.7 ± 5.2%. 44.4% of patients were admitted for uncontrolled diabetes with dietary errors in 26.4% of cases. The mean BMI was 20.3 ± 4.3 kg/m^2, it was inversely correlated with HbA1c (P = 0.001), 21.9% had a BMI > 25 kg/m^2 with a sex ratio M/W = 0.3, including moderate obesity in 3.4% and severe obesity in 0.9%. Hypertension was observed in 13.7% of cases, ischemic heart disease in 2%. 18% of patients had diabetic retinopathy, and 12% had diabetic nephropathy.
Discussion–conclusion
Patients with T1DM have more characteristics usually associated with T1DM patients with overweight, known as 'double diabetes'. This association seems to be an independent and important risk factor for the development of macrovascular and microvascular complications. Long-term studies are required to confirm the specific dietary patterns in this population.

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EP58

Overweight and obesity in a Tunisian population of medical students

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Introduction
Over the past decades, the prevalence of overweight, especially obesity, has steadily increased. This global scourge has affected all populations including that of medical students. The objective of our work was to determine the prevalence of this pathology in the population of future physicians and to study the factors associated with it.
Methods
This is a cross-sectional study including 120 medical students, recruited at the Faculty of Medicine of Tunis between November 2019 and March 2020.
Results
The average age of the students was 21.82 ± 2.09 years old. A female predominance was noted witha sex ratio (M/F) = 0.54. The average BMI was 21.4 kg/m^2 with extremes ranging from 16.87 to 35.67 kg/m^2. Overweight (BMI> or equal to 25 kg/m^2) was present in 30% of the cases of which 30 were pre-obese, 5 had class I obesity and only 1 student had class II obesity. The mean waist circumference was 79.73 ± 10.74 cm and abdominal obesity was noted in 36 students (30%). This excess weight was significantly associated with the female sex (P = 0.002). It was also significantly associated with college year repetition, noted in 36 students (P = 0.018) and was unrelated to the year of medical study. This overweight was significantly more noted in smokers (n = 36) (P = 0.049) and regular alcohol users (n = 37) (P <0.001). It was more common in students who used drugs without this being significant (P = 0.59). We did not find a significant association between the use of anxiolytics and antidepressant medication and overweight. The mean of the perceived stress scale (PSS) was higher in the presence of overweight (31.61 ± 5.85 versus 29.99 ± 5.61) without this being significant.
Conclusion
Overweight was common in our student population. Identification of potentially associated factors is necessary in order to reduce the prevalence of this pathology, a source of both physical and psychological disability.

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EP59

Overweight impact on the progression of non-alcoholic fatty liver disease and liver fibrosis

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Background
Currently, the overweight and obesity influence on human organs and systems is being studied all over the world, which are based on the violation of metabolic processes of fat and carbon metabolism, hyperglycemia with glucose toxicity, insulin resistance, obesity and metabolic syndrome. NAFLD progresses not only from steatosis to steatohepatitis (NASH), but is accompanied by liver fibrosis with transformation into cirrhosis and hepatocellular carcinoma in 20% of NASH patients. It is fibrosis that determines the further prognosis in patients and the risk of their death.
Objectives
To study the impact of overweight and obesity on liver fibrosis in NAFLD patients.
Methods
The object of the study was 59 patients without concomitant pathology with different body mass index and signs of steatosis and fibrosis according to ultrasound examination in combination with changes in the lipid profile or impaired glucose tolerance. for everyone Anthropometric examinations (weight, height, BMI), laboratory and instrumental examinations, biochemical studies to determine the functional state of the liver, liver elastometry and serum markers to determine liver fibrosis and steatosis (FIB4, NAFLD) were performed for each patient.
Results
Among the examined patients, there were 28 men (24.35%) and 31 women (26.95%) with an average age of 48.71 ± 2.37 and 51.1 ± 1.78. All patients were divided into groups depending on their body weight: Group I – normal weight (18.5–24.9 kg/m^2), II – overweight (25–29.9 kg/m^2), III – obesity I degree (30–34.9 kg/m^2). A direct relationship was established between weight and gender (r = 0.30, P < 0.05), which confirms the tendency to overweight in women. Going to the lipid profile, a direct relationship was established between BMI and very low density lipoproteins and triglycerides (r = 0.324, P <0.05 and r = 0.318, P <0.05). Observed growth rates of ALT, AST indices in the biochemical blood test with an increase in body weight (r = 0.679, P <0.05; r = 0.674, P <0.05). A direct strong relationship was found between BMI and the mean value of liver elastography data (r = 0.74, P <0.05), non-invasive FIB4 test (r = 0.88, P <0.05) and NFS (r = 0.89, P <0.05).
Conclusion
Overweight and obesity are the foundation for the fibrotic processes development in the liver, and its significant increase leads to pronounced fibrotic changes (F2–F3 according to METAVIR).

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EP60

A death case of type 1 diabetes mellitus due to COVID-19

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Introduction
The prevalence and mortality of the new type of coronavirus (SARS Cov-2) are high in patients with metabolic disease, especially in diabetes circumstances. Therefore, this study aims to present the changes in the clinical and biochemical parameters of a patient with Type 1 diabetes who died due to Covid-19.
Case
The case is a 24-year-old female patient who has been followed up in our hospital with the diagnosis of Type 1 diabetes, Celiac disease, and osteoporosis due to secondary hypogonadism for years. Again, this patient had been receiving treatment for chronic renal failure and hypertension due to diabetic nephropathy for 2 years. She was using inhaler ß2 agonists and corticosteroids for 1 year because of her asthma bronchiale. In addition, the case was underdeveloped compared to her peers and was 140 cm tall and 40 kg in weight. Initially, the patient was admitted to our hospital with a blood glucose level of 1050 mg/dl and a diagnosis of diabetic ketoacidosis (Table 1). In addition, since the patient was accompanied by dyspnea and nasal discharge, it was consulted with the clinic of infectious diseases. Her blood and urine cultures were taken and sent for Covid-19 PCR. The ground-glass images in the Thorax CT result were compatible with pulmonary edema and pulmonary embolism. Appropriate fluid replacement and intravenous insulin infusion treatment were initiated until the infection results were obtained. Despite all the treatments, target values determined for diabetes could not be achieved for this patient. We were able to reduce blood glucose by a maximum of 250 mg/dl. Additionally, the patient's electrolyte and blood gas were monitored. In its follow-up, treatment-resistant fever 39.5 °C was measured. Despite all efforts, the O2 saturation of the patient fell below 70 mmHg. As soon as Covid-19 was diagnosed, she was taken to the Covid-19 intensive care unit, and her glucose follow-up was followed up continuously and she was intubated. However, our patient died 1 day later.
Conclusion
As a result, it was observed that blood glucose regulation is more difficult in patients with new types of coronavirus infection.

Table 1. Laboratory findings of patient

eGFR (ml/min/ 1.73 m^2)	15
Glucose (mg/dl)	1050
HbA1c (%)	>15
WBC (10e3/µl)	6.56
Lymphocyte (10e3/µl)	0.85
Hgb (g/dl)	7.5
AST (U/L)	24
ALT (U/L)	8

Urea (mg/dl)	157
Creatinine (mg/dl)	3.89
Sedimentation (mm/h)	102
CRP (mg/l)	35.6
Ferritin (ng/ml)	1030
D-Dimer (mg/l)	0.4
Fibrinogen (mg/dl)	754
PO2/FiO2	118
Procalcitonin (mg/l)	0.38

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EP61

The diabetic foot : a descriptive study

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Introduction
The diabetic foot represents a public health problem with very important direct and indirect expenses. Multidisciplinary care and monitoring is essential. The aim of this Study was to describe the management of the diabetic foot in the endocrinology department.
Materials and methods
It was a retrospective study carried out in the Endocrinology and Diabetology department of the Hédi Chaker university hospital. It concerned patients with diabetic foot hospitalized between January 2010 and December 2018 regardless of the reason for hospitalization.
Results
Our study covered 130 patients with a mean age of 59 years and a sex ratio of 5 M/1 W. Our population comprised 83.7% of type 2 diabetic including 56.1% under insulin therapy and 16.3% of type 1 diabetic. The impairment was bilateral in 25.4% of cases. The mean duration of diabetes was 13.08 years. The insulin therapy was indicated for 70.8% of patients. We have found ulceration in 24.8% of cases and a perforating foot ulcer in 28% of cases. Neuropathy and arteriopathy were reported in 88.5% and 67% of patients, respectively. The infection was objectified in 42.2% of cases. The lesion recurred in 41.6% of patients. Amputation was reported in 39.1% of cases, of which 29.6% were major. The mortality rate was 4.9%.
Conclusion
Our results highlight the major impact of diabetic foot. Thus, a national care program is essential.

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EP62

Characteristics of non-alcoholic steatohepatitis in patients with type 1 diabetes: a study of 8 cases

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Introduction
Non alcoholic steato-hepatitis (NASH) is the most common chronic liver disease in developed countries rare in type 1 diabetes it is associated with an increased risk of complications in patients with type 1 diabetes mellitus (T1DM). The aim of this study is to clarify the characteristics of NASH in patients with T1DM.
Materials and methods
we conducted a retrospective descriptive study in non-alcoholic type 1 diabetes patients diagnosed with ultrasound of hepatic steatosis, hospitalized in the endocrinology department of the Hedi-Chaker University Hospital in Sfax between 2000 and 2020.
Results
8 medical records were analyzed, of which 6 women and 2 men, a sex ratio of 1 in 3, the average age was 27.25 years (16 -67 years), the average weight was 56.12 kg (41- 72 kg), with average BMI of 21.6 kg/m^2 (15- 28 kg/m^2). One patient has overweight. The average waist circumference was 82.3 cm (65–111 cm), 4 patients had dyslipidemia, no history of hypertension, no atherosclerosis was found. Only 2 patients had metabolic syndrome. History of: T2DM in 5 patients, android obesity in 1 single patient and dyslipidemia in 1 other patient, no family history of T1DM neither autoimmune pathologywas found. The metabolic assessment of our patients was as follows: the mean blood glucose level was 18.7 mmol/l (10.9–32), the mean HBA1c rate was 11.6% (7–14), the average creatinine rate of 66.4 µmol/l (41–117), with an average GFR of 130 ml/min (57–231). The average lipid level: total cholesterol: 5.7 mmol/l, triglycerides: 2.03 mmol/l, HDL: 1.25 mmol/l, LDL: 2.4 mmol/l. Thehepaticassessment was:meanASAT rate was 422 Iu/l (22-1430), the mean ALAT rate was 245.7 Iu/l (17-1420). The hepatic steatosis index measured was an average of 30.5 (23–40.7). The total daily insulin dose averaged 64.3 IU (20–106), equivalent of 1.14 IU/Kg (0.44–1.56), 5 patients receive insulin doses greater than 1 IU/kg per day. 2 patients were under mixed treatment (metformin + insulin). Diabetes duration average was 10 years (4–19). The duration of onset of NASH compared to the diagnosis of diabetes was on average 7 years (1–16). Degenerative complications related to diabetes were as follows: 2 patients had retinopathy, 2 patients had neuropathy and only one had nephropathy.
Conclusion
NASH should be researched and well monitored in type 1 diabetics especially in view of android obesity and high transaminase rate; the diagnosis of this liver disease should lead to the achievement of a metabolic and cardiovascular assessment.

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EP63

Pain in diabetic patients with lower limb amputation

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Introduction
The aim of our study was to search the causes of pain in diabetics followed for a lower limb amputation in physical medicine and rehabilitation (PMR) department.
Patients and methods
A retrospective study carried out between 2018 and 2020 on diabetic patients referred to PMR department for lower limb amputation.
Results
Forty-two patients were included in the study. Their mean age was 61.4 ± 15.7 years with a sex ratio of 3.2. Most patients (65%) were type 2 diabetics with a history of 15 years of diabetes, 52.4% were hypertensive and 40% had obliterating arteriopathy of the lower limbs (OALL). Infectious origin (gangrene) was the most common cause of amputation (90.5%), followed by vascular origin (4.4%). The mean delay to PMR consultation after amputation was 7.9 ± 9.5 months. Amputations involved the leg (84.4%), the thigh (13.3%) and the foot in 4.4% of cases. They were unilateral in 73.3% of cases. Re-amputation was necessary in 6 cases. Patients experienced neuropathic pain in 57.6% of cases and a sensation of non-painful phantom limb in 84.4% of cases. Neuromatous pain was noted in 6.7% of cases and overlying joint pain (in the knee or hip) was found in 17.8% of patients. Half of the patients (50.3%) received their prosthesis and 8% of them presented with a painful conflict prosthesis requiring some corrections.
Conclusion
Pain in amputees can have several aspects to consider and seek by the clinician to ensure adequate management.

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EP64

Critical Ischemia and albuminuria: positive correlations for prognosis of amputation in diabetic patients

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Background
Diabetic nephropathy complicated by albuminuria along with low estimated glomerular filtrate rate (eGFR) are a typical feature of Type 2 Diabetes (T2D) and it's related to a significant increase in mortality and chronic complications in diabetic patients However, data from the literature are still not conclusive regarding the direct association between albuminuria and risk of amputation for ischemic limb vascular disease, in diabetic patients. Therefore, in the present study we aimed to explore this association in a cohort of elderly diabetic patients treated with surgery for critical ischemic limb vascular disease.
Material and methods
We enrolled hospitalized patients for the management of the diabetic foot with critical ischemia of the lower limbs from February to November 2019 at the Unit of Endocrinology and Diabetology. The study cohort had the following characteristics: 1) 118 patients in total (82 men/35 female); 2) mean age 67.15 years (± 11.49 years s.d.); 3) mean average duration of T2D 19.59 years (± 11.83 years s.d.); 4) mean of body mass index (BMI) 28.64 kg/m^2 (± 5.55 kg/m^2 s.d.); 5) mean of HbA_{1c}: 8.4%–68 mmol/mol (± 1.87%- mmol/mol s.d.); 6) mean eGFR 84.24 ± 42.01 ml/min s.d. Patients were divided in 3 groups considering the surgical approach: 1) 78 patients treated with revascularization of the lower limb; 2) 34 patients treated with conservative medical treatment of the lesson; 3) 16 amputee patients, 10 out of 16 had already performed at least one procedure of revascularization during hospitalization. Linear regression model was used to find association between different groups and investigated outcomes. A $P<0.05$ was considered statistically significant.
Results
Macroalbuminuria were significanlty increased in patients who had a major amputation limb intervention (distal or proximal), when compared to non-amputated patients. In the same cohort, PCR values increased while eGFR values reduced in the amputee when compared to the non-amputee patients. Conversely, no significant difference was present comparing blood glucose values between the groups. Interesting, a trend for an increase on triglycerides level ($P = 0.06$) was present in amputee compared to non-amputees patients.
Conclusions
The present study reports as diabetic patients with critical ischemia of the lower limbs, and with chronic kidney disease, specifically with renal failure and increased levels of macroalbuminuria, have a significant increase in the risk of amputation. In addition, there was a specific correlation between major amputation and a high degree of marker of inflammations. Further studies in a larger population are needed to confirm present results.

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EP65

Glycemic control and microvascular complications in patients with type 1 diabetes and treated celiac disease

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Background
Celiac disease (CD) occurs in patients with type1 diabetes (T1DM) ranging the prevalence of 4.4–11.1% versus 0.5% of the general population. The mechanism of association of these two diseases involves a shared genetic background.
Aim
To investigate whether in type1 diabetes (T1DM) patients the concomitance of treated celiac disease (CD) impacts glycemic control and the prevalence of microvascular complications.
Methods
This retrospective study was performed in 20 patients with type 1 diabetes mellitus and treated celiac disease (CD) admitted to section C of National Nutrition Institute from 2017 to 2020. Age at CD diagnosis, gender, type 1 diabetes duration, glucose control (HbA1c) and insulin requirement before and after diagnosis of CD, status of microvascular complications and concomitant autoimmune diseases were evaluated. The control group consisted of 20 patients with T1DM and negative CD serology matched for age, gender, T1DM duration.
Results
Of the study population, 70% were females and 30% had concomitant autoimmune diseases (hypothyroidism). Mean age and mean duration of diabetes at CD diagnosis was 28 years, 9.5 years respectively. HbA1c levels at the moment of CD diagnosis were 10% and at the most recent visit 10.22% indicating no difference. A gluten free diet had little effect on insulin dosage (from 0.8 UI/Kg per day to 0.9 UI/Kg per day). Prevalence of diabetic retinopathy was higher in T1DM+CD group compared with controls (30% vs 10%, $P<0.05$) whereas no difference in the prevalence of diabetic nephropathy (10%) and diabetic peripheral neuropathy (5%) was found between the two groups.
Conclusion
The co-occurrence of T1DM + CD has no impact on glycemic control. However patients with T1DM + CD have higher prevalence of diabetic retinopathy than those with T1DM alone.

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EP66

Risk of pancreatitis in type 2 diabetes

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Introduction
Pancreatitis is an inflammatory condition of the pancreas, which has known an increased incidence over the last years. Gallstones and alcohol abuse are the most common causes. But many risk factors are associated with pancreatitis, including Type 2 diabetes who has an estimated risk of pancreatitis at nearly three times the risk of non-diabetics. The aim of our work is to study the relationship between these two entities.
Methods
This is a retrospective study involving 14 patients with type 2 diabetics who presented with acute or chronic pancreatitis during their hospitalization in the endocrinology department of the Hedi Chaker Sfax University Hospital, during the period from 2009 to 2020.
Results
The average age of our patients was 55.8 ± 16.6 years with a slight male predominance (gender retio H/F = 1.3). Diabetes was recently discovered in 6 cases and old in the rest of cases with a median length of 5 years. The reason for hospitalization was a diabetic imbalance or an acute metabolic complication in most cases. Digestive symtoms (epigastric pain, vomiting and diarrhea) were noted in 12 cases, a severe form with signs of extracecullary dehydration was noted in one case, whereas pancreatitis was asymptomatic in one case. The assay for amylase and/or lipase was high in all cases. Abdominal CT scan revealed an aspect of acute pancreatitis in 9 cases (stage A in 3 cases, stage C in 1 case, stage D in 1 case and stage E in 4 cases) and an aspect in favor of chronic calcifying pancreatitis in 1 case. In our series a lithiasic origin was noted in 4 cases, alcoholism was noted in 6 cases and hypertriglyceridemia was noted in 3 cases. However, pancreatitis was related to hypercalcemia due to primary hyperparathyroidism in one case.
Discussion–conclusion
Type 2 diabetes is an additional risk of pancreatitis and biliary disease and can also be a major complication of chronic pancreatitis. Further studies are required to identify causal factors that may account for the observed increased risk of pancreatitis associated with diabetes.

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EP67

Boerhaave syndome and 'Diabetic Ketoalkalosis' in a patient with type 1 diabetes mellitus: a case report

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A 20-year-old woman, with type 1 diabetes, presented to Emergency Department complaining of abdominal pain and vomiting for 3 days. She reported intermittent non-compliance with insulin therapy. Physical examination revealed epigastric tenderness. Blood glucose was 34.6 mmol/l, blood ketones 7.8 mmol/l, creatinine 131 µmol/l and CRP 31.47 mg/l (< 10). Despite clinical and initial laboratory features suggesting diabetic ketoacidosis, pH was 7.52 (7.32–7.43), pCO_2 5.9 kPa (4.6–6.4), HCO_3^- 33.5 mmol/l (22–26), potassium 3.4 mmol/l (3.4–4.5), chloride 73 mmol/l (normal 98–107) and anion gap was 16. As the ketoacidosis improved with treatment, the woman complained of retrosternal burning pain. Chest X-ray

suggested a pneumomediastinum, which was confirmed on CT thorax and barium swallow identified an oesophageal leak. A diagnosis of Boerhaave Syndrome was made. A laparoscopic esophagectomy and jejunostomy was successfully performed. We report a case of 'diabetic ketoalkalosis', where gastrointestinal pathology with metabolic alkalosis masked an underlying diabetic ketoacidosis. Alkalosis in patients with DKA is a rare phenomenon. This is the first case to our knowledge of diabetic ketoalkalosis in the setting of Boerhaave syndrome. The metabolic alkalosis in this patient was a clue to the presence of significant underlying GI pathology, which ultimately required surgical intervention.

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EP68

Temporal mandibular involvement in external necrotizing otitis

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Aims
To describe the epidemiological and clinical characteristics of temporal-osteomyelitis mandibular complicating necrotizing otitis externa and discuss how to take it in load.
Materials and methods
This is an 18-year retrospective study [2010–2017], conducted in our ENT department, collecting 74 hospitalized patients for management of necrotizing otitis externa.
Results
The average age was 67 with a sex ratio of 1.13. All patients were diabetic. Otalgia was the master symptom. A chewing pain with a limitation of the mouth opening was found in 3 patients. Clinical examination confirmed the diagnosis of otitis externa. The palpation was painful on palpation compared to TMJ in all patients. Trismus was present in 4 patients. A biological inflammatory syndrome was present in all patients. Otitis externa was bacterial in 4 patients with Pseudomonas and mycosic in 2 patients. A CT of the rocks confirmed the achievement of TMJ with signs in favor of temporo-arthritis mandibular in all patients. Facial mass MRI performed in addition to computed tomography in one case confirmed the extension of infection to the para pharyngeal space and showed condyle involvement mandibular and infiltration of the external pterygoid muscle. Treatment was medical in all cases.
Conclusion
Temporal-mandibular osteomyelitis is a rare complication of necrotizing otitis externa. The spread of infection may be secondary to tympanal osteitis or occur through congenital dehiscence of the external auditory canal. Pain, limitation of opening oral and pre-tragic swelling are the main clinical signs. The treatment is mainly medical, based on antibiotic therapy.

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EP69

Assessment of insulin injection technique among diabetic patients

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Introduction
Diabetes is a chronic disease and a public health problem. Insulin Injection is used as a treatment for type 1 diabetes and insulin-requiring type 2 diabetes. A well-made injection is the key to a good glycemic balance. However, many studies showed that diabetic patients did not master the injection technique, reflecting an empirical random or non-existent therapeutic patient education(TPE). Our objectives were to assess our patients' knowledge of injection technique, to identify factors associated with glycemic balance and pain.
Methodology
This is a cross-sectional and descriptive study involving 50 diabetic patients (DT1: 40%, DT2:60%) insulin-treated recruited from the endocrinology department of the military hospital of Tunis, based on a questionnaire inspired by validated questionnaire proposed by Francophone Society of Diabetes(SFD) for the evaluation of the acquired knowledge of diabetic patients. The assessment of pain was carried out by the visual analogue scale(VAS).
Results
Our population was predominantly male (sex ratio 1.27). The mean age was 56.4 ± 19.4 years. The mean duration of diabetes was 13.3 with an average HbA1c of 10.2%. Insulin therapy averaged 7.4 ± 5.5 years (22% bed time, 36% basal, 42% basal/bolus). The mean number of daily injections was 3 with extremes ranging from 1 to 6. Thirty-three patients received an education mainly on themes of 'insulin conservation' (78.8%) and 'choice of injection site' (63.6%). Deficiencies mainly concerned the rotation of injection sites (20%), the search of lipodystrophies (14%), the practice of skin fold (48%), the reuse of needles (86%), and the unsafe waste disposal (94%). Glycemic balance was associated with rotation of injection sites($P = 0.01$) and the practice of skin fold($P = 0.01$). The presence of pain and its intensity were associated with the average number of injections per needle ($P = 0.04$ and $P = 10$€respectively).
Conclusion
The role of caregivers is essential in the TPE of diabetic patients. However, they must be trained in this mission and guided through a pre-established program.

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EP70

Hospital admission, a good time to optimize treatment and rethink the diagnosis

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Introduction
Prediabetes and type 2 diabetes prevalence in children and teenagers has been rising lately, according to obesity increase in this population. Diabetes is the first cause of kidney failure in this individuals. These clinical entities are associated with hypertension and dyslipidemia, leading to an increased risk for cardiovascular disease. In this case, as a result of the presence of a diabetic complication, the differential diagnosis of the cause of diabetes is reconsidered.
Case report
33-year-old-woman diagnosed with hypertension, obesity and type 1 diabetes developed at the age of 14. She currently has no glycemic control (last HbA1c determination 2 years ago: 12%) and her diet is based on refined carbohydrates and processed food products. She is supposed to follow a treatment regimen consisting of insulin Glargine once a day and insulin Aspart at meals, but she acknowledges treatment nonadherence. She is admitted to the hospital because of fever, swelling and purulent drainage of second and fourth fingers of her left foot, being finally hospitalized for intensive intravenous antibiotic therapy and surgical drebidement. During the hospital admission she has normal glucose levels without insulin treatment, just following a balanced diet. Due to this unexpected well-controlled glucose levels, her diabetes diagnosis is reconsidered. Her disease history was checked: she was diagnosed with tuberculous meningitis at the age of 4 so she was under treatment with high-dose corticosteroids for several months. It led to iatrogenic Cushing syndrome, reduced growth and eventually short height. She received treatment with growth hormone during childhood and developed diabetes during puberty. She started treatment with oral antidiabetic drugs but due to uncontrolled glycemias she is finally treated with insulin regimen. In order to clarify her type of diabetes, some tests are done: glucose 175 mg/dl, HbA1c 8.7%, serum insulin level 7.1 (3–25 mUI/ml), C-peptide 2.63 (0.81–3.85 ng/ml), ACTH 16.1 (5–50 pg/ml), serum cortisol 9.8 (5–25 mg/dl), PCR-us 2.31. Anti-insulin, anti-tyrosine phosphatase y anti-glutamate antibodies were negative. Considering this results, she is finally diagnosed with type 2 diabetes. During the hospitalization she receives diabetes self-management education and at hospital discharge she is recommended to follow a treatment with Metformin twice a day and Losartan daily.
Conclusions
It is important to reconsider established diagnosis when a disease does not follow the expected progression and clinical manifestations. Nowadays, type 2 diabetes is a common disease in children and teenagers and its proper diagnosis is essential for an adequate treatment.

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EP71

Needs and expectations of Tunisian diabetic patients in terms of therapeutic education

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Background
Faced with the increase in the number of diabetic patients in Tunisia, an inventory of their needs as well as their expectations is necessary to help the medical staff deliver appropriate means of therapeutic education of the patient.
Aim
We aim to assess Tunisian diabetic patients' understanding of the disease, evaluate its impact on several aspects of their life, and classify their needs and expectations.
Methods
We used a semi structured qualitative interviews analyzed using SPSS. Tunisian adults (≥18 years) living with type 1 diabetes mellitus (DM) or type 2 DM able to describe their situation in Arabic were included.
Findings
We have collected 55 patients, 7 with type 1 DM and 48 with type 2 DM. Only half of interviewees think they have a good understanding of diabetes and its complications while two thirds of them think that they were not well educated concerning anti-diabetic therapies. For over 45% of patients, diabetes has badly impacted their life quality. In terms of satisfaction, 76% of interviewees were satisfied with the procured medical care while only 50% were satisfied with the financial and psychological support they receive. Interestingly, we found that over two thirds of diabetic patients find that they get an unsatisfactory therapeutic education. This goes hand in hand with the fact that two thirds of the interviewees were unaware of the existence of therapeutic educational programs. Regarding patients' expectations, we found that most of our patients consider getting information about the disease as their first priority. In the second place, our patients were expecting to be more informed about dietary and therapeutic issues. Thirdly, they expressed their need to be educated about preventive measures against diabetes complications. Education about economic, legal, psychological and social aspects of the disease came as a last tier concern. Finally, collected data suggest that whether a patient is treated in public or private sector had a significant influence on his priorities.
Conclusion
These findings highlight a need to develop and promote context-specific, patient-oriented therapeutic educational programs.

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EP72

Insulin Pen first demo effectiveness in Novel insulin pen users in Central Indian Population

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Introduction
Insulin remains the cornerstone of therapy in a substantial number of patients with type 2 diabetes mellitus (T2DM). Inadequate knowledge regarding insulin pen usage is likely to influence its acceptance and adherence, and outcome of therapy, underscoring need to teach proper injection pen technique to T2DM patients
Methods
In 2019–2020 we conducted survey of 328 respondents (male: 202, female: 126), novel Insulin pen user patients who were enrolled as outpatient in a Diabetes clinic during last one years (2019–2020), to assess the ability to use insulin pen after one demonstration by an insulin advisor.
Results
Out of 328 respondents 34% were not able to use insulin pen injections after first demonstration. the inability to use insulin pen was more in rural patients 63%, in females 58% as compared to males 42%, was more in lower educational status and was more in basic phone users 72% as compared to smart phone users 38%.
Discussion
This study shows that there is a pressing need to develop strategies to teach patient in a better way to self-administer insulin via insulin pen. We can predict based on educational status and other parameters mentioned in study to give more elaborate training to those groups in need. And there is a further need to study the efficacy and adaptability of various ways of teaching patients about the insulin pen.
Keywords
Diabetes, insulin injection, insulin pen, patient knowledge.
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EP73

Case of Mucopolisaccharidosis Type 4A (Morquio 4A)

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Introduction
Mucopolysaccharidosis type 4A (Morquio 4A) is an autosomal recessive lysosomal storage disease caused by a mutation in the gene encoding galactosamine 6 sulphatase (GALNS). It's main clinical features include short stature, skeletal dysplasia,cloudy cornea,hearing loss and dental anomalies. Herein, a case of Morquio 4A, a rare cause of short stature is presented.
Case report
A 41 year old female patient was admitted to our clinic for short stature. On physical examination height 95 cm,body weight 24 kg, kyphoscoliosis, short neck, pectus carinatum,genu valgum,nasal root flattened,coarse forehead and abnormal gait were detected. There was hearing loss and decrease in vision. There was no previous history fractures. Her parents were relatives and had normal height. Four of her ten siblings were short, two of whom died in the fifth decade. Laboratory tests were normal. DEXA with *Z* score for L1–L4 and femoral neck were −3.1, −1.7, respectively; BMD was 0.590 g/cm^2 and 0.600 g/cm^2 for L1–L4 and femoral neck respectively. Diffuse loss of height in the vertebrae (platyspondyle), sharpening of the anterior vertebrae,shortening of the long bones,enlargement of the metaphysis,diffuse decrease in bone density,irregularity in the epiphyses (epiphyseal displasia) were observed in bone survey examination. These findings were thouht to be compatible with mucopolysaccharidosis type 4A (Morquio 4A). *N*-acetylgalactosamine 6 sulfatase enzyme activity in leukocyte was<0.1 nmol/mg 17 h (>68). In the genetic analyses, homozygous mutation encoding the C.1157+2T>6(p?) nucleotid was detected in the GALNS (NM-001323544.1) gene. The patient was diagnosed with Morquio 4A (MIM#253000). Vitamin D and calcium were initiated for bone health. Enzyme therapy was planned.
Conclusion
Although Morquio 4A is a rare cause of short stature,it should recognise especially in those with a family history. Carriers of this disease should be determined by advising genetic counseling to the families of these patients. These patients may have many vital organs involvement other than bone,follow up and treatment with a multidisciplinary approach is required. Although there is an enzyme replacement therapy there is no curative therapy yet.

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EP74

Epidemiological aspects of differentiated thyroid carcinoma metastases

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Introduction
Differentiated thyroid cancer (DTC) is the most common thyroid cancer with a relatively high survival rate. Distant metastasis (DM) is not a frequent event in DTC but has an adverse impact on mortality of patients.
Purpose
The aim of this study was to determine the most frequent metastases and their prognosis after adequate treatment.
Methods
A retrospective study of patients who had DTC metastases and were treated in the nuclear medicine departement in Hbib Bourguiba hospital, Sfax, Tunisia.

Results
A total of 26 patients had remote metastases, 19 of whom had metastasis at the time of initial diagnosis. Metastasis locations in descending frequency order were : lungs (42.3%), mediastinum (15.3%), lungs + bones (15.3%), lungs + mediastinum (7.7%), liver (7.7%), eye (3.8%) and lungs + other locations (7.7%). For pulmonary metastases, it was a miliary lung in 64.7% of cases, a single or multiple pulmonary nodule in 17.4% each. Bone metastases were unique in 2 patients and multiple in the rest. In order of frequency : Sternum : 2 cases, pelvis : 2 cases, lumbar spine : 2 cases, femur : 2 cases, shoulder : 1 case, Skull :1 case. All of our patients had radioactive iodine ablation and 8 of them had additional therapies : surgery was performed to one patient with unique mediastinum meatastases, one with both mesdiastinum ang lung metastases and 2 patients with lungs and bones metastases. Radiotherapy was performed to 4 patients (3 cases of mesdiastinum ang lung metastases and one case of lungs + bones + liver metastases). Two cases of death were reported (mediastinum metastases, lungs and bones metastases). Recovery was observed in 15 patients whilst eight had a stable health state. High thyroglobulin level remained stable in one case of lungs metastases.
Conclusion
The most common sites of metastatic differentiated thyroid cancer are the neck lymph nodes, while distant metastases typically involve the lungs, the bones, and less frequently the brain. Uncommon metastatic sites include the liver, adrenal gland, kidney, pancreas, and skin. The epidemiological aspects of thyroid metastases in rare sites are largely unknown and their identification could have a significant impact on patients management.

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EP75

Systemic diseases and diabtes

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Introduction
The association of type 1 diabetes with other autoimmune diseases is well known due to a common genetic terrain of varied clinical expressions. However, the occurrence of systemic diseases in diabetic patient, whatever the type of diabetes, is poorly studied. The objective of this study is to describe autoimmune and inflammatory diseases associated with diabetes.
Materials and methods
It ' s a retrospective, descriptive study of the observations of diabetic patients followed up in our department, who have been diagnosed with an associated systemic disease based on clinical, immunological and/or histological data.
Results
We involved 22 patients: 20 women and 2 men with an average age of 49.9 years at the time of diagnosis of diabetes. They were type 2 diabetes in 19 cases (86.3%), type 1 diabetes in 1 case (4.5%), corticosteroid-induced diabetes: 1 case and gestational diabetes: 1 case. The discovery of diabetes is made in front of polyuropolydipsia in 14 cases, weight loss in 6 cases and fortuitous in 3 cases. Oral antidiabetic drugs (OADs) were prescribed in 18 patients and insulin therapy was immediately initiated in 3 cases. Metabolic syndrome was noted in 41% of patients. Vascular complications of diabetes were noted in 68% of cases. Associated systemic diseases were Rheumatoid Arthritis: 12 cases (54.5%), Sjogren's Syndrome: 4 cases (18%), Hashimoto's autoimmune thyroiditis: 2 cases (9%). Primary biliary cirrhosis, Horton's disease, Behçet's disease, antiphospholipid syndrome and Still's disease were objected in 1 case respectively. Diabetes preceded the systemic disease in 8 cases for an average duration of 11 years, succeeded it in 8 cases for an average duration of 11 years and occurred concomitantly in 6 cases. Diabetes was unbalanced at the time of relapses of the systemic diseases in 81.8% of cases.
Conclusion
Each of the two pathologies can influence the evolutionary course of the other, while underlining the effect of the outbreaks of systemic diseases on the imbalance of diabetes by the inflammation they generate or by the prescribed therapeutics.

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EP76

Hepatogenous diabetes: is it real?

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Introduction
Diabetes mellitus (DM) due to cirrhosis is described as hepatogenous diabetes (HD). Despite being frequently described in the literature, it is not recognized as an entity by the ADA/EASD.
Case report
Woman, 70 years old, previous history of autoimmune hepatitis with Child-Turcotte-Pugh A cirrhosis (CTP-A) since 2018, arterial hypertension and overweight (BMI 29.1 kg/m^2). No personal or family history of DM. Medicated with bisoprolol 5 mg, candesartan 8 mg, furosemide 20 mg, spironolactone 25 mg. Normal glycemic profile until May 2019, when was admitted in the Emergency Department with polydipsia, polyuria and loss of 10 kg in 2 months. No infectious complications or medication changes were noticed. The patient was diagnosed with hyperosmolar syndrome, with glycemia of 629 mg/dl, ketonemia 0.2 mmol/l, without acidosis (pH 7.43), HbA1c 14.2%. No increase in inflammatory parameters, amylase, lipase and no renal dysfunction was detected. Liver profile was according to the patient's baseline (AST 79 UI/L; ALT 43 UI/L; ALP 136 UI/L; total bilirubin 0.95 mg/dl). An optimal response to insulin therapy was observed, with discharge after 15 days. During hospitalization, an abdominal CT was performed, which excluded pancreatic lesions or masses. No changes in iron or cortisol metabolism were observed and anti-Langerhans islet antibodies, anti-insulin, anti-GAD studies were negative. During follow-up, after discharge, she maintained an excellent metabolic control (HbA1c 6.2%) medicated with metformin/empagliflozin 850/5 mg twice a day and 34 U/day of glargine insulin.
Discussion
The present case describes a newly diagnosed Diabetes in a patient with cirrhosis, suggesting a HD. The patient had no personal or family history of DM and did not show the progressive worsening usually observed in type 2 Diabetes. Infection, use of hyperglycemic medication, autoimmune and other causes for secondary DM were excluded. Although the prevalence of HD is related to the severity of cirrhosis, this prevalence may reach 20.5% in CTP-A, with an increase of 4.4% just 1 year after diagnosis. Liver dysfunction appears to cause hyperinsulinemia by decreasing insulin clearance and combined with an increase in inflammatory mediators, causes tissues' insulin resistance and pancreatic islets Œcells' toxicity. These changes lead to a deterioration in glucose metabolism that follows the worsening of cirrhosis. Treatment can be challenging in advanced stages of cirrhosis, due to dysfunctional liver metabolism, which can cause greater susceptibility to hypoglycemia and worse metabolic control.

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EP77

Does sars-cov 2 causes diabetes?

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Does COVID cause diabetes?

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Little is known on the impact of acute COVID-19 infection on causation of diabetes. We report on a 36 years old man from Nigeria who presented with diabetic ketoacidosis (DKA) with typical osmotic symptoms of polyuria and polydipsia, fatigue and weight loss over 2 weeks. He tested positive for SARS-COV2 by PCR. The initial laboratory results: Random glucose 30.6 mmol/l, capillary blood ketones 7.4 mmol/l, pH 7.22, bicarbonate 7.5 mmol/l. Despite insulinopaenic state, at presentation, he was insulin resistant requiring several upward adjustment of IV insulin therapy, requiring over 200 units IV Actrapid infusion in the first 24 h i.e. 8–9 units per hour. At 2 weeks, basal bolus subcutaneous insulin requirement was 1.2 U/kg per day. Currently, 6 weeks after diagnosis, insulin requirement was lower at 0.52 U/kg with drop in HbA1c from 125 to 67 mmol/mol. Retrospectively, random C-Peptide 0.41 µg/l (1.1–4.4) and repeated 6 weeks 0.9 µg/l, Islet cell Ab 14 U/ml (<28), AntiGAD Ab 24 IU/ml (<17) repeated 6 weeks 11 IU/ml.

Discussion
New presentation of DKA with acute COVID-19 in a young Nigerian man. Initially insulin resistant despite insulinopaenia but resolution of insulin resistance by 6 weeks, and persistence of ketonemia despite normal acid base. Initially elevated Anti GAD Ab but six weeks later normalised. Is it latent autoimmune diabetes, or ketosis prone diabetes, or a hybrid pleiotropic metabolic effects of COVID-19 infection from as yet undefined mechanism?

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EP78

Influence of diabetes mellitus on mortality in patients hospitalized with COVID-19

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Introduction
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has generate a pandemic disease around the world. It has been documented that diabetes mellitus (DM) acts as a risk factor among people hospitalized with coronavirus disease (COVID-19). The objective of this study is to test if DM may unfavorably influence the outcome of COVID-19.
Methods
Data from Hospital Universitario Central de Asturias (Spain) of patients older than 55 years hospitalized with COVID-19 between 3 March 2020 and 30 September 2020 were collected. We compared patients with previous diagnoses of type 2 DM and no diabetes patients. We analyzed the percentage of deaths according to glycosylated hemoglobin (HbA1c) in the last 365 days before admission. Analysis was performed by using GraphPad Prism, 8.0.1 version. Statistical differences were evaluated by Chi-square and Chi-square with Yates correction.
Results

		n	Age	Sex (M/F)	Death (%)	P
DM		116	75.67	72/44	26 (22.41)	0.5403
No DM		359	73.89	203/156	71 (19.78)	
Sorted by age						
55-69 years	DM	33	64.46	26/7	2 (6.06)	0.9632
	No DM	143	62.43	88/55	11 (7.69)	
70–79 years	DM	46	74.54	31/15	12 (26.09)	0.3665
	No DM	100	73.9	62/38	18 (18)	
> 79 years	DM	37	87.08	15/22	12 (32.43)	0.8253
	No DM	116	88	53/63	42 (36.21)	
Sorted by sex						
Male	DM	72	73.26		18 (25)	0.8171
	No DM	203	72.72		48 (23.65)	
Female	DM	44	79.61		8 (18.18)	0.5778
	No DM	156	75.40		23 (14.74)	
		n	Age	Sex (M/F)	Death (%)	P
HbA1c < 7		63	72.66	45/19	11 (17.46)	0.9868
HbA1c < 7		19	74.79	7/12	4 (21.05)	

Discussion
Our results suggest that diabetes mellitus could be a risk factor of death in patients hospitalized with COVID-19, even if there is no statistical association. According to our study, an innapropiate glycemic control could increase the risk of death. It is necessary to perform new researches to confirm these results. In conclusion, COVID-19 is a new reason to encourage our patients to achieve therapeutic goals.

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EP79

Diabetics hospitalized for COVID-19: descriptive study

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Introduction
The SARS-Coronavirus-2 pandemic affects 248 469 people with 28 341 deaths in Spain as of June 28, 2020. Severe infection is more prevalent in patients with advanced ages, cardiovascular risk factors (CVRF) and chronic diseases (diabetes mellitus, cardiovascular disease and asthma). Having diabetes implies vulnerability to serious complications and death from coronavirus; although, not all diabetics have the same level of risk. The oldest is present over 65 years of age. This study analyzes the profile of diabetics and baseline characteristics of those admitted for SARS-Coronavirus-2 in a third-level hospital in Granada (Andalusia, Spain).
Material and methods
Retrospective descriptive study. 102 diabetics admitted for COVID-19 treated with Glargine U100, between March 12-May 15, 2020 at Hospital Universidad San Cecilio. We reviewed electronic medical records to collect variables: gender, age, CVRF, type of diabetes, glycosylated hemoglobin (HbA1c), angiopathic complications, and home treatment.
Results
54% men. 97% diabetes mellitus 2, 2 debuts, and 0.03% diabetic due to high-dose corticosteroid therapy. Over 65 years, 76.47%. 92% associated comorbidities with diabetes: hypertension (82.35%, 60.7% were taking ACEI or AIIRA), dyslipidemia, hyperuricemia or angiopathic complications. 27.45% microangiopathic, the most frequent: 23.5% chronic kidney disease and 32.35% macroangiopathic: 13.7% cerebrovascular disease and 14.7% ischemic heart disease. At home, 36.27% were insulin dependent. 50.1% HbA1c (up to 1 previous year) lower than 7.5%. Mortality 17.65%, 88.8%> 65 years. Among the deceased, 100% hypertensive, 83% took angiotensin converting enzyme inhibitors or angiotensin receptor blockers, 100% some comorbidity and average HbA1c around 7.5%.
Conclusions
The most frequent diabetic profile hospitalized for COVID-19 has been DM 2 over 65 years with CVRF and/or angiopathic complications. It is deduced from the average HbA1c value among the deceased that diabetes per se is not a determining factor in the severity and/or mortality of the infection.

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EP80

COVID-19-associated syndrome of inappropriate anti diuretic hormone secretion in type 2 diabetic patient: A case report

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Introduction
Hyponatremia secondary to the syndrome of inappropriate anti diuretic hormone (SIADH) secretion is one of the most frequently observed electrolyte abnormalities in coronavirus disease -2019 (COVID-19). Herein, we report a new case of SIADH in a type 2 diabetic patient with COVID-19 pneumonia.
Observation
A 79-year-old man with type 2 diabetes mellitus was admitted for a poor general condition. On physical examination, he had a tachycardia and alveolar sounds. No other abnormalities were found. On biological investigations, he had a blood glucose level of 15 mmol/l, a serum sodium of 122 mmol/l, a potassium level of 4.1 mmol/l, a serum urea level of 0.17 g/l, a serum creatinine level of 7 mg/l, a C-reactive protein (CRP) of 53 mg/l, white blood cells of 3380 elements/mm^3, and lymphocytes of 660 elements/mm^3. Corrected natremia was 124.7 mmol/l and the plasmatic osmolarity was 270 mOsmol/l. Chest computed tomography-scan revealed a suggestive aspect of a moderate COVID-19 pneumonia. RT-PCR nasopharyngeal swab test was positive. The diagnosis of SIADH was established and the patient was put on a fluid restriction. The outcome was marked by the elevation of the natremia reaching 133 mmol/l.
Conclusion
Hyponatremia due to SIADH was reported in patients with COVID-19 infection. Its pathophysiological mechanism involves many factors associated with infection such as cytokine storm, stress, and pain. However,

it is important to rule out other etiologies of hyponatremia in order to ensure the appropriate management.

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EP81

Covid-19 and dexamethasone treatment as a cause of Hyperosmolar Hyperglycaemic State in a patient with unknown diabetes mellitus before. A case report

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Introduction
COVID-19 can precipitate hyperglycaemic emergencies like Hyperosmolar Hyperglycaemic State (HHS) in patients with or without DM. It is currently hypothesized that COVID-19 may have a diabetogenic effect in addition to the stress-related response of glucose metabolism in severe illness. Dexamethasone reduces mortality in people with COVID-19 who require ventilation or oxygen therapy but can impair glucose metabolism. We present a case with HHS precipitated by COVID-19 infection and corticoid treatment in a patient without prior history of Diabetes Mellitus.
Case presentation
We present a clinical case of a woman 85 years old, obese that was admitted to the emergency unit in coma. Medical history: She has been treated for high blood pression and bronchial asthma for 30 years but not known before for diabetes mellitus. No family history of diabetes. In early December 2020, she was diagnosed with COVID-19. Because of severe Covid-19 form, she was treated with antibiotics, oxygen therapy and dexamethasone 8 mg/day for 10 days. After one month, she was improved but she complained progressive fatigue and weakness, polyuria-polydipsia, anorexia. Every symptom was attributed to Covid-19 and it was hoped that over time they would disappear. But symptoms have been aggravated during the last 2 weeks and she was presented in emergency unit in coma. Laboratory examinations: Hyperglycaemia (1280 mg/dl),high level of urea and creatinine (222.4 mg/dl and 2.88 mg/dl) respectively, high level of cardiac enzymes (LDH693,Ck566 u/l, Troponin1, 86 ng/ml),High PCR16 mg/dl, high D-dimer418 mg/dl(<198) normal level of SGPT,SGOT. Na+153 mmol/l, K+4.3 mmol/l. WBC32000 with high neutrophils and low lymphocytes. Mild normochromic normocytic anaemia. HGA: Ph7.4 but O2 saturation83%. High plasma osmolarity = 402 mOsm/kg. Imaging examinations: Head-CT: without acute intracranial lesions. Lungs CT: Interstitial opacities in absorption with invadation of less than 10% of lung tissue, aspect in favour of post Covid-19 changes. After the examinations, it was concluded that, the situation was related to HHS precipitated by COVID-19 infection and corticoid treatment in a patient without prior history of Diabetes Mellitus. Initially she was treated in Intensive Unit Care with iv liquids, oxygen therapy, anticoagulants, antibiotics, insulin therapy. After 3 days, stabilised, she was transferred in the Endocrinology Department for further treatment. After 10 days in a good general condition, she was discharged from the hospital with endocrinologist follow-up under insulin therapy.
Conclusion
COVID-19 together with dexamethasone treatment can precipitate Hyperosmolar Hyperglycaemic State, a life threatening situation, in a patient without diabetes. All physicians must be aware about this situation, to prevent it.

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EP82

New onset type 1 diabetes during COVID 19 pandemic : experience of a single tertiary care Center

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Introduction
After the emergence of the COVID 19 pandemic, many publications have interested in type 2 diabetes mellitus with a dearth of papers regarding type 1 diabetes mellitus (T1DM), especially new-onset type 1 diabetes which entails a special concern. We report herein the experience of a single tertiary care Center.
Methods
A retrospective observational study including New-onset T1D patients between March 2020 and December 2020 comparing with the same period of the year 2019. Data were collected from patient charts, and teleconsultation reports.
Results
Between Mars 2020(Lockdown Covid-19) until December 2020, 29 patients have been admitted to our Department. The pediatric population represent 65.5% of them and the sex ratio H/F is 1.27. Compared to the same period of the last year we observed an increase of 22%. Severe ketoacidosis (DKA) was observed in 28% of patients in 2020 and 17.4 of patients in 2019 (P<0.001). The mean baseline Hba1c was: 12.72% (± 1.6). The follow-up was ensured using teleconsultation and the therapeutic adjustment was made daily for 2 weeks after discharge. No episode of decompensation or severe hypoglycemia was noted during follow-up and the mean Hb1Ac at 3 months was 7.2%
Conclusion
Several papers report an increase in the number of New-onset T1D diabetes and the severity of ketoacidosis DKA during the COVID-19 pandemic. The potential bidirectional link between COVID 19 and T1DM is being investigated. Telemedicine seems to be an effective approach for the management of patients with New-onset T1D.

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EP83

Assessment of biochemical indicators in laboratory diagnostics of metabolic syndrome

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Metabolic syndrome (MS) is one of the most pressing problems of modern medicine. MS is a symptom complex of impaired carbohydrate metabolism, abdominal obesity, dyslipidemia, hypertension with an increased risk of developing cardiovascular diseases and type 2 diabetes mellitus. The main reasons for the increase in the incidence of MS are a decrease in physical activity and a high-calorie diet. The prevalence of MS in different countries is 25–30% and varies depending on the criteria used. The aim of our study was to assess the role of blood biochemical parameters in the diagnosis of MS. Materials and methods. 60 patients with MS and 45 apparently healthy volunteers were examined on the basis of the therapeutic department of the Federal Research Center "Krasnoyarsk Science Center" of the Siberian Branch of the Russian Academy of Sciences. The glucose level was determined by the glucose oxidant method, the lipid profile was assessed using standard test systems. Insulin level was determined by enzyme immunoassay using the DRG test system. All examined persons signed an informed consent to participate in the study, approved by the ethics committee of the Federal Research Center "Krasnoyarsk Science Center" of the Siberian Branch of the Russian Academy of Sciences. Statistical data processing was carried out using the Statistica for Windows 8.0 software packages with the determination of the median (Me) and interquartile range (C25–C75). The statistical significance of differences was determined using the Mann–Whitney rank test, P <0.05. Results In patients with MS, the HOMA-IR index increased by almost 2 times (P = 0.003) relative to the control group, which is a predictor of the risk of developing vascular and diabetic complications in them. The non-esterification fatty acids (NEFA) content was increased in all patients with MS (P = 0.001), while the NEFA value was 2 times higher than normal values (P = 0.004). There was an increase in the content of insulin (P = 0.002) and glucose (P = 0.003) in the fasting blood in patients with MS in comparison with the control group. Conclusion The study confirmed that early diagnosis of vascular and diabetic complications in patients with MS requires a combined determination of the HOMA-IR index and the content of NEFA. These indicators were sensitive in all patients with MS.

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EP84

Assessment of the quality of life, anxiety-depressive disorders in patients with metabolic syndrome

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The prevalence of MS in different countries is 25–30% and varies depending on the diagnostic criteria used. The severity of the clinical manifestations of MS affects the quality of life (QL) of patients, while the indicators of physical and mental health decrease. The problem of QL of patients suffering from overweight and obesity is relevant and socially significant. Obesity leads to anxiety-depressive disorders, neurosis-like conditions, which contributes to a worsening of the prognosis of the underlying disease. The aim of the work was to assess QL, the level of anxiety, depression in patients with metabolic syndrome.
Research methods
60 patients with MS and 35 apparently healthy volunteers who did not have concomitant diseases and were not obese were examined. The study was carried out on the basis of the therapeutic department of the Federal Research Center "Krasnoyarsk Science Center" of the Siberian Branch of the Russian Academy of Sciences. Examination of patients, determination of anthropometric parameters (waist circumference, body weight, BMI) with an assessment of the quality of life (questionnaire SF-36, Russian version, Institute of Clinical and Pharmacological Research, St. Petersburg). The level of anxiety and depression was determined according to the hospital scale of anxiety and depression HADS (The hospital Anxiety and Depression Scale Zigmond A.S., Snaith R.P.). The statistical significance of differences was determined using the Mann–Whitney rank test, $P<0.05$.
Results
Indicators of the QL level were significantly higher in healthy individuals than in patients with MS (P = 0.001). Our study revealed a decrease in the average level of the parameters 'physical functioning' by 18.3% (P = 0.003), 'role functioning' by 32.1% (P = 0.002), 'general health' by 12.3% (P = 0.001), 'vitality' by 15% (P = 0.03), 'emotional functioning' by 51.1% (P = 0.03). The level of anxiety and depression in patients with MS corresponded to the subclinical level, the level of depression exceeded the value of the control group by 19% (P = 0.04).
Conclusion
QL in obese patients is one of the most important factors in the integrative assessment of patients' condition, the higher the patient's body weight, the worse his physical condition and the more pronounced concomitant diseases. Patients with MS are characterized by a decrease in quality of life indicators, subclinically expressed anxiety/depression.

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EP85

Assessment of obesity in patients with toxic hepatitis

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Background
Over the last years obesity has become an important medical and social problem in almost all countries of the world. The social significance of the problem is determined by the disability threat of patients and reduction of overall life expectancy due to the frequent comorbidities development. According to scientific data and modern ideas, there are a number of factors that affect not only the course of toxic hepatitis, but also the therapy effectiveness. The bulk is due to obesity.
Objectives
Examination of patients with toxic hepatitis for obesity detection as one of the hepatic fibrogenesis triggers.
Methods
To achieve this goal, 24 patients with toxic liver disease were examined. The body mass index (BMI, Kettle index) was calculated using anthropometric indicators. Due to the formula BMI is a person's weight in kilograms divided by the square of height in meters. BMI is an inexpensive and easy screening method for weight category—underweight, healthy weight, overweight, and obesity. For all our patient which are 20 years old and older, BMI is interpreted using standard weight status categories (classification of BMI adopted by the WHO (1997). The value of BMI in the range of 18.5–24.9 kg/m^2 should be considered optimal – normal or healthy weight; reduced BMI or underweight ≥ 18.5; overweight – 25.0–29.9; obesity I degree – 30.0–34.9; obesity II degree – 35.0–39.9; grade III obesity – ≥ 40 (kg/m^2).
Results
The examination revealed that the following changes were observed in BMI: 42% of patients were with normal weight, 21% were overweight, obesity I degree was detected in 25% of patients and 13% of patients were with obesity II degree.
Conclusions
Obesity of varying degrees was found in 58% of patients with toxic hepatitis. These data should be taken into account when choosing and prescribing adequate treatment. Last, but not least, nutrition should always be considered. Given that obesity can be a trigger of hepatic fibrogenesis in patients with toxic hepatitis this issue requires further research to identify the possible impact of concomitant non-alcoholic fatty liver disease on the course of toxic hepatitis.

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EP86

Bariatric surgery: a shift in metabolic control

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Introduction
Obesity is a chronic disease that is associated with several comorbidities, decreased quality of life, and increased mortality rate. Bariatric surgery is the most effective therapy for obese patients with class III and class II with metabolic diseases. Its effectiveness is not only related to the weight reduction, but also to the improvement of the metabolic profile. The aim of this study is to characterize the effects of gastroplasty with Roux-en-Y (gastric bypass – BG) and vertical gastrectomy (gastric sleeve – SG) in reducing obesity and associated comorbidities.
Methods
Prospective study of patients with class III and class II obesity with metabolic diseases who underwent BG or SG between May 2017 and May 2020. Clinical observation at 0, 6, 12, 18 and 24 months.
Results
43 patients, 53.5% male, mean age 49+9 years, mean BMI 41.9+2.9 kg/m^2, 67.4% submitted to BG and 32.6% to SG. The average excess weight lost percentage was 74.3+16.3% at 6 months (n = 43), 84.3+20.9% at 12 months (n = 39), 79.3+22% at 18 months (n = 28) and 73.3+24% at 24 months (n = 22). No difference between patients undergoing BG or SG (P-value = 0.2) or between men and women (P-value = 0.114) was observed. Mean abdominal circumference reduction was 20.6+5.5% at 24 months and body fat mass percentage reduction was 27.7+17.2%, with no difference between procedures (P-value = 1 and 0.114). 53.5% of patients had Diabetes mellitus or pre-diabetes, 60.8% achieved total remission at 24 months after surgery and 21.7% partial remission (pre-diabetes). 58% had arterial hypertension, 52% achieved remission and 40% reduced the number of antihypertensive drugs. 86% had altered lipid metabolism, 46% achieved remission and 5% reduced the number of drugs. 60% of patients suffered from obstructive sleep apnea syndrome, with remission achieved in 46% of patients and a 54% reduction in severity. 85.7% of the patients had steatosis on preoperative abdominal ultrasound, with 60% having hepatomegaly. In the reevaluation at 12 months, 53.2% maintained steatosis and 7.6% hepatomegaly.
Conclusion
Bariatric surgery is a treatment option that provides excellent results in reducing weight, abdominal circumference and percentage of fat mass. The underlying modification of the metabolism allows the correction of comorbidities associated with obesity, with remission in a large number of patients.

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EP87

Social phobia and predictive factors in obese adults

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Introduction
In Tunisia, obesity is a public health problem. In fact, it has been considered as a complex disease including alteration of the nutritional, somatic and psychological functioning of the individual. Various psychological disorders have been associated with it such as social phobia (SP). In this context, our study was conducted to determine the psychological profile in terms of SP in obese adults.
Methods
This was a cross-sectional descriptive study. We included obese adults aged 19 to 64 who consulted in the basic health districts of Sfax, South Tunisia,

and who had a body mass index (BMI) greater than or equal to 30 kg/m^2. Data was collected using a validated anonymous questionnaire: Liebowitz Social Anxiety Scale (LSAS).
Results
A total of 150 adults were included with an average age of 47.1 ± 12.5 years. Females accounted for 76.7% with a sex ratio H/F = 0.3. The mean BMI was 35.9 kg/m^2 (s.d. = 5.6). Eighty-two subjects (54.7%) had grade I obesity, 31 subjects had grade II (20.7%) and 37 subjects (24.7%) had grade III. Abdominal obesity was present in 142 people (94.7%). The study of the psychological profile revealed that 33.59 and 58 patients had respectively a mild, a moderate and a severe intensity of SP according to the LSAS questionnaire. the study of the factors which condition the severity of SP had shown that it was correlated with age (31% of the subjects of the age group [19,34] had severe SP vs 39% of the group [35,49] vs 41% of the group [50,64], $P = 0.01$). On the other hand it was not correlated with gender, the grade of BMI, the practice of a physical activity or the somatic impact of obesity.
Conclusion
The prevalence of SP was significant in our study population. As a result, the establishment of a national care program for obese patients including psychologists is mandatory.

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EP88

Rooibos tea (Aspalathus linearis) upregulates hepatic sex hormone-binding globulin production

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Sex hormone-binding globulin (SHBG) is a circulating plasma glycoprotein produced by the liver, which in the blood binds estrogens and androgens with high affinity and regulates its bioavailability. Low plasma SHBG levels are associated with obesity, metabolic syndrome and non-alcoholic fatty liver disease. Importantly, epidemiological studies have demonstrated that low plasma SHBG levels is a risk factor for developing type 2 diabetes and cardiovascular disease. In the last years, we have described the molecular mechanisms by which several nutritional factors including high carbohydrate diets, olive oil, red wine (resveratrol) and caffeine regulate hepatic SHBG production. In the present work we have studied the effects of Rooibos tea on hepatic SHBG production since Rooibos (*Aspalathus linearis*), a South African herbal tea, has been shown to possess anti-diabetic and cardiovascular protective effects. For this objective, we performed *in vitro* and *in vivo* studies. The results showed that Rooibos treatment increases SHBG production in HepG2 cells. These results were corroborated *in vivo* using *SHBG* transgenic mice. Our results showed for the first time that Rooibos consumption increases hepatic SHBG production. These results suggest that the anti-diabetic and cardiovascular beneficial effects of Rooibos may be explained by increasing hepatic SHBG production.

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EP89

The prevalence of masked hypertension in the obese

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Introduction
Obesity is a social scourge. Masked arterial hypertension (HTAM) is a relatively recently described entity that poses a diagnostic problem and places the patient with it at an increased risk of cardiovascular events. In this context we report a prospective study of 50 patients to determine the prevalence and predictive factors of HTAM.
Methods
Descriptive study of obese patients treated in the Endocrinology and Diabetology Department of the Hédi Chaker Sfax University Hospital, Tunisia. These patients had body mass index (BMI) > = 30 kg/m^2 with no history of hypertension. They all had normal blood pressure for the last 2 years of their chek ups.
Results
We recruited 50 patients whose mean age was 46.52 years with extremes ranging from 22 to 64 years. The average BMI was 36.03 kg/m^2. An android distribution of fat was objectified in all of our patients. The collection of blood pressure figures in consultation showed an average SBP of 120 ± 8.8 mmHg and an average DBP of 75 ± 7.3 mmHg. The prevalence of HTMA in our series was 36%, occurring in predominantly non-dipper subjects (38%). These results were statistically somewhat higher compared to those in the literature (between 17.1 and 30.9%). Sleep apnea syndrome, smoking, metabolic syndrome as well as high normal blood pressure values were factors associated with AMT in our patients.
Conclusion
It seems essential to perform outpatient screening for HTAM in obese patients. The induced morbidity and mortality and the cardiovascular risk would be significant and fully justify it.

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EP90

Vitamin D deficiency, associated factors and possible adverse outcomes in a tertiary care institute in Sri Lanka

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Background and objectives
Around 50% of the population is affected with vitamin D insufficiency worldwide. The increasing prevalence is attributed to change in lifestyle, reduced exposure to sunlight and other environment factors. Vitamin D has multiple actions in the body including calcium homeostasis and has impact on several biologic processes with several clinical implications including obesity, diabetes mellitus, and metabolic syndrome, cancer, cardiovascular disease and immune function. Studies on factors associated with vitamin D deficiency and its complications in local setting are lacking. We have studied the vitamin D status, associated factors and outcome of patients.
Methods
A descriptive cross sectional study was conducted from March/ 2019 to March/ 2020 at the Endocrinology Unit of the National Hospital of Sri Lanka. Consecutive sampling was done recruiting all patients who have had vitamin D assessment as part of the routine medical care. Interviewer administered questionnaire was used collect data. Vitamin D sufficiency, insufficiency and deficiency was defined on levels of >50 ng/ml, 20–30 ng/ml, <20 ng/ml respectively. Categorical and numerical variables were analysed using Chi-square and independent sample t-tests respectively.
Results
153 subjects who meets the inclusion and exclusion criteria were recruited in to the study over a period of one year. Out of the study population, majority were females (85.6%). The population mean age was 52.1 (s.d. ± 14.38) years and ranged from 18 to 89 years. The mean weight was 59.4 (s.d. ± 15.70) kg and BMI was 31.3 (s.d. ± 7.54) kg/m^{-2}. Out of the whole population 58.8% had vitamin D deficiency while 31.4% suffered from vitamin D insufficiency. Only 9.8% had the values within the normal range. The mean vitamin D status of the population is 9.8 ng/ml. Pearson chi square was significant in the frequency of fish/ meat intake/per week, screen time per day with vitamin D category. Multiple Linear Regression Analysis was carried out to determine the predictors of vitamin D status. Out of the possible factors skin colour had a significant association with vitamin D insufficiency and deficiency ($F = 4.355$, $P<0.05$).
Conclusions
Majority of the patients who has undergone vitamin D level assessment in the study setting had Vitamin D levels in the deficient or insufficient range. The skin color, frequency of fish/ meat intake/per week and screen time per day had a positive association with the vitamin D status. Further large scale studies to recognize potential causes and outcomes are needed in the future.

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EP91

Primary hypertriglyceridemia : an early and severe form

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INTRODUCTION
Type IV hypertriglyceridemia (HTG IV) or endogenous HTG is a rare inheriteddisorder of the lipoprotein metabolism due to increased hepatic triglyceride synthesis(TG). Although HTGIV is not usually expressed until adulthood, it might be unmasked earlier. We report the case of an early and severe HTGIV complicated with chronic pancreatitis.
Case report
A 6-year-old childwith no particular history was hospitalized in the paediatric department of the UHC Hedi Chaker sfax, Tunisia for an acute pancreatitis (amylasemiawas 264 IU/l). The appearance of the fasting serum was lactescent. The triglyceride level was high at 5.4 g/l with VLDL at 74% without chylomicrons, cholesterol levelwas normal at 1.65 g/l. The diagnosis of primary HTG type IV was retained after exclusion of secondary causes. Dietary modifications were initiated and then at the age of ten a pharmalogical treatment (fibrates) was added. Despite treatment, TG levels were always high and the child has several episodes of acute pancreatitis. At the age of 18, he was hospitalized in the endocrinology department of the UHC hedi Chaker Sfax, Tunisia for paroxysmal abdominal pain and polyuropolydipsic syndrome. A weightloss of 5 kg in 1 year has been noted. The biological assessment showed a blood sugar level of 21 mmol/l with a glycated hemoglobin at 14.7%, without acute metabolic complication. The liver profile was normal but a high lipasemia level of 3 times the upper limit was noted, hence an abdominal CT scan was done revealing an appearance of acute cephalic pancreatitis with atrophy of the pancreatic tail. The diagnosis of diabetes secondary to chronic pancreatitis complicating HTG IV was most likely, but antibodies directed to the pancreas were requested as well.
Discussion–conclusion
Primary HTG can be discovered at an early age. His management is difficult : dietary restrictions remains the mainstory of therapy supplemented by TG levellowering medications. Close monitoring is alsomandatory due to the risk of complications.

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EP92

Managing hypertension can be a night-mare!

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Introduction
Hypertension is a frequent finding amongst people having either Type1 or Type 2 diabetes. In Type 2 diabetes, hypertension is present in a great number of persons, at the time of diagnosis but it's occurrence is low with the diagnosis of Type 1 diabetes.
Case presentation
A 34 years old Saudi male, non-smoker, had been following up at our University Diabetes Center since February, 2020. He had Type1 diabetes for 23 yrs, hypertension for 2 yrs, chronic kidney disease G4A2 and vitamin D deficiency with secondary hyperparathyroidism. The patient had a strong family history of hypertension & diabetes. There was no previous history of ketoacidosis or any other illness. Systemic review unremarkable. The patient had Stage 2 Hypertension, as per office & home BP readings, despite being compliant to all antihypertensives. He was on Basal bolus insulin, Angiotensin receptor blocker, B-blocker,Calcium channel blocker, hydrochlorthiazide,Spironolactone and Cholecalciferol replacement. Exam-BP 160/90 mmHg with no postural drop, pulse 72/m,regular, RR 20/m,afebrile,O2sat 99%. BMI 32.93 kg/m^2. Rest of the general and systemic exams unremarkable.
Investigations
(25.11.20) Normal CBC(Hb% 14 g/dl),liver & thyroid parameters. BUN 10 mmol/l(10–6.4),Creatinine 239 µmol/l(62–115),eGFR(EPI)–29 ml/min, Albumin:Creatinine 161.33 mg/g(0–30),HbA1c 8.2%(4.3–5.8),Bone profile(corrected S.Ca++2.41 mmols/l(2.1–2.55),25-OH Cholecalciferol 27 nmol/l(75–250),PTH 18.24 pmol/l(1.6–6.9). Rest normal). Aldosterone:Cortisol 0.07(0.1–3.7). CXR & ECG normal. Echocardiogram-mild concentric left ventricular hypertrophy & moderate LA enlargement. US renal arteries doppler-normal. The patient was referred to the Nephrology clinic for further management.
Conclusions
Chronic kidney disease in people with diabetes increases the chances of resistant hypertension. Resistant hypertension runs parallel to the worsening renal parameters i.e.eGFR and albuminuria.

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EP93

Corticosteroid-induced diabetes during pregnancy: case report

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Introduction
Glucocorticoids are among the most widely used treatments for controlling inflammatory or autoimmune diseases. However, their metabolic side effects are not negligible, particularly on carbohydrate metabolism. Corticosteroid-induced diabetes is an identity frequently found in the clinic. Its occurrence during pregnancy can affect the maternal and foetal prognosis. After the illustration of a clinical case, we will discuss the definition, risk factors and treatment of cortico-induced diabetes during pregnancy.
Observation
Q.B 36 years old, followed since 2003 for lupus nephropathy class 2 under corticotherapy and Immurel with the notion of several relapses and self-medication, known hypertensive under dual therapy, 6G2P with a history of 3 miscarriages and 3 neonatal deaths. Patient admitted to our department for Added Preeclampsia on a pregnancy of 26SA+6 days, with proteinuria at 5.5 g /24 h on the biological assessment. The use of corticosteroids was accompanied by a frank glycemic imbalance with postprandial hyperglycemia greater than 2 g/l and normal glycated hemoglobin at 5.5% which defines corticosteroid-induced diabetes. The patient was put on Lantus in the evening and rapid insulin therapy. Glycemic imbalance, the presence of hypertension, the existence of renal impairment and corticosteroid therapy at a dose higher than 20 mg/d were all factors that affected the foetal prognosis and fetal death in utero was declared at tenth day of hospitalization.
Conclusion
The beneficial effects of glucocorticosteroids are sometimes outweighed by significant deleterious effects such as corticoid-induced diabetes. The diagnostic criteria and therapeutic objectives are close to those for type 2 diabetes, its occurrence during pregnancy increases foetal and neonatal morbimortality, and diabetes in general, its management remains disparate due to the absence of evidence-based recommendations.

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EP94

Diabetic pregnancy and gestational diabetes: high-risk gestational situations

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Introduction
Pre-pregnancy diabetes and gestational diabetes are gestational risk situations. The objective of our study is to evaluate the course of these pregnancies in order to improve their management.
Patients and methods
Descriptive retrospective study, including 175 patients with diabetic pregnancy followed in the department of gynecology and obstetrics of the Ibn Rochd University Hospital in Casablanca between October 2019 and September 2020.
Results
The study included 175 patients with an average age of 28.8 years, 30% had gestational diabetes and 70% had pre-gestational diabetes. The mean pre-gestational BMI was 26.9 kg/m^2. For gestational diabetes, the mean gestational age of discovery was 21.7 SA, with 71.4% fasting blood glucose levels versus 21.4% for oral glucose tolerance test (OGTT). Concerning pre-gestational diabetes, 24.5% of patients had type 1 diabetes and 43.5% had type 2 diabetes, of which 4.5% had planned their pregnancy. The average

HbA1c was 7.9%. For treatment, 75% of the patients were on insulin and 25% were undergoing hygienic and dietary rules. Glycemic control was perfect in 50.4% of patients, 70.3% of whom had pre-gestational diabetes and 29.7% had gestational diabetes. Concerning the obstetrical complications observed pregnancy-related hypertension in 15.5%, pre-eclampsia in 5%, macrosomia in 13%, threat of premature delivery in 4.5%, malformations and hydramnios in 3.5%. Discontinued pregnancies were observed in 2.9% with no significant difference in complications between patients with and without hypertension.
Discussion
The management of diabetic pregnancy remains a challenge, including pregnancy planning, detecting gestational diabetes, and achieving and maintaining glycemic control to prevent complications.

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EP95

Upper limb infections in diabetic patients

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Introduction
The diabetic is characterized by his vulnerability to infections of the upper limb compared to the general population realizing the tropical diabetic hand. So this is a very serious problem, especially in emerging countries in tropical regions. The aim of this work is to study the clinical, therapeutic and progressive aspects of infections of the upper limb in diabetic patients.
Materials and methods
This is a cross-sectional study spread over 6 years, including diabetic patients with lesions of the upper limb who consulted in the emergency room of the Mohamed VI university hospital in Marrakech, Morocco.
Outcomes
We saw 44 diabetic patients with upper limb infection. The majority of our patients had peripheral neuropathy. The average time between consultation and onset of lesions was 15.3 days. The lesions involved several parts of the upper limb: the hand in 30 cases, the arm in 8 cases, the entire upper limb in 6 cases. Various lesions were observed, phlegmon: 17 cases, panaris: 6 cases, necrotizing fasciitis: 7 cases, erysipele: 8 cases, gangrene: 4 cases, ulceration: 1 case, anthrax: 1 case. Bacteriological study of pus was only carried out on 13 lesions. Therapeutic management consisted of intensifying insulin therapy, with strict glycemic control. Triple probabilistic intravenous antibiotic therapy was initiated and then adapted to the results of the antibiogram in patients who received a bacteriological sample. As for surgical management, drainage represented 78.6% of cases, including 5 necrosectomies in 41%.
Discussion/conclusion
Lesions of the upper limb in the diabetic concern patients most often from a low socio-economic level. The lack of intrinsic coordination between the medical and surgical structures in the management of lesions of the limbs, is not likely to favor the vital prognosis of both the limb and the patient. In some cases, these injuries have been the cause of death. Indeed, the treatment of diabetes and lesions of the limbs is not confined to a drug prescription only, but requires above all patient education; it is the cornerstone of treatment, with goals to be established consistently.

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EP96

Analysis of HMBS gene in Chinese patients with acute intermittent porphyria

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Background
The reported HMBS mutations of acute intermittent porphyria(AIP) have been increasing gradually in China. We aim to explore its mutation characteristic in China and improve the understanding of its molecular heterogeneity.
Material/methods
We searched the literature about Chinese AIP patients with HMBS mutation in the PubMed,CNKI,Wanfang and CQVIP database, and 3 AIP patients with HMBS mutation in our hospital were included. We analyzed the characteristic of these mutations in mutation site, type and frequency. The pathogenicity of all exon mutations were predicted by Mutation Taster.
Results
Totally, 66 unrelated AIP families were enrolled in this study, and 50 mutations were detected, including 17 missense mutations, 15 frameshift mutations, 11 splicing mutations, 6 nonsense mutations and 1 codon mutation. Exon mutations were mainly concentrated in exon 11 and 14(50%). Most of the mutations had the family specificity, but there were 8 mutations occurred in multiple families. P.R173W was the most common mutation, which occurred in 8 unrelated families. The predicted effects of c.913C>A, c.1071delT and c.1078_1132del were polymorphisms, but the others were pathogenicity. C.160delA could not be predicted by Mutation Taster because it was located in the junction of exons and introns.
Conclusion
This is the first comprehensive analysis of HMBS mutation in China. Genetic analysis revealed that missense mutation accounted for the largest proportion and the p.R173W was the most common mutation. In addition, the pathogenicity prediction of bioinformatics software can only provide reference value, so further functional verification test is necessary.

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EP97

Immüne checkpoint inhibitors induced an autoimmune diabetes

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Diabetes caused by immune checkpoint inhibitors is extremely rare. A 48-year-old male patient with a diagnosis of squamous cell cancer in the external auditory canal and operated on received adjuvant radiotherapy. When relapse was seen, 6 cycles of 5-fluorouracil, carboplatin, and cetuximab were administered. The patient was admitted to the hospital with nausea, vomiting, and abdominal pain 10 days after the second cycle infusion, when pembrolizumab was started when the cranial MRI showed progression 6 months later. Serum glucose: 717 mg/dl (70–100), creatinine: 1.5 mg/dl (0.7–1.2), sodium: 132 mmol/l (136–145), potassium (K): 5.5 mmol/l (3.5–5.1), amylase 55 U/l (13–53), blood pH: 7.02 (7.35–7.45), pCO_2: 29 mmHg (35–45), HCO_3: 8 mEq/l (22–26), lactat: 1.9 mmol/l (0.5–1.6), urinalysis; ketons: ++++, glucose: ++++. Treatment was started with the diagnosis of diabetic ketoacidosis and the desired c-peptide due to possible immune checkpoint inhibitor-induced diabetes mellitus: <0.001 ng/ml, anti-insulin antibodies: 1.5 U/l (0–10), GAD antibodies: 718 IU/ml (0–10) were found. TSH required for other possible immune-related adverse events: 1.6 µIU/ml (0.2–4.2), free T4: 1 ng/dl (0.9–1.7), anti thyroid peroxidase: 11 IU/ml (0–34), anti thyroglobulin: 11 IU/ml (0–115), cortisol: 16 µg/dl (6–18), and no other immunocheckpoint-related endocrinopathy was detected. The patient who responded to ketasidosis treatment was discharged with insulin therapy. The treatment was not stopped because the patient's response to pembrolizumab treatment was good. The side effects of these drugs, whose immune checkpoint inhibitors act by blocking the inhibitory mechanisms on the immune system, are also autoimmune events that occur as a result of excessive immune response. There were no other more common autoimmune side effects in our patient, who was diagnosed with autoimmune diabetes. While using these drugs, patients should be followed up carefully for other possible side effects, as well as for autoimmune diabetes.

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EP98

Novel toxicological method to investigate the increased ROS in mouse kidney stem cell mitochondria by doxorubicin

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Mitochondria play a key role in hormone biosynthesis and involve in renal cell proliferation by producing about 90% of cellular energy and controlling cell apoptosis. Doxorubicin is commonly used for many tumor treatments. However, its clinical utility is limited by the adverse reactions, which are

known to be nephrotoxic. The mechanism by which doxorubicin induced kidney damage is still not completely understood, however nephrotoxicity by doxorubicin might be related to mitochondrial dysfunction. In this experiment, the following mitochondrial toxicity test was performed after doxorubicin was treated to mouse kidney stem cells. First, we identified IC_{50} values for doxorubicin in mouse kidney cells. We investigated that mRNA expression level of Mn-SOD, the neutralizer of reactive oxygen species (ROS), in the mitochondria increased in a concentration-dependent manner of doxorubicin. To confirm the relationship between mitochondrial toxicity and ROS, MitoSOX red assay was performed. The results showed that the ROS level increased according to the ascending concentration of doxorubicin. Further experiment should be conducted for assessing the apoptosis pathway induced by doxorubicin. This research was supported by grants (20183MFDS525) from the Ministry of Food and Drug Safety in 2021.

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EP99

Hyperandrogenia and non-alcoholic liver fatty disease: what is the prevalence?

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Introduction
Non-alcoholic liver fatty disease is one of the metabolic consequences found in patients followed for hyperandrogenia, especially those with polycystic ovary syndrome. Studies have suggested that hyperandrogenia is considered as an additional risk factor in synergy with obesity and insulin resistance in the development of non-alcoholic liver fatty disease. The aim of our work was to study the prevalence of non-alcoholic liver fatty in patients consulting for hyperandrogenia and to identify these predicting factors.
Material and methods
This is a retrospective descreptive study involving 98 patients followed for hyperandrogenia in Endocrinology-Diabetology-and-Nutrition Department of the Mohammed VI University Hospital Center of Oujda, Morocco. All patients were provided with a complete clinical examination and laboratory analysis, and the abdominal ultrasound was performed in only 25 patients.
Results
We collected 98 patients having a hyperandrogenia with an average age at 24.6 ± 6.2 years old. Abdominal ultrasound showed non-alcoholic liver fatty in 8 patients, varying in age from 23 to 41 years with an average of 30.5 ± 6.3 years old. The mean BMI of these patients was elevated above 32.1 ± 10.2 kg/m^2, obesity was noted in 50% of cases, and overweight in 12.5%. Abdominal obesity was objectivated in 75% of cases, with an increased average waist circumference at 110.7 ± 28.4 cm. Insulin resistance was present in 50% of cases. Dyslipidemia was reported in all patients, with hypoHDlemia in 87.5% of patients, hypertriglyceridemia in 25% and hypercholesterolemia in 12.5%. 50% of patients with non-alcoholic liver fatty had polycystic ovary syndrome, 37.5% had idiopathic hirsutism and 12.5% had Cushing disease.
Discussion–conclusion
The present study shows a high prevalence of non-alcoholic liver fatty (NALF) in overweight and obese patients with lipid and carbohydrate metabolism disorders notably those with insulin resistance, especially patients followed for polycystic ovary syndrome (PCOS). This is in agreement with the data reported in the literature, which find an increased prevalence of NALF in women with PCOS. Further, that obesity and insulin resistance (IR) seem to be the main contributing factors to NALF. In particular, IR is linked to impaired suppression of lipolysis in adipose tissue, leading to higher levels of free fatty acids in the liver, and steatosis. Hence the interest of systematic screening for non-alcoholic liver fatty at diagnosis and during follow-up, in patients followed for hyperandrogenia, especially those with PCOS, to avoid the risk of progression to cirrhosis or even hepatocellular carcinoma in the absence of early and adequate management.

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EP100

Obesity in Bardet–Biedl syndrome

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Introduction
Bardet–Biedl syndrome (BBS) is a rare autosomal recessive ciliopathy characterized by rod-cone dystrophy, learning difficulties, polydactyly, obesity, genital malformations, and renal abnormalities. We report the case of a young patient followed for this syndrome, which is revealed by early obesity.
Observation
This is a 23-year-old patient from a consanguineous marriage with a personal history of well-substituted peripheral hypothyroidism. Received in consultation for obesity. the history revealed excessive weight gain and an eating disorder such as polyphagia and active search for food. On clinical examination, the patient presented with pronounced obesity with a body mass index (BMI) of 37.2 kg/m2, BP = 160/100 mmHg, deformation of the fingers of the hands and feet type axial polydactyly, syndactyly and brachydactyly. There is a difficulty in adapting to the dark followed by a gradual decline in visual acuity, retinitis pigmentosa in the fundus. Cardiovascular: Arterial hypertension well controlled under ARB 2 with normal heart echo. Renal: Moderate renal failure with an estimated renal clearance of 53.9 ml/min, ultrasound shows bilateral renal atrophy with loss of cortico-medullary differentiation. the Patient was put under hygieno-dietetic rules with a monitoring protocol.
Discussion
Despite normal birth weight, most individuals with BBS experience rapid weight gain in early childhood, with high rates of overweight/obesity sustained through adolescence. The diagnosis of SBB is retained in the face of obesity associated with polydactyly, retinitis pigmentosa and renal impairment. The obesity observed in our patient is almost constant and genetic, early and difficult to treat. Although the mechanisms for obesity in BBS remains incompletely understood, disruption of the hypothalamic leptin-melanocortin signaling pathway is evident. THe molecular mechanistic pathways leading to renal disease in BBS remain unelucidated. It has been suggested that aberrant mTOR signaling may contribute to the development of cystic kidney disease. Another theory proposes that ciliary dysfunction leads to aberrant non-canonical Wnt signaling and planar cell polarity, which may contribute to the development of cysts. At least 25 causative genes have been identified in BBS. Previous reports document that truncating variants in BBS genes predict greater risk for severe chronic kidney disease and increased cardiovascular disease markers compared to missense variants.
Conclusion
Obesity and renal failure are common manifestations in the autosomal recessive Bardet–Biedl (BB) syndrome. Bardet–Biedl syndrome is currently treated symptomatically focusing in particular on aggressive management of diabetes, hypertension, and metabolic syndrome

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EP101

Type 2 diabetes mellitus and vitamin D deficiency among women of reproductive age

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Background and aim
Vitamin D may affect glucose homeostasis, vitamin D levels having been found to be inversely related to glycosylated hemoglobin (HbA1c) levels in type 2 DM. With the scarcity of the regarding data in Ukraine, the aim of this study was to assess the relationship between hypovitaminosis D and glycemic control in type 2 DM women of reproductive age.
Material and methods
To test the hypothesis that 25(OH)D levels may be lower in a cohort of type 2 DM women and that 25(OH)D levels may be related to glucose control in this group of patients, 25(OH)D and HbA1c levels were measured in 90 women with type 2 DM and in 55 persons of control group. In a group of 90 type 2 DM patients, aged 20–45 years, mean age 36.2 ± 1.3 years, 25(OH) D levels and HbA1c levels were measured. The study was conducted during the summer.
Results
HbA1c levels were higher in the group of type 2 DM patients than in the control group, HbA1c levels being 7.8 ± 0.19% and 5.2 ± 0.07% in the patient and control groups, respectively ($P < 0.01$, Student's t-test). In the group of type 2 DM patients, 25(OH)D levels were lower than in the control group, 25(OH)D levels being 17.42 ± 0.98 ng/ml and 24.03 ± 1.04 ng/ml in the patient and control group, respectively ($P < 0.05$). In the group of type 2 DM women, 17 of 90 (18.9%) as opposed to 3 of 55 (5.5%) in the control group had vitamin D levels ≤ 10 ng/ml ($P = 0.0067$). 25(OH)D levels were

found to be inversely associated with HbA1c levels in the group of diabetic type 2 women ($P = 0.007$, $r = 0.054$). When the analysis was performed in all participants, type 2 DM patients and controls, it was found that 25(OH) D levels were inversely associated with HbA1c levels ($P < 0.01$, $r = 0.082$).
Conclusion
Vitamin D levels appeared to be lower in type 2 DM women of reproductive age than in the control group. Vitamin D levels being related to glycemic control in type 2 DM. These findings may have therapeutic implications as cautious vitamin D supplementation may improve glycemic control in type 2 DM.
Keywords: diabetes mellitus type 2, glycemic control, vitamin D, women of reproductive age.
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EP102

You name it & she had it'

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Introduction
Metabolic syndrome is the concurrence of the metabolic risk factors for both diabetes and cardiovascular disease, namely, hypertension, hyperglycemia, dyslipidemia and abdominal obesity.
Case presentation
We report a case of 59 years old morbidly obese, Saudi lady, who had been following up at our outpatient diabetes clinic, since last many years. She had Type2 diabetes for 34 yrs, hypertension, advanced proliferative diabetic retinopathy (S/P laser), ischemic heart disease, chronic kidney disease 5-A3, dyslipidemia, osteoarthritis knees & obstructive sleep apnea (on O2 inhalation, 4 l/m & BiPAP). The patient was non-compliant to medications, diet, exercise & follow-ups. No hypoglycemic episodes at home. She had decreased hearing from both ears. There was a past history of left breast abscess (status post incision & drainage twice), recurrent urinary tract infections, acute right hemispheric stroke, following acute coronary syndrome (5 years ago, status post percutaneous coronary intervention & stenting), ischemic neuritis right ear & cataract extraction. There was a positive family history of Type 2DM and obesity. She was allergic to Ceftriaxone & Strawberries & was on Basal bolus insulin regime, Linagliptin, dual anti-platelets, statin, Hydralazine, calcium carbonate, 1 alphacalcidol & a proton pump inhibitor. On evaluation lastly on 10.11.20, the patient had moderate bilateral pedal edema (L > R) & absent vibration sensation at left ankle. Her available records had indicated the following trends for her physical & biochemical values, from 2015 to 2020:BMI (41.33–53.24 kg/m^2), HbA1c (14.1–6.5%), eGFR (44–10 ml/min), Albumin/Creatinine ratio (643–1119.58 mg/g).
Conclusions
Our case depicts the legacy effect of uncontrolled diabetes (with microvascular & Macrovascular sequelae) and the tendency for recurrent infections. It's also apparent that as the patient's renal function progressively deteriorated, her blood glucose started coming under control, due to reduced insulin clearance thru the affected kidneys.
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EP103

From type 2 diabetes to cardiac arrest

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Introduction
Gastrointestinal adverse effects such as nausea and vomiting are widely described for GLP-1 receptor agonists (arGLP-1). We highlight Semaglutide, a drug that needs to start its administration at a reduced dose, to be able to increase the dose later with better tolerance and adherence of the patient. Not doing it this way can lead the patient to have serious adverse effects such as incoercible vomiting or profuse diarrhea that entails serious ionic alterations.
Case report
A 70-year-old man, living independently, diagnosed with type 2 diabetes mellitus and grade 2 obesity, treated with Empagliflozin 10 mg and Semaglutide 1 mg. He presented symptoms of general malaise, frequent vomiting, hyporexia and weight loss of 25 kg in the last 6 months (coinciding with the initiation of Semaglutide at an initial dose of 1 mg subcutaneous weekly). He suffers from worsening with incoercible vomiting and instability, so he goes to the emergency room, where he suffers a tonic–clonic crisis and cardiorespiratory arrest. Advanced cardiopulmonary resuscitation maneuvers were started and the patient proceeded to oropharyngeal intubation, recovering a pulse after 3 min, and he was transferred to the ICU. In the blood test extracted, severe hypocalcemia (< 5 mg/dl) and hypomagnesemia (1.2 mg/dl) stand out, the rest without relevant alterations, with these values in range in previous tests. In the study of hypocalcemia and hypomagnesemia, parathyroid hormone (PTH) 404 pg/ml, 1,25-(OH)2 Vit D 32 pg/ml is observed, with a calcium excretion fraction < 0.01 and a magnesium excretion fraction 0.7%. After correction of calcium and magnesium levels, a new determination of PTH 57.5 pg/ml is performed, where normalization is observed. During the diagnostic process, occult neoplasia, thyroid disease, severe deficiency or resistance to vitamin D and resistance to PTH were ruled out. Given the patient's history and the initiation of treatment with Semaglutide at 1 mg weekly, a dose higher than that indicated in the technical data sheet (0.25 mg weekly), we consider that serious gastrointestinal effects occurred in the patient, the deficiency etiology of hypocalcemia and hypomagnesemia being the most probable cause.
Conclusion
arGLP-1, and specifically Semaglutide, are excellent drugs for the control of patients with DM2, but they require that we know in depth the possible adverse effects and the appropriate form of administration of each of them.
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EP104

Weight gain and insulin therapy in patients with type 2 diabetes mellitus

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Introduction
Traditionally, there has been a stepwise introduction of glucose-lowering interventions, with the final 'step' of insulin therapy being administered 10–15 years after diagnosis. Both patients and physicians are often reluctant to start insulin because of fears of painful injections, hypoglycemia, and weight gain. The aim of our study was to assess the effectiveness of initial basal insulin therapy on glycaemic control in type 2 diabetic patients and to study the effects of this treatment on body weight.
Methods
We conducted a retrospective study including patients with type 2 diabetes previously on oral agents, followed up in our department 6 months after initiating insulin therapy.
Results
97 patients were included with a mean age of 59 ± 9.5 years. More than half of patients were women (61%). The duration of diabetes was meanly 9.5 ± 6.2 years. The mean glycated hemoglobin (HbA1c) before starting insulin therapy was 10.8% ± 2.2. Six months after initiating insulin, the mean HbA1c was 9.2% ± 1.6 and the mean weight gain was 4.2 kg ± 4.9. The majority (89%) were taking metformin in association with insulin. Higher doses of insulin therapy were associated with a greater weight gain and a better glycemic control with a significant $P = 0.01$. Weight gain was significantly smaller when metformin was associated to initial insulin therapy ($P = 0.02$).
Conclusion
Insulin therapy is associated with both a better glycemic control and a greater weight gain. Use of metformin in combination with insulin is commonly recommended as a way to limit weight gain in patients with type 2 diabetes. For lasting weight control, lifestyle interventions need to continue throughout the course of treatment.
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EP105

Hypertriglyceridemia and glycemic control among patients with type 2 diabetes

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Introduction
Moderate hypertriglyceridemia is exceedingly common in diabetes, and there is growing evidence that it contributes to residual cardiovascular risk in statin-optimized patients. Added to lipid lowering drugs and lifestyle intervention, an optimal glycemic control is necessary. The aim of our study was to compare triglyceride levels in diabetic patients before and after initiating insulin therapy.
Methods
We conducted a retrospective study including patients with type 2 diabetes on insulin therapy for more than one year. We compared the triglyceride levels before and one year after initiating insulin therapy.
Results
Our study enrolled 97 patients. The mean age was 59 ± 9.5 years. Women represented 61% of the patients. The duration of diabetes was meanly 9.44 ± 6.31 years. The mean glycated hemoglobin was 10.7% ± 2.24. A total of 61% patients were receiving lipid-lowering medications. Hba1c was significantly correlated with high triglyceride levels (P = 0.032). The mean triglyceride level decreases on insulin therapy but not significantly (1.78 g/l ± 0.98 before switching to insulin therapy vs 1.26 g/l ± 0.46)
Conclusion
Elevated triglyceride levels were associated with inadequate glycemic control; thus, suppressing triglyceride levels may attain more optimal glycemic control in patients with type 2 diabetes mellitus.

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EP106

Initiation of insulin therapy in obese patients with type 2 diabetes mellitus

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Introduction
Weight gain represents a considerable challenge in type 2 diabetes mellitus patients with insulin therapy and a frequent cause of delay in initiation of treatment with insulin. The aim of our study was to describe the features of diabetic obese patient when switching to insulin therapy.
Methods
It was a retrospective study which enrolled 61 patients with type 2 diabetes divided in two groups: patients with a normal Body Mass Index (BMI) < 25 kg/m^2 and obese patients with BMI > 30 kg/m^2. All patients were on oral **hypoglycemic medications** and were admitted in our department to switch to insulin therapy.
Results
In obese patients' group: the mean age was 55.5 ± 8.2 years, the duration of diabetes was meanly 8.2 ± 5.6 years, the mean initial weight was 84.3 kg ± 10.1 and the mean glycated hemoglobin was 10.4% ± 1.96. In the other group, the mean age was 60.6 ± 8.2 years, the duration of diabetes was meanly 10.6 ± 7.1 years, the mean initial weight was 60.8 kg ± 7.33 and the mean glycated haemoglobin was 11.6% ± 2.1. Hypertension and dyslipidemia were more frequent in the obese patients' group (74% and 71% respectively). These two comorbidities were found in half of patients with BMI < 25 kg/m^2. Polymedication were more frequent among obese patients (71% vs 36.7%). Obese patients were receiving lower dose of insulin than normal weighted patients (0.35 UI/kg ± 0.13 VS 0.43 UI/kg ± 0.16). Weight gain was smaller in obese patients compared to the other group (4.55 kg ± 8.7 vs 8.77 kg ± 12.06).
Conclusion
Earlier and lower doses of insulin therapy was indicated in obese patients while weight gain was less noticed in this population. Weigh control and lifestyle intervention are needed for optimal diabetes control especially for obese patients.

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EP107

Initial daily insuline dose and diabetic retinopathy

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Introduction
Diabetic retinopathy is a serious complication of type 2 diabetes, which compromise the visual function and impair the quality of life of these patients. A rapid lowering of blood glucose especially when starting insulin therapy can worsen this retinopathy. We studied the variation of the initial daily insuline dose in the presence of diabetic retionopathy.
Methods
Our study is prospective randomized and comparative. We recruited patients with type 2 diabetes hospitalized for a switching to insulin in the C department of diabetology and nutrition at the national nutrition institute in Tunis, during 6 months, we compared the average of the initial daily insuline dose calculated on the day of discharge between the group with diabetic retionopathy and the group not affected using the Mann Whitney test.
Results
We included 50 patients with type 2 diabetes, 54% were men and 46% were women, with an average age of 59 years (± 10.7), the averge duration of diabetes was eight years (± 7).32% (95% CI 20–46) had diabetic retinopathy. The average of initial daily insuline dose was 0.42 IU/kg/d (95% CI 0.4–0.5) in the group not having diabetic retinopathy and it was 0.47 IU/kg/d (95% CI 0.4–0.6) in the affected group. No significant difference was found (P = 0.58).
Conclusion
This study did not show a variation in the initial daily insuline dose in the presence of diabetic retinopathy. Long-term ophthalmological follow-up of patients with retinopathy is necessary to judge the effect of a rapid lowernig of glucose serum level on this complication.

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EP108

Impact of diabetes mellitus on baseline SpO2 levels and Chest CT severity score in patients affected with COVID-19

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Coronavirus disease 2019 (COVID 19) caused by severe acute respiratory syndrome corona virus 2 (SARS – CoV-2) which predominantly affects lungs and leads to COVID 19 pneumonia. India is second worst affected country in the world after U.S having more than 10 Million COVID 19 cases till date. Diabetes is frequently associated with severe COVID-19 infection and with a worse prognosis. This retrospective study aims to evaluate the impact of diabetes mellitus on baseline SpO2 levels on admission and Chest CT severity score in patients affected with COVID-19 infection.
Materials and methods
In this observational study 157 symptomatic COVID-19 patients were included at a dedicated COVID hospital in Rural India from July 22, 2020 to Oct 12, 2020. The COVID19 positivity was defined on the basis of RT PCR. Baseline SpO2, HRCT Chest scans, inflammatory markers such as CRP, Ferritin and D-Dimer were done at the time of admission. A semi-quantitative CT severity score was calculated based on the extent of lobar involvement (0:0%; 1: < 5%; 2: 5–25%; 3: 26–50%; 4: 51–75%; 5: > 75%; range 0–5; global score 0–25). Data were compared using Mann Whitney U test.
Results
In this study baseline SpO2 levels were 90.24 ± 4.61 (Mean ± S.D.) in patients with diabetes and 92.72 ± 4.09 (Mean ± S.D.) in patients without diabetes. Patients with diabetes had lower baseline SpO2 levels which were statistically significant (P: < 0.001). CT severity score in patients with diabetes was higher than patients without diabetes with t value of −1.833 (P: 0.069).
Conclusions
This study data suggests the potential role of simple and cost effective measurement like baseline SpO2 on room air for predicting the severity of lung involvement in SARS-CoV-2 patients with diabetes mellitus. This observational study shows COVID-19 patients with diabetes had significantly lower SpO2 levels. This study also shows that CT severity score was higher in diabetics compared to non-diabetics. COVID-19 infection with diabetes is more likely to cause more severe pneumonia with severe hypoxia. CRP and other inflammatory markers were also elevated in diabetics. This could be also due to people with diabetes have a dysregulated innate and adaptive immune response and their already having chronic low-grade inflammation which makes them more susceptible to more severe pulmonary disease. Further large scale studies are needed to validate the clinical implications of this study.

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EP109

Is total body fat more strongly correlated with lipid profile than the body mass index in type 2 diabetes?

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Background
In type 2 diabetes, abnormalities of lipid metabolism and tissue distribution are common and associated with an increased risk of cardiovascular disease. The aim of this work was to study the relationship between the impedancemetric parameters and the lipid profile in a population of type 2 diabetics followed in the Endocrinology Department MED VI of Marrakech.
Methodology
Body fat was assessed using a body composition analyzer. Serum triglyceride, total cholesterol and low and high density lipoprotein cholesterol levels (LDL-c and HDL-c) were determined by standard enzymatic procedures. Relationships between age, impedancemetric parameters with several metabolic elements including serum lipid levels and HBA1c were analyzed in both sexes separately.
Results
The correlation of the lipid profile was higher with body fat compared to the Body Mass Index(BMI):LDL-C $r = 0.32$ vs 0.26, HDL-C $r = -0.46$ vs -0.43, total cholesterol $r = 0.15$ vs $r = 0.08$.
Conclusion
To sum up, in light of our study, compared to BMI, body fat measured by impedancemetry more accurately reflects the lipid profile in type 2 diabetics.
Keywords
lipid profile- association-body fat percent –body mass index-type 2 diabetes
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EP110

Ketosis-prone diabetes presenting with an atypical phenotype (A + /β +)

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Introduction
In clinical practice, differentiating between the types of diabetes is not always possible. In recent years, there has been an increase in the cases of Type 2 diabetes triggered by diabetic ketoacidosis in young-adult age individuals, and this condition is known as ketosis-prone diabetes (KPD). In this report, we present a case of autoantibody-positive KPD who had an adequate pancreatic reserve and an atypical phenotype due to having a normal body weight, in whom the presence of ketosis could not be confirmed by laboratory tests.
Case presentation
A 33-year-old female patient presented to an Internal Diseases clinic with complaints of frequent urination, increased water consumption, and weight loss. In that clinic, the patient was diagnosed with diabetes mellitus (DM) due to increased blood glucose (413 mg/dl) and HbA1c (9.5%) levels, and the patient was initiated on an intensive insulin therapy although no blood gas or urine test was performed. After one month, the patient presented to our Endocrinology clinic. Her body height was 152 cm, weight was 56 kg, and body mass index was 24 kg/m^2. Her sister and niece had been previously diagnosed with Type 1 DM. The C-peptide level, which was measured due to the lack of insulin resistance findings, uncontrolled weight loss, and the young age of the patient, was sufficient (6.02 µg/l). Moreover, the islet cell antibody and the anti-glutamic acid decarboxylase antibody, which were assessed twice, were positive with a high titer (> 250.00 IU/ml). Basal insulin and metformin treatment was initiated, considering that the patient might need insulin due to autoantibody positivity. Throughout the follow-up, no decrease has been detected in her C-peptide level. Additionally, the patient is still being followed up, with her blood sugar regulated and her HbA1c level being at the target range.
Conclusion
Ketosis-prone diabetes (KPD) is an atypical form of diabetes whose frequency has increased in recent years. There are four variants of KPD defined in the literature. In one of these, the beta-cell reserve is preserved but the islet cell antibody is positive. In such patients, the progressive beta-cell loss may develop, which may require lifelong insulin therapy. More over autoantibody positivity is a strong determinant of subsequent insulin need, and in such cases, patients should be re-evaluated with clinical and laboratory findings and treatment revisions should be performed as needed.
Key words
Ketosis-prone diabetes, insulin autoantibodies
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EP111

'Not everything is as it seems' – a case report of Ketosis-Prone diabetes

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Introduction
Ketosis-Prone Diabetes (KPD) is a heterogeneous condition that shares clinical characteristics of type 1 and type 2 diabetes. It is usually a challenging diagnosis because patients are prone to develop diabetic ketoacidosis (DKA) without having the classic clinical phenotype of autoimmune type 1 diabetes.
Case report
A Caucasian 26-years-old female with known history of renal transplant, morbid obesity (BMI 41.5 kg/m^2), hypertension and dyslipidemia was diagnosed with pregestational diabetes during her first pregnancy. During the actual pregnancy, insulin was required to achieve controlled blood glucose levels and maintenance of this therapy was necessary after delivery. Some months after, she was brought to the emergency room due to polydipsia, polyuria, blurred vision, mild asthenia and paresthesias of the upper extremities. The arterial pH was 6.99, glucose 657 mg/dl and bicarbonate and aniogap were unmeasurable. Urinalysis was positive for ketonuria (high unmeasurable value). Laboratory tests revealed no evidence of infection, cardiac ischemia, renal or liver dysfunction. The patient was admitted with severe DKA and promptly received appropriate treatment. Low C-peptide levels (0.19 ng/ml [RR:1.1–4.4 ng/ml]) and HbA1c 12.3% were document. Beta-cell specific autoantibodies were all negative. She was discharged with a basal-bolus insulin regimen. One month after her C-peptide level was 1.76 ng/ml and HbA1c was 11.8%, her insulin needs were much lower and at that time she initiated GLP-1 receptor agonist.
Discussion
This case report presents us a young obese woman with dysmetabolic traits that clearly suggests a Type 2 DM. The therapeutic non-compliance determined this severe hyperglycemic presentation that usually is a typical expression of insulinopenia and Type 1 diabetes. The autoimmunity against Ɓcell was negative and after glucotoxicity the presence of pancreatic insulin reserve was proven. The presented case of KPD should alert clinicians to this entity. Although the presentation is similar to Type 1 diabetes the evolution appears to resemble Type 2 DM. This has impact on misclassification and mistreament of patients.
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EP112

Coefficient of variation

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We studied how to achieve 'target coefficient of variation (CV)' ['TCV']. In a cross-sectional study, we analyzed 24-h glucose levels measured using CGM (iPro2) in 150 patients with type 2 diabetes. We analyzed 51 time in range (TIR) (reference ranges [RRs]: mean glucose level (M) ± M ÷ 100 × 10, M ± M ÷ 100 × 11…M ± M ÷ 100 × 60 mg/dl [we referred to the underlined numbers as 'percentages which compose margins' (P)]). We analyzed 'optimal cutoff values' (C) of TIR to predict CV below target, corresponding to 51 TIR × 26 TCV (15, 16…40%), using ROC analysis. Of the 51 RRs, the RR for which TIR had the largest AUC for each TCV was referred to as optimal RR (ORR). Table shows the P of ORR (PO) and C of TIR for ORR (CTO) for each TCV. TCV correlated to PO ($r = 0.82$ $P < 0.001$, PO = 1.09 × TCV + 6.6) ($n = 26$). In 26 TCV, the CTO was 80.8 ± 10.7, the sensitivity of CTO was 97.1 ± 2.4, and the specificity of CTO was 97.2 ± 2.5. If ORR is used as an alarm threshold in a personal CGM and TIR for ORR > 80% is achieved, CV below the target may be achieved.

TCV,%	15.0	16.0	17.0	18.0	19.0	20.0	21.0	22.0	23.0	24.0	25.0	26.0	27.0
PO,%	20.0	23.0	28.0	30.0	31.0	29.0	29.0	31.0	33.0	36.0	36.0	28.0	25.0
CTO,%	81.6	85.4	92.0	92.0	89.9	85.1	82.6	85.4	86.8	87.5	85.8	63.2	57.3
TCV,%	28.0	29.0	30.0	31.0	32.0	33.0	34.0	35.0	36.0	37.0	38.0	39.0	40.0
PO,%	25.0	41.0	41.0	41.0	49.0	50.0	50.0	35.0	35.0	51.0	51.0	51.0	51.0
CTO,%	57.3	84.7	84.7	84.4	89.6	89.9	89.9	63.2	59.4	80.9	80.9	80.9	80.2

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EP113

Infections revealing type 2 diabetes

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Introduction
Type 2 diabetes is a field of immunosuppression predisposes to infections in all its locations. The mode of revelation by degenerative or infectious complications is frequent. The aim of our work is to study the epidemiological, clinical and therapeutic aspects of infections that reveal type 2 diabetes.
Material and methods
This is a retrospective study, including 35 type 2 diabetic patients, hospitalized in an Endocrinology–Diabetology department over a 6-year time period, and in whom an infectious complication was the factor revealing type 2 diabetes.
Results
The mean age of our patients was 53.7 ± 14.9 years, with a female predominance at 68.6%. The mean HbA1c at the diagnosis of diabetes was 12.5 ± 3.1%, decompensation revealed 57.14% of patients, and 62.9% of patients reported a cardinal syndrome. The infections were: skin infections in 47% (intertrigo, fungal infections in skin folds, onychomycosis, erysipelas, diabetic foot), urinary tract infections in 40% (cystitis, acute pyelonephritis), pleuropulmonary infections in 25.71% and vaginal infection in only 1 case. All of the patients received large specter antibiotic therapy, adapted to each case after the results of the antibiogram. 34.2% of patients treated by insulin alone, and 5.7% by oral antidiabetics, 34.2% were treated on combined therapy insulin + oral antidiabetic medication. Macroangiopathic complications were present in 17.14% of cases, including coronaropathy (8.57%), ischemic stroke (2.85%), peripheral arteriopathy (2.85%).
Discussion–conclusion
Infections revealing type 2 diabetes are frequent, a systematic screening for diabetes in patients with severe or recurrent infections is required.

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EP114

Homozygous LMNA p.R582H in dunnigan-type familial partial lipodystrophy

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Dunnigan-type familial partial lipodystrophy (FPLD2) is a rare genetic disease associated with loss of subcutaneous adipose tissue and metabolic involvement such as diabetes, hyperlipidemia, and hepatosteatosis. We aimed to present a rare FPLD2 caused by an atypical Lamin A/C gene (LMNA) mutation. We report a case of an Algerian 31 year-old female with a lamin A specific pathogenic variant in exon 11, denoted LMNA (c.5454G > A; p.R582H), present in the homozygous state. The patient consulted for a male morphotype, with a personal and a family history of diabetes including a sister with a similar pattern. First she noticed well-defined muscles in her arms and legs around puberty and gradual disappearance of subcutaneous fat. Although the patient was unable to define a clear period of time when subcutaneous fat disappeared. At 21 years, she was diagnosed diabetes militus currently on 1.6 IU/kg of insulin without achieving glycemic target. Physical examination revealed generalized fat loss with lunar fascia, with massive muscles of the arms and thighs, but also visibility of veins and absence of subcutaneous tissue, with curled fingers. Her body mass index (BMI) was 24 kg/m^2, her gonadal axis does not find any cycle disorders nor hirsutism. Her biological assessment find several desorders such as HbA1c above 12% and elevated triglyceride at 3000 mg/dl. Hepatic, Cardiac and neurological regular assessments were normal. In conclusion, lipodystrophy is a very heterogeneous disease with a current classification based on clinical and morphometric features, LMNA undergoes alternative splicing to produce two nuclear laminar proteins – lamin A and C. Multiple missense mutations associated with FPLD2, most of which are located in exon 8 at the codon position 482, have been reported, The mutation c.5454G > A; p.R582H in homozygous state is rarely found.

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EP115

Metabolic disorders at a young age

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Risk factors were assessed, including lipid spectrum studies, among young patients. The survey included 225 men and 327 women. All examined patients had no clinical signs of diseases of the cardiovascular system and type 2 diabetes mellitus. The median age was 33.35 (31.15; 35.52) years. Obesity was 1.6 times more common among young men than among women ($\chi 2 = 4.67$; P = 0.03). The relative risk of developing (RR) obesity in (men/women) was 1.79 (1.23 ÷ 2.60); $P = 0.0007$. Type 2 diabetes mellitus was not diagnosed in those examined. Impaired glucose tolerance (IGT) have been identified among women and men. IGT in men occurred 2 times more often than in women ($\chi 2 = 4.94$; $P = 0.03$), RR (men/women) was 2.12 (1.14 ÷ 3.92); $P = 0.01$. The incidence of type IV dyslipidemia in men was 3.12 times higher than in women ($\chi 2 = 18.20$; $P = 0.00001$), RR in men (in relation to women) was 3.64 (2.04 ÷ 6.64); $P = 0.0003$. This study demonstrates the high risk of metabolic disorders in men already at a young age.

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EP116

Vitamin D as a biomarker of long of hospital stay in geriatric department – preliminary study

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Introduction
Inadequate low serum of 25(OH) vitamin D leads to skeletal effect (rickets, osteoporosis, osteomalacia) and furthermore exhibits nonskeletal effects – increase the risk of cardiovascular diseases, type 2 diabetes, mental illness and many others. Vitamin D deficiency is associated with a severe morbidity burden and low functional performance among elderly patients. A long length-of-stay (LOS) among elderly patients is related to revere morbidity burden and low functional performance too.
Aim
The aim of the study was to determine the association between concentration of 25(OH)D and duration of hospitalization at Geriatric Department.
Material and methods
To the study was enrolled 152 patients above 60 years, hospitalized in Geriatric Department in hospital in Piekary Slaskie (Poland). The study was conducted between 2013 and 2015. Each patient provided consent before included to the study. Blood samples were collected after overnight fasting. The serum level of 25-hydroxyvitamin D (ng/ml) was measured by enzyme-linked immunosorbent assay (ELISA).
Results
Mean age of the study group was 76.24 ± 7.47 years. The mean 25(OH) D level among study group was 14.61 ± 5.96 ng/ml. The mean time of hospitalization was 10.25 ± 3.95 days (minimum was 2 days and maximum was 22 days). We observed correlation between serum level of 25-hydroxyvitamin D and long of hospitalization geriatric patients ($r = -0.25$; $P = 0.0085$). We also observed that mean time of hospitalization among group patients with deficiency of vitamin D (defined as 25OH D below 20.0 ng/ml) was a little longer in comparison to group of patients with suboptimal vitamin D (defined as 25 OH D between 20.0–30.0 ng/

ml), but this different was no statistically significant (10.46 ± 4.29 days vs 9.55 ± 2.70 days; $P = 0.6463$). Also we divided patients into three group with serum level of 25-hydroxyvitamin D of below10.0 ng/ml (first group), 10.0–20.0 ng/ml (second group) and 20.0–30.0 ng/ml (third group). The mean time of hospitalization was the highest among the first group of patients (12.15 days) and lower into second and third group (respectively 9.77 and 9.55 days), but this was no statistically different ($P = 0.0981$).
Conclusion
25(OH)D should be considered as a potential biomarker of long length-of-stay among elderly patients hospitalized in Geriatric Department. More researches are needed to confirm this thesis.

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EP117

Retropharyngeal abscesses in diabetic adults

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Aim
identify the clinical presentation of retropharyngeal abscesses in adults and the therapeutic management modalities.
Materials and methods
We illustrate two cases of retropharyngeal abscess in two elderly subjects collected in the ENT department of the Farhat Hached hospital in Sousse.
Observations
1-/It is about a 70-year-old man, diabetic (DNID) who consulted us for intense cervicalgia, torticollis, and odynophagia. The physical examination found an apyretic and eupneic patient. Oropharynx examination: Halitosis, bulging of the posterior wall with thick pus issue. In profile cervical radiography: thickening of the retropharyngeal space with the presence of an air opacity in relation to the cervical vertebral bodies (C2–C4). The patient had drainage under general anesthesia endoorally with triple antibiotic therapy: Claforan – Fosfomycin- Flagyl. The bacteriological samples did not isolate any germs. A control MRI at J10 of treatment showed: extensive thickening of the soft parts prevertebral retropharyngeal affected by the adjacency of vertebral bodies from C3 to C5 without signs of discitis. The development was favorable. 2-/it is about a patient, 57 years old, diabetic (DNID) who consulted us for mixed high dysphagia associated with cervicalgia and a limitation of the mobility of the cervical spine and the left upper limb. The clinical examination found: torticollis, monoplegia of the left upper limb, tight trismus, a bulge in the posterior wall of the pharynx. Cervical MRI: an important pre-vertebral abscess collection spanning 11 cm responsible for a significant mass effect on the aerodigestive chain and spondylodiscitis advanced to C3–C4 stage. The patient had an endobuccal floating with a safety tracheotomy in front of significant glottic edema and has been given triple antibiotic therapy. The evolution was favorable with regression of trismus, resumption of oral feeding, and regression of the Left upper limb deficit. Decanulation was made at J10.
Conclusion
The pharyngeal abscess must be suspected before any neck stiffness, trismus or dysphagia, associated or not with febrile syndrome especially in immunocompromised persons such as diabetic.

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EP118

The traditionnel bath: it's time to put an end to this dangerous ritual for diabetics!

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Introduction
In Morocco, the Moorish bath is an important social ritual. All categories of society frequent it very regularly. The traditionnel bath can lead in the diabetic, by the means of acute decompensations, serious falls and burns, with heavy functional, social and psychological consequences. Through this observation, we report the risks associated with the Moorish bath, and we underline the value of educating diabetic patients and making them aware of the dangers of frequenting Moorish baths.
Case report
A 78-year-old patient, known to be diabetic for 20 years on oral antidiabetics, admitted to the intensive care unit for burns of the 2 lower limbs following a fall in a heated Moorish bath, in a context of consciousness disorders without idea on capillary glycemia, this incident had taken place during the afternoon without notion of taking the meal of the lunch. On clinical examination, the patient was conscious, hemodynamically and respiratory stable, apyretic, with a glycemic cycle of blood glucose levels around 3 g/l without ketosis. The skin surface area burned to the second degree was estimated at 18%. The patient received rehydration and appropriate daily dressings. He was put on a hyperglycemia correction regimen adapted to his cardiac and renal functions, then on a basic regimen of intensified insulin therapy. The course was marked by the installation of functional renal failure with necrosis of both feet. The patient died with suspicion of pulmonary embolism.
Discussion
Diabetic patients are usually complicated patients, due to the strong presence of systemic micro and macro vascular damage affecting multiple organs. Also, diabetes is well known to be associated with decreased healing ability. The Moorish bath can cause serious burns in these patients by several mechanisms: diabetic retinopathy, a source of reduced visual acuity that can be responsible for falls, neuropathy with skin insensitivity, as well as the significant effort deployed in the activities of the Moorish bath which could induce hypoglycemia.
Conclusion
In our society, the traditionnel bath is a synonym for hygiene and cleanliness, but it can be responsible for serious accidents in diabetic patients. Our observation elucidates the risks of the Moorish bath in these particularly vulnerable patients, hence the importance of prevention which involves educating diabetic patients or even banning the use of Moorish baths.

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EP119

Gluten free diet in real life

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Introduction
The only currently available treatment of coeliac disease is a gluten-free diet (GFD). It improves outcomes, and reduces health-care costs. However, adhering to a gluten-free diet is difficult for many people. The aim of this study is to evaluate the diet adherence in real life and his impact on disease evolution.
Patients and methods
This is a descriptive transversal study carried out over a period of 10 years. All patients with celiac disease were included.
Results
Forty one patients were included; the average age of patients was 36 years (17–75 years) with a sex ratio (M/F) equal to 0.46. The follow-up was assessed in 35 patients; the monitoring rhythm was 3 to 6 months according to the clinical state of the patient at the last visit. Diet adherence was limited to a few months after the introduction of the gluten-free diet in 37.1% of patients. Seventeen patients adhered to the diet during the follow-up period. A Non–observance to GFD was described in 5 patients. The main cause was the cost of it. Clinical improvement was noted in 20 patients after a mean delay of 3 months. Some cases of relapses (28.6%) were noted due to a poor gluten-free diet adherence. A normalization of celiac serology was noted in 44% of cases after an average delay of 34 months. Histologically, subtotal or total atrophy persisted in 10 patients.
Conclusion
Heightened awareness by patients can help maximize successful treatment, Routine follow-up is necessary to reinforce the need for a GFD, provide social and emotional support. Finally the role of associations should be encouraged to resolve financial problem.

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EP120

COVID-19 in diabetic and non-diabetic patients hospitalized to private medical center: a retrospective analysis

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Keywords diabetes, COVID-19, medical care
COVID-19 belongs to the global problem and health systems are faced with severe challenges. Diabetic patients are in the group of risk, especially among elderly people. The aging of the population leads to the comorbidity of diabetic patients with a high risk of death in the case of severe COVID-19 complications. Never doubt it could be fatal for diabetic patients more often than among non-diabetic. Patients with chronic diseases try to avoid visiting medical centers for check-ups or regular tests or consultations concerning social distancing strategies. As a result, a lot of them are hospitalized to COVID departments too late than advisable with severe respiratory disorders. Using glucocorticoids in critically ill patients can lead to decompensation of diabetes which could be potentially life-threatening. We analyzed a group of 393 patients treated in the medical center in Kyiv from September till December of 2020 in 3 infectious departments. Information was received from the database of the clinic, and 100% of patients signed an agreement on using their personal data. No personal data (including name and others) was published. The average duration of in-patient treatment was for 8.78 days. 19 patients died (4.83%). In the group of critically ill diabetes was significantly more often than in the control group. The average duration of treatment was higher in the 1st department due to intensive care wards where were treated critically ill patients. The reason of death was SARS, sepsis, respiratory and heart insufficiency. All of the patients had COVID-19 which was proved laboratory and/or instrumentally (in a small number of cases CT was not performed due to severity of the condition with intensive oxygen supply with higher risks of transportation in the clinic. For such patients, we used ultrasound of lungs for control in dynamics. Some patients reported rapid progression of respiratory insufficiency in the absence of low-grade fever and they tried not to visit a doctor. As a result, the start of intensive care was termed latter. Patients were treated by multiple specialty teams of health professionals including infectionists, internists, anesthesiologists, endocrinologists, specialists in rehabilitation, and sometimes neurologists, cardiologists, nephrologists. It was important to react rapidly in the case of acute kidney injury (including urgent dialysis), acute coronary syndrome (with further stenting of coronary arteries in specialized cardiosurgical centers).
Conclusion
COVID-19 challenges are extremely important for analysis as we are focusing on the improvement of health care.

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EP121

Macrovascular complications in adult-onset type 1 diabetes

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Introduction
Type 1 Diabetes (T1D) diagnosed during adulthood is a form of diabetes which is underdiagnosed and underreported. Lower incidence of cardio metabolic risk factors such as atherogenic dyslipidemia, high blood pressure and obesity have been reported in T1D patients compared to type 2 diabetes. In this study, we aimed to determine the prevalence of and predictive factors for macrovascular complications during T1D diagnosed in adulthood.
Patients and methods
Patients over 20 years diagnosed with diabetes were included. Data from 166 patients were analyzed. Levels of antibodies to glutamic acid decarboxylase (anti-GAD), protein tyrosine phosphate (IA2) and islet cell (ICA) were quantified in all patients. T1D was diagnosed in patients testing positive for at least one of autoantibodies.
Results
The mean age was 31.81 years (range: 20–64 years). In our study, 95 were male (57.2%), and 71 (42.8%) were female. The median disease duration was 7.34 ± 6.73 years. The mean of basal metabolic index (BMI) was 21.05 kg/m^2. Underweight was found in 23.5% of cases and 63.9% of patients had normal BMI. Overweight and obesity were observed in 9% and 3.6% of patients, respectively. The incidence for the composite macrovascular outcome was 7.8%. Hypertension occurred in 6% of patients after a mean diabetes duration of 16.5 ± 7.23 years (range:10–35 years). About half of those patients were grade 1 hypertensive, while 40% and 10% were grade 2 and 3 hypertensive, respectively. Coronary artery disease was observed in 2.4% of patients after a mean diabetes duration of 13.5 ± 13.77 years (range: 3–32 years). Only 3 patients (1.8%) developed peripheral arterial occlusive disease after a mean duration of 21.3 ± 15.5 years (range:10–39 years). A higher incidence of macrovascular complications among T1D adults was significantly observed in patients with longer disease duration ($P < 0.5$). Moreover, macrovascular complications are more prevalent among adults who were hypertensive and smokers ($P < 0.05$). No significant correlation was identified between obesity and macrovascular complications.
Conclusion
This research provides insights into the association between T1D diagnosed during adulthood and macrvascular complications and highlights the importance of a screening approach in order to enhance therapeutic outcome.

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EP122

The activity of inflammatory markers in patients with nonalcoholic fatty liver disease and type 2 diabetes

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Purpose of research
To determine the level of insulin content, the content of nitric oxide metabolites, Malondialdehyde, the activity of lipoprotein-associated phospholipase A2 (FLA2), in the blood serum of patients with NFLD with type II D and impaired glucose tolerance.
Material and methods
The study included 74 patients with non-alcoholic fatty liver disease. 30 of them have diabetes of the second type, and 34 patients have impaired glucose tolerance. The average age of patients is 55.6 ± 2.2 years. Body mass index is 34.85 ± 1.79 kg/m^2. Phospholipase A2 was determined by chemiluminescent immunological analysis on the device 'Siemens'. Fatty acids were determined by enzyme method using test-systems (England). Metabolites of nitric oxide were determined by the method Metel'skaia V. A., Malonicdialdehyde (MDA) was determined by the method of Andreeva.
Research result
Insulin levels were determined in all 74 patients. Hyperinsulinemia was observed in 30 patients with low glucose tolerance. 34.65 ± 4.16 mkme/ml. Readings in the control group total 8.3 ± 1 mkme/ml. In patients with diabetes, the insulin content was 6.28 ± 0. 4 ($P = 0.001$), which caused the expression of phospholipase A2 3 times in diabetes and twice with low glucose tolerance. In non-alcoholic fatty liver disease activity of nitric oxide and its content increased. The level of metabolites increased in parallel with the activity of alanine Aminotransferase. The content of malonic aldehyde in patients with diabetes increased and made up 24.12 + - of 1.64 mmol/l. patients with low tolerance to glucose the content of MDA made up 16.91 ± 3.87. Monitoring indicators equal to 9.94 ± 1.62 µmol/l, $P = 0.001$. A negative correlation between insulin and Malon aldehyde was revealed. ($r = -0.31$). The interrelation of the lipid peroxidation and leading to phospholipase mechanism of damage to the lipid membranes of hepatocytes FLA2 and MDA $r = -0.53$; $P = 0.001$; between NO and FLA2 = 0.625. $P = 0.001$.
Summary
High activity of inflammation markers in patients with NAND with type 2 diabetes is a diagnostic and prognostic criterion for the activity of the inflammatory process in the liver with a high risk of complications. Hyperglycemia induces the production of free radicals, reduces the activity of nitric oxide synthase and disrupts the sensitivity of insulin receptors.

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EP123

Nutritional medical practice for assessment and therapeutic intervention patients with colorectal cancer

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Introduction
Candidate patients for colorectal cancer surgery may present malnutrition due to the tumor pathology itself. This must be corrected preoperatively in order to achieve good surgical results.
Methods and objectives
Objectives
Determine the nutritional status in our population and to know the type of nutritional support necessary.

Methods
Descriptive study including preoperative patients for scheduled surgery for colorectal carcinoma and excluding those who require neoadjuvant treatment or urgent surgery, during a period of 12 months (May 2019 to April 2020). In the month prior to the intervention, they are evaluated in a nutrition consultation, indicating the nutritional support, according to their condition.
Results
123 patients, aged 68.8 ± 10.19 years old, were studied, 59.3% were men. The Global Subjective Assessment was 51.2% type A (well nourished), 39% type B (moderate malnutrition or risk of malnutrition) and 8.9% type C (severe malnutrition). The anthropometric variables analyzed were weight in men (presented at the time of consultation) of 82.40 kg ± 17.14 and BMI of 28.92 ± 5.31 kg/m^2, in women weight of 69.52 ± 14.71 and BMI of 28.90 ± 5.32 kg/m^2. Abdominal circumference of 105.8 ± 12.1 cm. Regarding the analytical values, they presented Albumin of 3.66 ± 6.13 g/dl and Transferrin of 270.4 ± 61.7 mg/dl. The results indicated a high prevalence of abdominal obesity and mild protein malnutrition. 4.4% of the patients received complete home enteral nutrition, generally due to intestinal subclusive symptoms (from the consultation assessment until the day of the intervention). In 91.1%, oral nutritional supplements were indicated as presurgical preparation during the 5 days prior to surgery.
Conclusion
The PCCR colorectal cancer patients, preoperatively after scheduled surgery, presented a low prevalence of severe malnutrition, which required total enteral nutrition until the intervention. The prevalence of abdominal obesity was high. Studies are needed to assess the surgical impact of the improvement in nutritional status in these patients.

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EP124

Does the initial daily insuline dose vary with the duration of diabetes ?

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Introduction
Uncontrolled patients with oral antidiabetics may require injectable treatment including insulin. We studied the variation of the initial daily insuline dose with the duration of diabetes.
Methods
We conducted a prospective randomized study. We recruited patients with type 2 diabetes hospitalized for a switching to insulin in the C department of diabetology and nutrition at the National Nutrition Institute in Tunis, during 6 months. We correlate the initial daily insuline dose and the duration of diabetes using the Spearman test.
Results
We included 50 patients with type 2 diabetes, 54% were men and 46% were women, with an average age of 59 years (± 11), the averge duration of diabetes was 8 years (± 7). We found no statistically significant correlation between the initial daily insuline dose and the duration of diabetes ($r = 0.006$, $P = 0.966$).
Conclusion
Our results showed that the initial daily insuline dose prescribed for type 2 diabetes is independent of the duration of diabetes. This proves that the recommendations concerning the doses prescribed when switching to insulin can be used for all insulin-dependent patients with type 2 diabetes, regardless of the duration of diabetes.

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Endocrine-Related Cancer

EP125

Relationship between phase angle and urinary tract infection in hospitalized cancer patients

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Background
Bioelectrical impedance analysis (BIA) has been widely used in the evaluation of body composition. Phase angle (PhA) is obtained from the direct measurements of resistive (Rz) and reactive (Xc). Pha and can be interpreted as an indicator of fluid distribution, electric resistance and cellular membrane capacitance of the human body, and is associated with nutritional status. Its screening, and an early intervention in patients with a low PhA, may help to prevent malnutrition. However, there are no studies on its role in urinary tract infection. We aim to establish the association between PhA and urinary infections in hospitalized cancer patients.
Methods
Prospective observational study carried out in hospitalized cancer patients at the General University Hospital of Valencia, from November 2019 to March 2020. BIA and other anthropometric parameters were evaluated within the first 48 h after admission. PhA was measured using a bioelectrical impedance (Akern®). Inpatient were followed-up through daily medical oncologist reports, and urinary infections were registered during hospitalization.
Results
A total of 100 cancer patients were evaluated. The mean age was 66.1 years and 66 were males. Most patients (74%) had an advanced stage disease, mostly lung (29%) and gastrointestinal tumors (32%). Mean weight and BMI was 68 kg and 24.73 kg/m^2 respectively. During admission, 10% developed a urinary infection. PhA was significantly lower in patients who developed an urinary infection (OR 0.531; CI 95%: 0.293 – 0.022; $P = 0.022$).
Conclusions
A low PhA is associated with a higher risk of urinary infections in hospitalized cancer patients. An adequate nutritional evaluation is essential to detect patients with a low PhA. A timely implementation of nutritional support during hospitalization could avoid urinary infection risk.

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EP126

Hyperprogression of Merkel cell carcinoma during immunotherapy

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Introduction
Merkel cell carcinoma-MCC) is a rare, aggressive, neuroendocrine skin tumor with a poor prognosis. Chemotherapy (CT) and/or local/locoregional radiotherapy (LRRT) are first-line MCC therapies, but disseminated/locally advanced MCCs often become resistant to this treatment. The use of programmed cell death receptor1/programmed cell death ligand 1 (PD-1/PD-L1) monoclonal antibodies is a new type of therapy for MCC. While PD-1 monoclonal antibody (pembrolizumab) is registered for the treatment of various types of aggressive tumors, PD-L1 monoclonal antibody (avelumab) is registered exclusively for the treatment of locally advanced/metastatic MCC. Significant efficacy of these drugs has been shown by prolonged stabilization or partial regression (PR) of the disease in 30–60% of patients with MCC.
The aim
A case report of a patient with locally advanced MCC who developed tumor hyperprogression during immunotherapy.
Case presentation
A 47-year-old patient was diagnosed with MCC (Ki67 index 97%) in the subcutaneous tissue of the left pectoral and axillary region, size 9×10×10 cm. The tumor was inoperable, and the diagnosis was made by biopsy. Treatment started with 4 cycles of HT (etoposide–platinum), followed by LRRT and 2 more cycles of HT, and the effect of therapy was PR (tumor reduction by 90%). One month later, the disease progressed – several confluent tumors with a total size of 5×2×2 cm were diagnosed outside the field of LRRT (left hemitorax and hemiabdominal region). Pembrolizumab was administered in 3 doses, after which the disease progressed: multiple confluent tumors in the left hemitorax and hemiabdomen, size 11×7×9 cm. Retreatment with the same HT was performed in 3 cycles, which was complicated by significant myelotoxicity (pancytopenia grade III–IV) and sepsis. Because

of this adverse event, further application of HT is abandoned, although PR of tumors has occurred (three tumors, size: 4×3 cm, 4×4 cm and 2×1.5 cm). After 3 doses of avelumab, a rapid tumor growth was registered (one tumor size 9×7 cm-increase by 120% in comparison to pre-avelumab size and second tumor size 12×8 cm-increase by 90%). An emergency LRRT was performed in order to stop the further tumor growth, which threatened to exulcerate. Three months later, the patient died.
Conclusion
Unlike pseudoprogression, which occurs due to immune cell infiltration of the tumor and is followed with tumor shrinkage (relatively common during immunotherapy), tumor hyperprogression during immunotherapy is a rare phenomenon and has not been described in patients with MCC.

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EP127

Advanced metastatic disease in a low-grade pulmonary neuroendocrine tumor: a case report with partial response to targeted therapy

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Background
It has been well recognized that grade heterogenity exists within well-differentiated neuroendocrine tumors (WD-NETs). Targeted therapy plays an important role in metastatic disease control.
Case presentation
We present the case of a 58-year-old male patient who was diagnosed with a pulmonary tumor on computer tomography (CT) and underwent a posterobasal left lobectomy. On immunohistochemical staining, synaptophysin and chromogranin A were positive, and the Ki-67 index was 10%, thus the tumor was graded as G2. Treatment with interferon alfa was administered for 7 months, followed by somatostatin analogues (Octreotide). Tumor markers increased suddenly withing a year from diagnosis. Bone scintigraphy identified multiple hypermetabolic lesions, also confirmed on 18F-FDG PET CT and Ga68-DOTATOC PET CT, along with hepatic and splenic high-uptake lesions. Octreotide dose was increased from 30 mg to 60 mg every 28 days. The patient also underwent at this point 2 peptide receptor radionuclide therapy (PRRT) sessions with Lu-177-DOTATATE but at reevaluation with Ga68-DOTATOC PET CT, multiple liver metastasis, with no SSR expression appeared. Percutaneous liver biopsy of the avid nodules showed tumor cells similar to the primary tumor, with a Ki 67% index of 12%. Treatment with Everolimus was initiated in order to decrease hepatic tumor burden, but it produced mild to moderate adverse effects (e.g. rash, fever), which in the end led to dose reduction. During reassessment, the CT scan showed slight progression of the liver metastasis and the tumor markers increased due to tumor necrosis.
Conclusion
Prognostic parameters should be established for WD-NET in order to prevent progression of the disease. Furthermore, in cases of progressive disease, different anti-tumor agents are necessary in order to ensure progression-free survival.

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EP128

A neuroendocrine tumour presenting with double vision

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Carcinoid tumours are low grade neoplasms usually arising from neuroendocrine cells of the bronchial and gastrointestinal tracts. Carcinoid tumours metastasise in 50–75% of patients, most commonly to lymph nodes, liver, and bones, but intra-orbital metastases have only rarely been reported. Here, we describe a patient who presented with an intra-orbital neuroendocrine tumour which was successfully treated with surgery and radiotherapy. A 70-year-old female patient presented with diplopia and was found to have a right orbital tumour which was excised by craniotomy. Surprisingly, the histology revealed a neuroendocrine tumour of small bowel origin. Subsequent imaging identified a small bowel primary tumour for which she underwent surgical removal. The histological diagnosis was a grade 1 neuroendocrine tumour (Ki-67 proliferation index of 2%) with 6/14 lymph nodes involved and extra-nodal spread and the histological features matched those of the orbit. Further disease recurrence in the bowel necessitated repeat bowel surgery and ileocaecal tumour resection. Follow-up Gallium-68 DOTATATE PET scanning showed a DOTATATE-avid recurrence of her orbital diseases more than 5 years after her original surgery. She underwent successful Gamma Knife radiosurgery and remains free from recurrence 12 months later. Neuroendocrine metastases to the orbit are extremely rare, but can have a significant impact on patients' quality of life. Treatment options for orbital neuroendocrine tumour metastases include surgical excision, orbital exenteration, radiotherapy, as well as chemotherapy. As demonstrated in this case, metastatic neuroendocine tumours of the orbit can lead to local recurrence many years after surgical excision and/or radiotherapy. Therefore, longterm surveillance imaging is mandatory to allow early detection of recurrent disease.

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EP129

PRPF8 regulates FAK/AKT pathway and cytoskeleton remodeling through modulation of fibronectin 1 splicing in liver pathologies

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Obesity is emerging as a prevalent cause of chronic liver damage, which can lead to the development of metabolic-associated fatty liver disease (MAFLD), nonalcoholic steatohepatitis (NASH), or even hepatocellular carcinoma (HCC). Increasing evidence suggests a profound dysregulation of the splicing machinery (spliceosome and splicing factors) in these pathologies; however, the role of PRPF8, a pivotal spliceosome element, has not been described in chronic liver pathologies. Thus, we aimed to analyze the expression of PRPF8 in different liver cancer cohorts, and to characterize its putative role in tumor development/progression. PRPF8 expression (mRNA and protein) was analyzed in a retrospective cohort (n = 172 samples) and validated in two *in silico* cohorts (TCGA and CPTAC) of HCC samples with different aetiologies and their adjacent non-tumor control samples. Functional and molecular consequences of *PRPF8* silencing (using specific siRNAs) were evaluated in liver-derived cell lines (HepG2, Hep3B and SNU-387) and in Hep3b-induced xenograft tumors. Moreover, RNAseq and eCLIP data generated in HepG2 cells were analyzed. This study shows that PRPF8 expression is elevated (at the mRNA/protein levels) in HCC samples from different aetiologies in all the cohorts analysed. PRPF8 levels were associated with: i) increased tumor aggressiveness (tumor size, patient survival, etc.), ii) the expression of HCC-related splicing variants and, iii) the alteration of critical genes related to cancer-associated pathways. *PRPF8* silencing reduced *in vitro* aggressiveness of liver cancer cell lines (reducing proliferation, migration, tumorospheres-/colonies-formation, while increasing apoptosis), and decreased xenograft tumour growth *in vivo*. CLIPseq data in HepG2 demonstrated that PRPF8 binds preferentially to exons of protein-coding genes, and RNAseq analysis showed that *PRPF8*-silencing altered numerous splicing events, mainly exon skipping, of multiple genes. Integrated analysis of CLIPseq and RNAseq and *in vitro* experiments revealed that *PRPF8*-silencing modulates fibronectin (FN1) splicing, promoting the exclusion of exon 40.2, which is paramount for binding to integrins. Consistently, *PRPF8* silencing reduced FAK/AKT phosphorylation and blunted stress-fibres formation. Finally, HepG2 cells exhibited lower invasive capacity in membranes treated with media from PRPF8-silenced cells compared to that observed with media from scramble-treated cells. Altogether, our data demonstrate that PRPF8 is overexpressed and associated with aggressiveness in alcoholic, viral and metabolic-associated HCC. Indeed, PRPF8 seems to play key roles in chronic liver disease progression and hepatocarcinogenesis by modulating FN1 splicing, which leads to FAK/AKT activation and stress-fibers formation.

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EP130

Bilateral pheochromocytoma in MEN 2A

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Introduction
Pheochromocytoma is rare neuroendocrine tumor arising from the chromaffin cells of the adrenal medulla. It can be even sporadic or take part of inherited syndromes.
Observation
We report the case of a young 32 year-old woman followed by her oncologist for medullary thyroid cancer treated with surgery and radiotherapy. On the examination of the removed tissue, there was a bilateral cancer, measuring 30 mm in diameter on the right lobe and 40 mm in diameter on the left lobe of the thyroid, associated to a parathyroid hyperplasia. As part of the assessment of the extent of extra-thyroidal extension of the cancer, the CT-scan showed a multiple bilateral adrenal masses, with a spontaneous density > 10 UH, 15 mm in diameter on the right gland, and two masses on the left gland ; 13 mm and 8 mm respectively. The patient was asymptomatic with normal tension and absence of any abnormalities in the examination. First, the adrenal insufficiency was eliminated, then the hormonal exploration revealed a pheochromocytoma (urinary normetanephrine 436 nmol/creat, urinary metanephrine 618 nmol/creat, two-fold and five-fold the upper normal limit respectively). The 123I-MIBG-Scintigraphy was in favor of a bilateral pheochromocytoma without any other locations. The patient was presented for bilateral adrenalectomy. Meanwhile, the genetic diagnosis of the mutations in the RET proto-oncogene (chromosome 10) is being tested.
Conclusion
This case describes a condition named multiple endocrine neoplasia type 2A (MEN 2A), where medullary thyroid cancer is present in 98-100% of cases, parathyroid hyperplasia in 5–10% and pheochromocytoma in 50% ; among them more than 60% are bilateral. The MEN 2A is a genetic condition which follows an autosomal dominant inheritance pattern. Our patient didn't have any similar cases in her family which make her a part of less than 5% of people with MEN 2A thought to have a novo mutation. Genetic screening of family members of MEN 2A is an early detection tool allowing to predict phenotypic characteristics and the association to other endocrinopathies, by detecting the specific RET mutation.

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EP131

Endocrine monitoring after severe hypercalcemia due to primary hyperparathyroidism. In search of lost…MEN 2A?

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The association between primary hyperparathyroidism and pheochromocytoma is present in multiple endocrine neoplasia type 2A (MEN 2A) along with medullary carcinoma or it can be a simple simultaneousness. The presence of the genetic mutation is mandatory in order to have a positive diagnosis of MEN. We report the case of a female patient 63 years old admitted in our department for a large adrenal incidentaloma (10 cm) with no clinical signs of adrenal dysfunction. An adrenal biopsy was already performed in the urology department and the histological result was positive for pheochromocytoma. The medical history of our patient revealed the presence of primary hyperparathyroidism 12 years ago. At the time, the severe hypercalcemia (14 mg/dl total plasmatic calcium) was the trigger for the diagnosis. After we normalize the calcium and we identify the parathyroid adenoma (ultrasound and sestamibi scan) the right inferior parathyroidectomy was performed along with subtotal thyroidectomy for multiple thyroid nodules. After the surgery our patient did not follow any treatment or medical control. The family medical history was negative for medullary carcinoma, pheochromocytoma and hyperparathyroidism. In our department hormonal tests showed: upper limit for plasmatic metanephrines, over 1000 ng/ml chromogranin A, normal PTH and slightly increase calcitonine 12 pg/ml (NV:0–10 pg/ml). The patient is currently on alpha-blocker medication as pre-surgical protocol requires. After surgery a calcitonine stimulation test is planned in order to check for medullary carcinoma. If this test is positive the genetic testing for RET mutation is necessary. This case report emphasizes the importance of medical follow-up after severe hyperparathyroidism no matter patient's age. The voluminous pheochromocytoma shows a long evolution. Lack of hypertensive crisis and other specific symptoms are explained by the intratumoral consumption of catecholamine. A close monitoring is necessary for the possible thyroid involvement (medullary carcinoma) and also for the parathyroid and adrenal function.

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General Endocrinology

EP132

The prevalence of common risk factors for depression development in diabetes mellitus of the type 2

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Objective
To evaluate the frequency of common risk factors for depression development in patients with the diabetes mellitus of the type 2 (DM 2).
Materials and methods
163 patients with DM 2 at the age of 40–65 years old, period of DM is 11.18 [4.28; 22.33] years. The evaluation of the anxiety and depression level was carried out with the use of the Hospital anxiety and depression scale *(HADS);* a questionnaire was carried out with the use of specially developed form to reveal common risk factors for depression development. A study group was divided into 2 subgroups depending on the level of depression in accordance with the HADS: group 1 included patients with DM 2 and depression (n = 46) and group 2 included patients with DM 2 without depression (n = 117).
Results
1. There are more patients that live alone (23.9% in comparison with 9.4% consequently,C= 0.04) and person with disability status (69.6% in comparison with 47.9% consequently, C= 0.03), among patients with DM 2 and depression, than among patients with DM 2 without depression.
2. The disability status is associated with the risk for depression development in DM 2 (OR = 2.41; P = 0.01; 95% CI 1.16–4.19)

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EP133

Severe hypertriglyceridemia in young adults

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Introduction
Severe hypertriglyceridemia (sHTG) (plasma triglycerides > 10 g/l) is a rare but pernicious and understudied condition.
Objective
Our objective was to evaluate the etiology, characteristics, and complications of sHTG.
Methods
It's a retrospective study including 10 patients with (sHTG) diagnosed between 1998 and 2020, at the department of endocrinology at Hedi Chaker-hospital Sfax-Tunisia.
Results
Notable male predominance was noted (sex ratio = 4), the mean age was 30.1 years (18–40). Family history of metabolic disorders was reported: dyslipidemia (50%), HTA (80%), diabetes (60%). Past history of Diabetes was reported for 5 patients: diabetes type 2, diabetes type 1, and diabetes

secondary to chronic pancreatitis, maternally inherited diabetes in 60%, 20%, 20%, and 20% respectively. 6 patients were being followed for dyslipidemia, 2 of them had chronic pancreatitis due to sHTG in pediatric age. 70% of patients had body mass index (BMI) between 25 and 30 kg/m^2. Also, alcohol consumption was reported in 3 cases with mean consumption of 55 g/per day. All of diabetic patients had a poorly controlled diabetes during hospitalization with mean HBA1c of 11.6%. Symptoms reported were: vomiting (6 patients), epigastria pain (7 patients), and weight loss (7 patients). Eruptive xanthoma was notable only for one patient. The mean fasting Plasma TG level was 19.92 g/l (10.5 to 34). Extremely severe hypertriglyceridemia TG > 30 g/l was reported in 2 cases. Abdominal imaging findings included acute pancreatitis signs (7 cases) in addition to hepatic steatosis. Necrotizing pancreatitis occurred in about 71% of acute pancreatitis cases. Lipoprotein electrophoresis helped to determine the causes of dyslipidemia in our study. Dyslipidemia type IV was the most common etiology (6 patients) and dyslipidemia type IIB was observed in 30% of cases. However, dyslipidemia type V was notable only for 1 patient. All patients received a fibrate (range of dose from 160 to 320) as either monotherapy or part of combination lipid-lowering therapy. We report a case of rhabdomyolysis induced by high dose of fibrate 320 mg/day associated with statin 20 mg/day. These therapeutic strategy including diet and intensification of diabetes treatment contributed to a decrease in the average triglyceride level of 72.8%.

Conclusion

These findings highlight the importance of early identification and successful treatment of severe HTG and its underlying disorders to reduce the risk of recurrent pancreatitis.

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EP134

Autoimmune polyglandular syndrome type 3: a case report

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Introduction

Autoimmune polyglandular syndrome (APS) is a rare endocrinopathy, characterized by the coexistence of two or more glandular autoimmune diseases that can appear at different intervals of time.

Observation

Herein the case of a young woman descendant of first degree consanguineous marriage, diagnosed since the age of six with celiac disease (CD) where gluten-free diet was not respected due to poor socio-economic conditions, and an important retardation regarding the pondero-statural development was present. She consulted at the age of 33 year-old for recent onset of diabetes mellitus (DM), the anti-GAD antibodies were positive at 36 UI/ml, in favor of the diagnosis of latent autoimmune diabetes in adults (LADA). The biological exploration of the hypophyseal function revealed a primary hypothyroidism (TSH > 100 µU/ml), with negative TPO antibodies. And on the cervical ultrasound, the thyroid gland appeared to be atrophic.

Conclusion

This association of auto-immune thyroiditis to other auto-immune disorders represent the autoimmune polyglandular syndrome type 3 (APS 3: APS3A with DM, APS 3C with CD), it is an autoimmune condition that affects the body's endocrine glands. The cause is still unknown, but multifactorial mecanisms are to be involved (genetic and environmental).

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EP135

Multiple endocrine neoplasia type 1 presenting with foreneck swelling

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Introduction

Multiple endocrine neoplasia type 1 (MEN-1) is a hereditary condition with neoplastic lesions in multiple endocrine organs, which most frequently involves pituitary, parathyroid gland, and pancreas.

Case report

A 53 y/o male visited endocrine clinic with the chief complaint of foreneck swelling for 1 month. He had history of renal stone for years. He had normal fT4 (1.13 ng/dl, reference 0.93–1.7), normal TSH (0.3 µIU/ml, reference 0.27–4.2), elevated PTH (125.3 pg/ml, reference 18.4–80.1) and elevated serum calcium (11.9 mg/dl, reference 8.6–10.2). Thyroid echo revealed a cystic lesion at the right thyroid lobe but no definite parathyroid lesion. Aspiration from the cystic lesion got 17 ml chocolate-colored fluid. Levels of PTH and thyroglobulin in the washout fluid were > 3000 pg/ml and 211 ng/ml respectively. Cytology revealed sheet of follicular cells with macrophages and colloid. Sestamibi parathyroid scan with SPECT revealed focal hot spots at left upper and right lower thyroid beds, and a large cold area at right lobe of thyroid. Pituitary and adrenal endocrine survey revealed hormone levels within normal reference ranges. A 0.4 cm hypoenhanced nodule in posterior portion of the pituitary gland was identified by MRI. Further studies to screen possible pancreatic neoplasms and parathyroidectomy are scheduled.

Conclusions

Hemorrhagic thyroid cyst is one of common causes of foreneck swelling. With detailed history taking and logically reasoning, the patient with foreneck swelling was finally diagnosed as MEN-1. Patients with MEN-1 may have manifestations of various endocrine disorders in different lifetime. Genetic study and long-term follow-up are warranted.

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EP136

Clinical implications for the variations in the BMI in the clinical trial population with obstructive sleep apnea and narcolepsy evaluated for excessive sleepiness with Solriamfetol: a rapid review

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Introduction

Solriamfetol is a dopamine and norepinephrine reuptake inhibitor, indicated to improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA). Decrease in the body weight as an adverse effect of < 2% incidence in both the narcolepsy and OSA patients has been reported. We hypothesise that the baseline Body Mass Index (BMI) may be a an independent predictive marker for the decrease in the body weight in narcolepsy and OSA

Methods

We conducted a rapid review in accordance with PRISMA guidelines for the published randomised controlled clinical trials that document BMI in studies for Solriamfetol, across PubMed and Cochrane library. We eliminated duplication by excluding publications for subgroup and post hoc analysis

Results

A total of eight clinical trials were identified and four unique studies that included BMI as baseline demographic parameter were included for narrative synthesis. The BMI range varied from 18 to < 45 kg/m^2, across dose groups. The mean BMI was 32 (s.d. ± 2.5, minimum 28, maximum 33, range 5.4, 95% CI 28 to 36). The patients in the OSA group had a higher BMI (33 kg/m^2) which was 19.1% greater (5.35 kg/m^2) than the patients with narcolepsy (28 kg/m^2). We evaluated four Phase 3 trials, three for 12 weeks and one open label trial evaluating the safety and efficacy for long term (50 weeks)

Conclusions

OSA patients tend to be more obese. Baseline BMI appears be an important determinant for appropriate patient selection to initiate and predict the decrease in body weight. Mechanistically, dual reuptake inhibition properties of solriamfetol distinguishes it from the amphetamine stimulants by its lack of release of monoamines, which may have varied long term outcomes for excessive sleepiness in patients with narcolepsy and OSA. Periodic body weight monitoring would add value to the emerging clinical evidences especially for varied doses of solriamfetol.

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EP137

Extra-digestive manifestations of celiac disease

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Introduction

Celiac disease is an autoimmune enteropathy secondary to gluten intolerance developing in genetically predisposed patients. The atypical presentation is the most common form of the disease. The aim of this work is to report the various extradigestive manifestations associated with celiac disease.

Patients and methods
This is a descriptive transversal study carried out over a period of 10 years. All patients with celiac disease were included.
Results
Forty one patients were included; the average age of patients was 36 years (17–75 years) with a sex ratio (M/F) equal to 0.46. The typical clinical presentation including chronic diarrhea and/or weight loss was observed in 29 patients, it was atypical in 10 patients and suspected in 2 asymptomatic patients with type1 diabetes. The extra-digestive manifestations associated with celiac disease were: anemia (83% of cases), amenorrhea (73% of cases), sterility (2.4% of cases), delayed puberty (2.4% of cases), coetaneous signs (12% of cases), psychiatric disorders (12% of cases), myalgia (9.7% of cases), hypocalcaemia (51% of cases), hypo albuminemia (73% of cases)), cytolysis (9.7% of cases), and cholestasis (7.3% of cases). All patients received a gluten-free diet and symptomatic treatment of extra-digestive manifestations. The evolution was marked by a clinical and biological improvement in 75% of cases.
Conclusion
Asymptomatic and atypical presentations are frequent in celiac disease, justifying a disease screening in order to start early the gluten free diet and improve the prognosis of the disease.

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EP138

Functional hypoglycemia: clinical and biological characteristics

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Introduction
As hypoglycemia is a common symptom, an organic cause is always the first diagnosis looked for as it can be associated with a specific medical or surgical treatment. Diagnosis of functional etiology isn't as precise, as the whipple triad can be incomplete. We herein report a serie of confirmed etiology for functional hypoglycemia.
Methods
This is a descriptive retrospective study including 20 cases of functional hypoglycemia. The etiology was assessed either by using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) or by performing an oral glucose tolerance test (OGTT).
Results
Four patients had gastric emptying disorders, three men and one woman. Mean age was 49 years, 3 patients had a history of pyloroplasty and vagotomy, and one patient had partial gastrectomy. Neurogenic signs were noted in all patients, and 3 patients had neuroglycopenic symptoms such as headaches in 3 patients and loss of conscience in one. In 3 cases, body mass index (BMI) was normal, one patient was overweight. None of the patients changed weight. All patients had an early postprandial hypoglycemia, with hypoglycemia at 60 min in 2 cases and at 120 min in 2 cases at OGTT, with a mean glycemia of 0.52 ± 0.07 g/l. They were put under dietary measures with approvement of symptoms. Ten patients had a risk state of diabetes mellitus, 7 men and 9 women. Mean age was 37 ± 12 years. Twelve had family history of type 2 diabetes. Three patients had a normal BMI, 7 were overweight and 6 were obese. All patients had neurogenic symptoms and 12 had neuroglycopenic signs. Hypoglycemia was late post prandial in 13 cases and without clear timing in 3 cases. Mean glycated hemoglobin was 5.62 ± 0.48% in the 10 cases it was assessed. Kidney, liver and thyroid parameters were normal. Hyperinsulinism and insulin resistance was confirmed with a HOMA-IR at 6.35 ± 3.65 in 11 cases, and in the 5 cases with no confirmed insulin resistance, there was an inadequate insulin response to OGTT with a mean hypoglycemia at 210 min, mean glycemia at 0.6 ± 0.06 g/l and insulin 5 times more than basal insulin. Prediabetes was confirmed in 7 cases. All patients had dietary measures with improvement of hypoglycemia.
Conclusion
Functional hypoglycemia remains an important diagnosis to think of in the situation of spontaneous hypoglycemia, as investigations differ from organic etiologies and first line treatment is dietary intervention that can improve and treat efficiently the symptoms.

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EP139

Vitamin D status and the association with metabolic risk factors in polycystic ovarian syndrome patients attending a tertiary hospital of Morocco

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Introduction
Polycystic ovary syndrome (PCOS) is the most common female endocrine disorder with a prevalence of 8– 13% in women of reproductive age. Accumulating evidence suggests that vitamin D deficiency might have multiple impacts on the disease process ; and is involved in the pathogenesis of metabolic syndrom in PCOS. This notion is carried by the fact that the vitamin D receptor gene regulates about 3% of the human genome. The purpose of this study is to elucidate vitamin D status and the potential association with metabolic factors in polycystic ovarian syndrome patients followed-up in our center
Patients and methods
This is a retrospective data analysis of 51 PCOS patients, attending the endocrinology department of Oujda's Mohammed VI university hospital. The levels of 25OHD in the serum were determined using Architect chemiluminescent immunoassay technology, and Insulin resistance was estimated by the HOMA-IR. For all statistical tests, *P* value below 0.05 was pictured as statistically significant
Results
A total of 51 patients were involved in the study. The mean age was 24.83 ± 5.62 years. The majority of PCOS subjects (69.2%) were found to be vitamin D deficient,; with an average vitamin D concentration of 13.54 ± 7.14 ng/ml. Serum 25-hydroxyvitamin concentrations less than 10 ng/ml were classified as severe vitamin D deficiency and were found in 25% of cases. Overweight was noticed in 67.3% with a mean body mass index (BMI) of 26.12 ± 5.86 kg/m^2 and a mean waist circumference of 91.25 ± 17.61 cm. All PCOS patients underwent a 75-g oral glucose tolerance test, and the association between vitamin D status and HOMA-IR was statistically significant ($P < 0.001$), whereas the association between vitamin D status and BMI ranges was not statistically significant ($P = 0.52$). 25-hydroxyvitamin D concentrations were positively correlated with high-density lipoprotein cholesterol ($P < 0.05$).
Conclusion
Vitamin D deficiency is highly prevalent among women with PCOS, with an increasing evidence that vitamin D deficiency is associated with multiple metabolic risk factors in PCOS syndrome. In order to prove these findings, large intervention trials with vitamin D supplementation are warranted in PCOS women.

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EP140

Thrombosis and coeliac disease

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Introduction
The occurrence of thromboembolic events in celiac disease has been reported in the literature, especially in adults. The objective of our study is to determine the prevalence and clinical characteristics of thrombosis in celiac disease and to clarify the role of thrombophilic factors.
Patients and methods
This is a retrospective series of four observations of thrombosis among a cohort of 41 patients with celiac disease revealed in adulthood. Laboratory workup for acquired or constitutional thrombophilia was performed in all four cases.
Results
Between 2000 and 2014, celiac disease was diagnosed in 41 patients, among whom 5 cases of thrombosis were collected, for an overall prevalence of 12%. They were 4 women and 1 man with an average age of 43 years [18–61]. No patient had a family history of thrombosis. Thrombotic manifestations preceded the diagnosis of celiac disease in two cases. Two patients presented with two concomitant thrombotic locations: one had deep vein thrombosis of the left lower limb associated with portal thrombosis, the other had intracardiac thrombus and extensive portal thrombosis. The thrombosis was mesenteric-portal in the third case, cerebral in the fourth

case and hepatic in the fifth case. Risk factors for thrombosis were identified in the five patients and could all be linked to celiac disease: hyperhomocysteinemia (n = 2), antiphospholipid antibodies (n = 1) and protein C and S deficiency (n = 2) linked to vitamin K deficiency,. The outcome in the three patients was good under anticoagulant treatment and a gluten-free diet.
Conclusion
The diagnosis of celiac disease should be made in case of unexplained thrombotic manifestations even in the absence of digestive signs. Risk factors for thrombosis can be acquired during this disease. These factors must be investigated, corrected, or even indicate thromboembolic prophylaxis.

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EP141

Wermer syndrome: different phenotypes for the same disorder

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Introduction
Werner syndrome (WS) is a rare genetic disorder that displays clinical features suggestive of accelerated aging. Also known as adult progeria, it is caused by mutations in the *WRN* gene, which encodes a RecQ DNA helicase. Primary characteristics of this syndrome are progeroid changes of hair, bilateral cataract, atrophic skin, soft-tissue calcification, bird-like face, abnormal voice and many others features. Here we report 5 patients that presented with different phenotypes of this syndrome showing the heterogenicity of this genetic disorder.
Case report
All of our 5 patients were born from consanguineous parents. The first 2 patients are brother and sister. The older sister was 22-year-old and followed for short stature and hypogonadism. She had a bird-like face with an atrophic skin. She developed over the years bilateral cataract and adrenal insufficiency. She was treated with hormonal replacement therapy and hydrocortisone. As for her brother, the diagnosis of WS was evoked at the age of 10, when he consulted for short stature and bird-like face. A hypothyroidism and adrenal insufficiency were also diagnosed later. The second family consist of 2 brothers aged 34 and 32, who consulted for short stature, hypogonadism and hypothyroidism. Both presented with pinched facial appearance, pitched voice, skin atrophy, diabetes mellitus (DM), dyslipidemia and cataract. And the last patient, is 36-year-old male patient who was first followed for hypothyroidism and DM. Considering the association with hypogonadism, short stature and atypical facial features, the WS was probable. All the 5 patients were treated with hormonal replacement to compensate for the different deficiencies. Unfortunately, the genetics test was not available to confirm this disorder.
Conclusion
WS is a rare syndrome but it must be evoked, considering its association with different malignancies such as thyroid follicular carcinomas, malignant melanoma, meningioma, soft tissue sarcomas, primary bone tumors and leukemia. They also develop premature atherosclerosis, which is the second cause of death for those patients. The discordances between the signs and the age of diagnosis may be attributed to numerous factors, such as differential expressions and regulations of the WRN protein in various cell types and tissues, rates of cell turnover, and variations in the replicative potentials of various types of stem cells. The role of the genetic tests is becoming more and more necessary to unsure the proper diagnosis and to eventually lead a standard follow-up of the different comorbidities.

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EP142

K^+-dependent Na^+/Ca^{2+} -exchangers 3 aggravates experimental colitis in mice

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Calcium signaling plays a regulatory role in the events of cellular proliferation. In immunocytes such as T cells, B cells, mast cells and many other cell types, Ca^{2+} signals show to control the proliferation, differentiation, and function. Furthermore, Ca^{2+} has been shown to act as a second messenger to regulate innate immune cell function and activation. Here, we found that loss of Nckx3, a potassium-dependent Na^+/Ca^{2+} exchanger, up-regulated of innate immune response-associated genes in the duodenum. In addition, Nckx3 KO mice showed an increase in inflammatory bowel disease- and tumorigenesis-related genes. In DSS-induced experimental colitis mice models, Nckx3 KO mice attenuated the severity of colitis. There were higher in the cumulative injury score, histopathology and evident at both the levels of mucosal inflammation and crypt injury in the DSS-treated Nckx3 KO mice than in the wild-type mice. Together, these results highlight that Nckx3 plays a critical role in the innate immune and immune response, may be central to the pathogenesis of inflammatory bowel diseases.

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Pituitary and Neuroendocrinology

EP143

Pituitary stalk interruption syndrome: a clinical case report

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Introduction
Pituitary stalk interruption syndrome (PSIS) is a rare entity characterized by a triad of thin or interrupted pituitary stalk, aplasia or hypoplasia of the anterior pituitary and absent or ectopic posterior pituitary seen on magnetic resonance imaging (MRI). We are presenting the clinical case of a child who presented for short stature.
Case presentation
We present the case of a 4 year and 8 months old child who presented for short stature in our outpatient department. He was the first child born to a non-consanguinous young couple, with a normal gestational period. The parents denied any significant pathological history. The child was born full term by caesarean section, Apgar score 9, birth weight of 3.7 kg and a prolonged physiological jaundice treated with phototherapy. In the neonatal period he presented episodes of hypoglycemia, considered secondary to a transient adrenal insufficiency, treated until the age of 6 months with hydrocortisone, later being lost from monitoring. He has been well with no chronic medical problems, no hospitalizations, and no surgeries, until this evaluation. Physical examination showed no facial dysmorphia, with a height at −3.5 s.d., with a normal weight, with stage 1 Tanner of pubertal development, micropenis, with both testicles present in the scrotum. Hormonal analysis showed normal thyroid stimulating hormone (TSH), freeT4, prolactin and a normal fasting morning cortisol: 10 µg/dl (n = 5–25 µg/dl). Furthermore growth hormone (GH) stimulation test (clonidine) was abnormal with a value < 1 ng/ml (normal > 7 ng/ml), together with low IGF1 value. The bone X-ray of the hand was 1 year old (bone age). In addition, MRI brain revealed anterior pituitary hypoplasia and absent pituitary stalk with normal neurohypophysis.
Conclusions
We present the case of a pituitary stalk interruption syndrome in a 4 year child, in which case hormonal replacement therapy was started.

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EP144

Co-existing microprolactinoma and meningioma – a rare case

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Introduction
Meningiomas and pituitary tumours are two most prevalent benign tumours of the CNS but neither are common and without a history of radiotherapy their concomitant existence is extremely rare. Meningiomas comprise 15–25% of all intracranial neoplasms while prevalence of benign pituitary adenomas is 10–23%. We report a rare case of co-existing Brain tumours.
Case
51 year old lady presented with deteriorating vision in left eye with deteriorating visual acuity. No other significant medical or family history. Examination revealed significant right hemianopia. The CT scan showed

a suprasellar tumor of 32×31×13 mm. Short synacthen test and pituitary hormones were all normal. IGF-1 Prolactin 605 mIU/l. MRI suggested it to be a meningioma rather than a primary pituitary tumour which was confirmed by histopathology obtained by Transfrontal Debulking surgery followed by Radiotherapy for residual disease which she tolerated really well. Few months later she complained of some headaches, some weight gain, secondary amenorrhoea & galactorrhoea. Blood test for prolactin, LH, FSH, Oestradiol, TFTs, IGF1 and Cortisol was arranged and showed Prolactin 2225 mIU/l and normal other hormones. MRI was difficult to interpret due to recent surgery but showed no interval change from previously and she was started on Cabergoline following which her symptoms improved.
Conclusion
In our case the cause of rise in prolactin level post-surgery was unclear. Radiation induced hypopituitarism could be one of the causes but the fact that all other pituitary hormones were stable makes it less likely. A co-existing microprolactinoma is more likely. The diagnosis of co-existing brain tumours is not easy to make based only on MRI, but it is important to distinguish between them as the treatment strategy for these tumours are different. Post-surgical evaluation in cases of suprasellar meningiomas with regular monitoring of the pituitary function might be beneficial.

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EP145

A case of Cushing syndrome misdiagnosed as treatment with antiepileptic drug

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Introduction
The most common causes of pseudo Cushing syndrome are alcoholism, chronic kidney disease, neuropsychiatric diseases, pregnancy, uncontrolled diabetes, and drugs. We present a patient who was operated on suspected Cushing syndrome based on abnormal results in overnight dexamethasone suppression tests.
Case presentation
A 49-year-old female patient was referred to our clinic for reoperation due to persistant cushing syndrome after first pituitary surgery in another center. Cortisol had been found to be 10.2 µg/dl after overnight 1 mg dexamethasone suppression test (DST) performed in aforementioned center with suspicion of cushing syndrome in the patient with type 2 diabetes mellitus and obesity. Basal morning ACTH and cortisol had been found 44 pg/ml and 12.7 µg/dl respectively. The cortisol response to 48-h, 2 mg/day low-dose DST was 6.24 µg/dl. 24-h urinary free cortisol (UFC) had beenfound to be normal. Heterogeneous contrast enhancement was observed in the right half of the pituitary gland, and no mass lesion had been detected in pituitary magnetic resonance imaging,. She was diagnosed with bilateral cushing disease in inferior petrosal sinus sampling and operated. On the first postoperative day morning cortisol was 14 µg/dl. At the 3rd month control, the cortisol levels after 1 mg DST was 4.4 µg/dl. The patient was referred to our clinic with the diagnosis of persistant cushing disease. Beside facial plethorea and abdominal obesity (body mass index 41.2 kg/m^2) her physical examination was unremarkable. Past medical history revealed carbamazepine use for 10 years due to epilepsy. Recurrent tests performed in our clinic showed that, midnight serum cortisol was 1.79 µg/dl, and 24-hour UFC was 150 µg/day (43-403). No pathological signal change was observed in the control pituitary MRI. When the pathological specimens were re-evaluated in the pathology department no adenoma was identified, it was observed that the normal reticulin structure was preserved, Ki67 proliferation index was < 1%, and diffuse strong cytoplasmic staining was observed with GH, ACTH and PRL. Telangiectasias of the face were evaluated in favor of rosacea disease by the dermatology clinic. We concluded that there was no clinical evidence of Cushing's syndrome and that failed dexamethasone suppression tests were due to the effect of carbamazepine.
Conclusion
Some drugs such as carbamazepine induce CYP3A4 activity and may lead to false positive dexamethasone suppression test results. The results must be properly evaluated to avoid misdiagnosis.

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EP146

A case of primary amenorrhea revealing a macroprolactinoma

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Introduction
Primary amenorrhea should be considered in any patient who has not experienced periodic menstruation by 16 years regardless of the presence of normal growth and development of secondary sexual characteristics.
Observation
17-year-old patient, who exhibited normal secondary sexual characteristics, normal auxiliary and pubic hairs, normal breast development since the age of 12 with the non-appearance of menstruation beyond 16 years. No history suggestive of hypothyroidism, repeated infections, raised intracranial pressure was there. No history of difficulty in walking, deformity of extremities and nothing contributory from developmental and birth history. No similar history in family was present. Physical examination revealed Height: 162 cm, Weight: 74 kg, BMI: 28.24 kg/m^2. Secondary sexual characteristic: Pubic hair P 4, Breast development B 4. No signs of hirsutism and no clitoromegaly was seen and other systemic examinations were normal. The hormonal profile of the patient revealed hypogonadotropic hypogonadism, hyperprolactinemia at 2390 ng/ml and MRI showing a pituitary macroadenoma of 25 × 16 mm. It is extending into the left cavernous sinus. The *patient* was already *treated* with *dopamine agonists* with a decrease in the level of prolactin and the size of the pituitary adenoma.
Conclusion
The prolactin adenoma in our patients probably set in during puberty after the normal development of secondary sexual characteristics and stopped puberty development before the onset of menstruation.

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EP147

A challenging case of Cushing's disease complicated with diverticular rupture and multiple thrombotic phenomena following trans-sphenoidal surgery

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Background
Cushing's syndrome (CS) occurs due to cortisol overproduction. Endogenous hypercortisolemia can be secondary to Adrenocorticotropic hormone (ACTH) dependent as well as independent causes (1). Early identification and prompt definitive management is crucial to minimize mortality. Successful management of CS becomes extremely challenging due to multiple associated complications, especially the thrombotic events which are even more prominent in post-operative period needing close monitoring. We report a case of Cushing's disease (CD) in a young female managed with trans-sphenoidal surgery, followed by a challenging post-operative period due to multiple thrombotic phenomena, ultimately succumbed.
Case presentation
A 32-year-old Sri Lankan female presented with overt features of CS and diagnosed to have CD with pituitary microadenoma. Pre-operatively she was medically managed with Ketoconazole. She underwent trans-sphenoidal surgery and despite achieving normalization of post-operative day2 cortisol, she developed multiple complications including diverticular rupture and ischemic colitis, needing hemicolectomy, followed by parieto-occipital infarction, which ultimately lead to her death despite aggressive management.
Conclusion
This case highlights important and aggressive complications associated with CS giving rise to a challenging post-operative course. Diverticular rupture had been rarely described in association with hypercortisolemia, due to multiple mechanisms, and this case adds to the existing literature (2). Post-operative ischemic colitis and stroke which lead to the death of this patient are seen with procoagulant state associated with CS, with a high risk during the immediate post-operative period. Venous thrombo-embolism is the most commonly reported thrombotic phenomenon while acute mesenteric ischemia as seen in our patient is only rarely reported (3). This emphasizes the need to consider thromboprophylaxis for patients with CS in the immediate post-operative period, although clear guidelines regarding this do not exist.

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EP148

Double localization of a cerebral germinoma, a case study

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Introduction
Germ cell tumour are embryonic tumour localized mainly at the gonads level, their cerebral localization is rare with less than 1% of intracranial neoplasia.
Observation
We have reported a 20 years old girl case without pathological history who had progressive diabetes insipidus for one year associated with spaniomenorrhea, the MRI revealed an aspect suggesting a pineal stem germinoma (12 mm of major axis), with a second localization at the pituitary stalk (12 mm of major axis) and a disappearance of the spontaneous hyper signal of the post-pituitary gland, measurement of tumour markers: was positive for the B HCG at 8.33 u UI/ml (normally < 2 m UI/ml) and normal for the other markers, which confirmed the diagnosis of pure germinoma without biopsy.
Discussion
Germinomas of suprasellar and pineal dual localization remain rare and present only 5–10% of germinomas with only 15 cases reported in the literature, the clinical expression is polymorphic and imaging provides a highly evocative radiological semiology, the treatment is mainly based on radiotherapy and sometimes on a combination of radio and chemotherapy this last alternative was our therapeutic choice with a good clinical and biological evolution.

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EP149

Apparently non secreting adenoma: a new challenge

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Introduction
Silent corticotroph adenoma represent an uncommon subtype of nonfunctioning adenoma, immunoreactive for ACTH, without clinical or biochemical evidence of hypercortisolism and unclear pathogenesis. Usually, they present with local mass effect (visual deterioration being the most common) and endocrine dysfunctions. They carry a more aggressive behavior, particularly upon earlier recurrence.
Case presentation
A 47-year-old, obese male patient, recently diagnosed with pituitary macroadenoma, came to our clinic for emergency endocrine evaluation, accusing suddenly visual field dysfunction and headache 7 days before admission with the left temporal hemianopsy development. At admission, IGF-1, thyroid and adrenal hormone status within normal, mild hyperprolactinemia and hypogonadotrophic hypogonadism. A second opinion on CT and IRM cerebral scans certified pituitary macroadenoma with suprasellar and intrasellar extension, optical chiasm compression and pituitary apoplexy. Ophthalmological examination confirmed right quadranopsy-superior temporal and left temporal hemianopsy. Transphenoidal adenomectony was performed. The immunohistochemistry exam showed positive staining for ACTH, Ki67 proliferation index-4%, p53 positive in rare tumor cells, positive cytokeratin CAM 5.2 and cromogranin with variable intensity in the tumor cells. Visual dysfunctions have markedly improved post surgery. He was discharged with hydrocortisone, levothyroxine and testosterone replacement therapy and periodic follow-up.
Particularities
Silent corticotroph macroadenoma probably grew aggressively. Despite the local mass effect and visual deterioration that are the most common manifestations, our patient didn't complain about sexual dynamic disorder. Age at diagnose is also peculiar with peak incidence in the 3rd decade, being more frequent in women. The presence of tumor proliferation markers such as ki67 and p53 associate an aggressive pattern and a poor prognosis.
Conclusions
Management of silent corticotroph macroadenoma is complex. Surgery remains the main therapeutic approach. This patient needs to be monitored closely for quick hypopituitarism onset and careful follow-up due to frequent and early recurrences. Rarely, they can change to a more aggressive phenotype or possibly transform to Cushing disease and multimodal therapy is necessary.

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EP150

A rare etiology of hypopituitarism in adulthood

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Introduction
Rathke Cleft Cysts (RCC) are common benign cystic lesions in the sellar region. These cysts are often small, intrapituitary and asymptomatic. Voluminous forms are rare and can be symptomatic by compressing the adjacent structures. We report the case of pituitary insufficiency related to RCC.
Observation
A male patient aged 49 years old, diagnosed with type 2 diabetes since 8 years treated with metformin and glimiperide, was addressed to the endocrinology department for additional exploration of frequent hypoglycemic episodes occurring despite stopping glimepiride. The patient was also presented with hormonal findings of central hypothyroidism. Patient complained of headache and erectile dysfunction. No Polyuria-polydipsia syndrome was found. Exploration of the other pituitary axes concluded to central hypogonadism and central adrenal insufficiency. The patient was treated with hydrocortisone and levothyroxine. The pituitary MRI showed a posterior intrasellar expansive process, extended to the suprasellar space and compressing the optic chiasma. Fundus and visual field examination were normal. The patient underwent endoscopic endonasal transsphenoidal surgery. Pathological examination was in favor of RCC. After surgery, hypopituitarism was persistent.
Discussion
Symptomatic RCC represent 5 to 15% of operated sellar region tumors. This pathology is often diagnosed in children. Our case is particular because of the appearance of symptoms in adulthood and the atypical radiological presentation, mimicking a tumor of the post pituitary gland.

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EP151

Fasting glucose and other metabolic features of 17 Brazilian women with microprolactinomas

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Introduction
Among other organic functions, Prolactin (PRL) can influence metabolism.
Aim
To evaluate basal glucose metabolism in women with prolactinoma, according to menstrual cycle, presence of hyperprolactinemia, and dopamine agonist (DA) treatment.

Material and methods
Cross-sectional study of 17 women with microprolactinoma and 11 healthy controls. Variables evaluated: PRL, FSH, LH, estradiol, GH, IGF1, fasting glucose and insulin, Homeostatic Model Assessment (HOMA), HOMA-beta, body mass index (BMI), waist, hip, and waist-to-hip ratio (WHR). Group comparison between controls and patients with: (I) normal (NPRL, $n = 6$) and elevated PRL (EPRL, n = 11), (II) eumenorrhea (EU, $n = 10$) and oligomenorrhea (OLIGO, $n = 7$), and (III) bromocriptine (BC), cabergoline (CAB, $n = 5$) or no DA (NDA, $n = 7$) treatment.
Results
(I) Comparisons between NPRL, EPRL and controls: WHR was higher in NPRL (0.89 ± 0.04) than controls (0.80 ± 0.09; $P = 0.0292$). GH levels were lower in EPRL (0.50 ± 0.38 ng/ml) than controls (1.76 ± 1.17 ng/ml; $P = 0.0275$). (II) Comparisons between EU, OLIGO, and controls: PRL levels were higher in OLIGO (83.74 ± 54.04 ng/ml) than controls (13.82 ± 5.74 ng/ml; $P = 0.0017$). WHR was higher in EU (0.87 ± 0.05) and OLIGO (0.87 ± 0.05) than controls ($P = 0.0380$). GH levels were lower in EU (0.50 ± 0.43 ng/ml) than controls ($P = 0.0210$). (III) Comparisons according to DA treatment: CAB had higher PRL levels (77.08 ± 57.18 ng/ml) than controls ($P = 0.0085$). BC had lower fasting glycemia than CAB (77.0 ± 7.6 vs. 89.4 ± 3.6 mg/dl; $P = 0.0220$) and NDA (89.4 ± 5.2 mg/dl; $P = 0.0021$). HOMA-beta was higher in BC ($P = 0.0347$). GH levels were lower in NDA (0.41 ± 0.32 ng/ml) than controls ($P = 0.0439$). There were no other significant differences in variable comparisons between groups. Linear regression models did not show influence of GH on clinical-biochemical parameters of the patients. The influence of PRL and estradiol suggested by linear regression models was not confirmed by multivariate analyses, which only corroborated the influence of BC treatment on fasting glycemia ($r^2 = 0.6159$; $P = 0.0020$).
Conclusions
Patients with EPRL, NPRL, eumenorrhea, and oligomenorrhea had changes in WHR and GH levels. Treatment with BC was the main influence on fasting glucose. The authors emphasize the need for metabolic evaluation of patients with microprolactinoma and, despite the small sample size, our data indicate special attention to GH assessment, aiming at early detection of GH deficiency.

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EP152

Management of malignant insulina

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Introduction
Malignant insulinoma is a rare pancreatic neuroendocrine tumor that accounts for only 10% of all cases of insulinoma. The clinical picture is characterized by the presence of severe hyperinsulinemic hypoglycaemic syndrome in a patient with pancreatic tumor with locoregional and/or distant metastases. Therapeutic management is challenging due to the need to control both hypoglycemic syndrome and tumor growth. Curative surgery is rarely applicable due to widespread metastases. We analyze clinico pathological characteristics, treatments and prognosis of 3 patients diagnosticated from 2009 to 2015.

	CASE 1	CASE 2	CASE 3
SEX	Female	Female	Male
AGE	37	37	77
TUMOR SIZE	4.5	5	5
METASTASIS	Hepatic + lymph node	Hepatic + lymph node	Hepatic + lymph node
GLUCOSE	10	42	38
INSULINE	86	38	40
C PEPTIDE	7.7	8.7	9.5
PROINSULINE	> 100	> 100	> 100
KI67	20%	> 20%	5-10%
HYPOG TREATMENT	Diazoxide + Dexameta	Diazoxide	Diazoxide + Dexameta
SURGERY	No	No	No
S. ANALOGS	Lanreotide LAR	Lanreotide LAR	Lanreotide LAR
2º LINE	Hepatic mets embolizat	Everolimus	Everolimus
3º LINE		Temozola + Capecita	Sunitib
SURVIVAL	22 months	26 months	29 months

Surgery was the first choice of treatment in all the cases but it was dismissed from surgeon. Glycaemic control was the therapeutic challenge in these patients. In case 2 the hypoglycemic was controlled with diazoxide and lanreotide LAR. The others needed corticosteroid therapy and high doses of diazoxide to avoid hypoglycemia. After somatostatin analog Everolimus was the first line treatment. Case 1 refused this therapy and case 2 took only for one month because of bad tolerance. Hepatic metastases embolization improve the glycemic control in case 1. Lu- DOTATE was not available in our center.
Conclusion
Surgery is the unique curative treatment but is rarely applicable due to the widespread metastasis at diagnosis. The hypoglycemic syndrome is often refractory and decreased quality of life of these patients, in addition to medical treatment, debulking surgery or locoregional therapies can improve the symptoms control.

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EP153

ABSTRACT WITHDRAWN

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EP154

Hydrocephalus associating Hakim-Adams syndrome as unusual manifestation of pituitary adenoma

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Introduction
Non-functioning secretory pituitary adenomas are usually characterized by the lack of associated hormone overproduction. The absence of symptoms of excess hormone production results in a delayed diagnosis: sometimes as an incidental diagnosis, sometimes due to compressive symptoms with visual involvement or neurological symptoms as headache. However, hydrocephalus associating Hakim-Adams Syndrome caused by foramen of Monro obstruction secondary to pituitary adenoma is an unusual manifestation.
Case presentation
We present the case of a 64-year-old man admitted to Emergency Department for a gradual development of gait disturbance and primarily urinary incontinence for the past three months, as well as the onset of cognitive impairment (disorientation, frequent medication forgetfulness, driving disability). He had a previous medical history of hypertension and chronic daily headaches. He had recently consulted Neurology, being diagnosed of atypical parkinsonian syndrome and having started the combination of levodopa and carbidopa medication, with no apparent improvement. At physical examination he presented decreased alertness, memory loss and postural instability. His walk was characterized by short and shuffling steps on widely spaced legs and loss of balance. Head magnetic resonance (MR) revealed a 44 × 48 × 35 mm pituitary Knosp 3a macroadenoma with suprasellar extension, compressing the optic chiasma and associating a remarkable hydrocephalus, particularly of the right ventricle resulting from obstruction of the foramen of Monro. Visual field revealed paracentral scotomas. On admission, laboratory findings showed prolactin levels 9.2 ng/ml [2.6–13.1], TSH and T4L levels 0.40 mUI/l [0.380–5.330] and 0.58 ng/dl [0.54–1.24], respectively; IGF-1 levels 82.6 ng/ml [67–141] and testosterone levels < 0.10 ng/ml [1.75–7.81]. LH 0.42 UI/l [1.2–8.6] and FSH 2.93 UI/l [1.27–19.26]. Cortisol and ACTH not valuable due to treatment with dexamethasone when MR images were assessed by neurosurgery on

admission to the emergency room. Sodium levels 135 mmol/l [134–145], without any clinical symptoms suggestive of diabetes insipidus. Due to COVID-19 pandemic and overcrowding hospital the patient had to be transferred to a free-Covid hospital for surgery, with pathological pattern and immunohistochemical analysis pending.

Conclusion

Hydrocephalus as a complication of pituitary adenomas is infrequent. Pituitary tumours rarely become large enough to cause an obstruction at the foramen of Monro. This case is an illustration of this unusual clinical manifestation: hydrocephalus caused by foramen of Monro obstruction associating the classical picture of Hakim-Adams Syndrome in a patient misdiagnosed with atypical parkinsonian syndrome. The considerable overlap of symptoms for atypical parkinsonian syndromes with symptomatic hydrocephalus makes clinical diagnosis challenging and may lead to delay in diagnosis.

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EP155

Coexistence of papillary thyroid carcinoma and primary hyperparathyroidism in a patient with acromegaly.

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Introduction

Acromegaly is an endocrine disorder resulting from an excess of growth hormone (GH). The cause is almost always a pituitary adenoma, and it affects through the insulin-like Growth Factor 1 (IGF-1) the cellular proliferation, increasing therefore the risk of malignancy. Herein, we describe a case of coexistence of papillary thyroid carcinoma and primary hyperparathyroidism in a patient with acromegaly.

Case report

A 58-year-old woman was referred to our department for suspicion of acromegaly. Her past medical history included diabetes mellitus, hypertension and dysmorphic syndrome for last 4 years. On physical examination, she had a blood pressure of 120/80 mmHg, an acrofacial dysmorphia, a goiter with a firm left nodule. On laboratory investigations, she had a glycated hemoglobin of 8.28%, a calcemia level of 121 mg/l, a serum phosphate level of 22 mg/l, a PTH level of 209 pg/ml (nr: 15-68), an IGF-1 level of 646 ng/ml (3 times normal), GH level at 18.93 mUI/l. The pituitary hormonal evaluation revealed a corticotropin deficiency, without gonadotropin nor thyrotropin deficiency. The pituitary magnetic resonance imaging showed a 28 mm macroadenoma invading the cavernous sinuses. Cervical ultrasound found a 57 × 44 × 73 mm goitre with a 70 mm left nodule classified TIRADS 5. Parathyroid imaging investigation (ultrasound, CT-scan and scintigraphy) didn't individualize any adenoma or hyperplasia. She had a total thyroidectomy and a parathyroidectomy of the right inferior gland containing an adenoma and parathyroidectomy of the right superior gland. The histopathological examination confirmed the diagnosis of papillary thyroid carcinoma and parathyroid adenoma.

Discussion and conclusion

This case highlights the importance of the screening for malignancies associated with acromegaly and the evaluation of other endocrine neoplasia. The coexistence of parathyroid and anterior pituitary tumors is part of either multiple endocrine neoplasia type 1 or type 4. In addition, papillary thyroid carcinoma is reported as a part of the clinical presentation of multiple endocrine neoplasia type 4. Genetic investigations are mandatory to assess the responsible mutation.

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EP156

Functional pituitary gonadotroph adenoma in male patients: a case study

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Background

Pituitary gonadotroph adenomas are common but very rarely do they secrete biologically active luteinizing hormone (LH) and follicle-stimulating hormone (FSH). There have been case studies reporting high sex hormones (testosterone/estrogen) in the presence of high or normal LH and FSH.

Case presentation

Here we report two cases who presented with visual disturbance and headache at a tertiary care hospital, Karachi, Pakistan. Brain imaging of both patients revealed a pituitary macroadenoma. Hornonal workup of our patients is shown below.

Hormonal workup of case 1 and case 2

Laboratory Parameters	Case 1		Case 2		Normal values
	Pre-Surgery	Post-Surgery	Pre-Surgery	Post-Surgery	
FSH	36.66	4.97	13.61		1.4–15.4 MIU/ml
LH	7.09	0.99	4.45		1.2–7.8 MIU/ml
Testosterone	952.7	176.8	> 1500	20.14	193–740 ng/dl
Cortisol	2.60	7.40	12.60	11.10	4.3–22.4 ng/dl
FT4	0.69	1.65	0.84	0.88	0.89–1.76 ng/dl
Prolactin	12.40		36.80		3–14.7 ng/ml
GH	< 0.50	0.06	0.13		2.0–5.0 ng/ml

Figure Legend: FSH, Follicle stimulating hormone; FT4, Free Thyroxine; LH, luteinizing hormone; MIU/ml, milli-international units per milliliter; ng/dl, nanogram per deciliter; ug/dl, microgram per deciliter; GH, Growth hormone; Both patients underwent transsphenoidal resection of the tumor and tissue histopathology confirmed pituitary adenoma. Postoperatively, improvement in hormonal profile was observed along with the resolution of visual disturbances and headaches.

Conclusion

Thus, functional gonadotroph adenoma should be considered in the presence of elevated testosterone/estrogen and normal or elevated follicle-stimulating hormone (FSH)/ luteinizing hormone (LH). Early diagnosis leads to a better outcome.

Keyword: Pituitary Neoplasms, Gonadotrophs, Follicle Stimulating Hormone, Luteinizing Hormone, Adenoma, Testosterone

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EP157

Psychological effects of cabergoline in a patient with a giant prolactinoma.

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Introduction

Psychological disorders may be expected in patients with hyperprolactinemia. Indeed, they generally have poor quality of life, anxiety, depression and certain personality troubles. Dopamine agonists are the first-line treatment of prolactinoma. Recently, an increasing number of reports emphasized on dopamine agonists psychological side effects. Effectively, some patients develop de novo psychiatric symptoms or have exacerbation of pre-existing conditions during dopamine agonist therapy. We report the case of a patient with prolactinoma who developed a psychiatric disorder after cabergoline therapy initiation.

Observation

A 42-year-old woman was referred to our department for pituitary apoplexy. Her past medical history revealed a type 2 diabetes mellitus. She presented with headaches and disturbed vision. Pituitary MRI showed a giant pituitary adenoma with hemorrhagic necrosis extending to the sphenoid sinus and optic chiasm, and complicated by hydrocephalus. On physical examination, she had a body weight of 75 kg, a body mass index of 27 kg/m^2, a blood pressure of 120/70 mmHg. Biological investigations revealed hyperprolactinemia (2975 ng/ml) with gonadotropic deficiency. After ruling out a neurosurgical indication, the patient was put on dopamine agonist therapy (Cabergoline 1 mg/ week). One day after treatment initiation, the patient developed an acute delirium with temporo-spatial disorientation and a suicide attempt. No further treatment was needed, just a close follow up. One week after, neurological and psychological condition was stabilized.

Conclusion

Patients with hyperprolactinemia receiving dopamine agonists may develop changes in mood and behavior regardless of prior psychiatric history.

Larger prospective controlled clinical studies are needed to delineate the prevalence of these psychiatric complications and to assess their appropriate management.

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EP158

Rapid decrease of a pituitary mass with gonadotrophic and thyrotrophic insufficiency – the case for lymphocytic hypophysitis?

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Background
Lymphocytic hypophysitis is an unusual inflammation of the pituitary gland affecting mostly women. Its pathogenesis is still poorly understood and the presentation and clinical course vary largely. Serum prolactin levels may be low, normal, or elevated. Unlike what is observed in clinically nonfunctioning pituitary adenomas, there is not a clear hierarchy of anterior pituitary hormone deficiencies. Hypophysitismay resolve spontaneously, may relapse, and in some cases may be refractory to treatment.
Case presentation
A 47-year-old woman with history of sudden secondary amenorrhea at the age of 46 andsubsequent hot flashes, discovered galactorrhea incidentally after 6 months. Her initial evaluation revealed mild hyperprolactinemia 1532 uIU/ml (127–637), significantly low FT4 5.7 pmol/l (12–22), T4, FT3 and T3 0.8 nmol/l (1.3–3.1), mildly increased TSH 5.61 uIU/mLand increased TPOAb. Levothyroxine (LT4) 50 µg was introduced, but T4 and T3 remained low despite normal TSH, indicating central hypothyroidism, interestingly without any clinical signs. Gonadotrophic insufficiency was documented: FSH 5.4 uUI/l, LH 0.92 IU/L, E2 < 5 pg/ml. MR imaging revealed aninhomogeneous, hypodense, contrast enhancing 1.1 cm sellar mass in contact with the optic chiasm, and left deviation of pituitary stalk. Cabergoline (CAB) 0.5 mg/week was added, with rapid PRL decrease to subnormal values, but amenorrhea persisted. At presentation in our clinic, the patient had only amenorrhea with nogalactorrhea, headaches, visual impairment orpolyuria. On LT4 35 µg/day and CAB 0.25 mg/week, TSH: 4 uIU/ml, FT4 10.5 pmol/l (9–19), T3: 72.8 ng/dl (80–200), morning cortisol 12.33 µg/dl (6–22), low PRL, IGF1 83.15 ng/ml (60–240), low FSH, LH and estradiol (2.74 IU/l, 0.92 IU/l, 20.52 g/ml, respectively). A rapid GnRH test showed partialresponse of LH (4.66 IU/l), with an estradiol increase to 110.7 pg/ml. Repeated imaging (at 3 months) showed a significant shrinkage of the more inhomogenousand hypodense pituitary mass. This rapidly decreasing infiltrative-like pituitary mass associated with partial pituitary failure, possibly due to pituitary stalk compression (gonadotrophic&thyrotrophic insufficiency and mild hyperprolactinemia) suggests a possible lymphocytic hypophysitis. Confirmation could be obtained only by pituitary biopsy or surgery, which were not recommended yet.
Conclusions
Lymphocytic hypophysitis is a rare inflammatory disease of the pituitary gland which is frequently a diagnosis of exclusion. It can be associated with atypical pituitary insufficiency and with spontaneous remission of the pituitary mass. Of note, central hypothyroidism may present with low FT4/T4 and low, normal or even mildly elevated TSH.

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EP159

Diabetes insipidus

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Background
Diabetes Insipidus is a complex and heterogeneous clinical syndrome affecting water balance, resulting in large volumes of dilute urine. Determining the mechanism and etiology of diabetes insipidus, as well as differentiating it from other pathologies that cause polyuria and polydipsia has always been a challenge since water deprivation test is not always conclusive and antidiuretic hormone can not be reliably measured in the circulation.
Aim
The aim of this study is to analyze the most common causes of diabetes insipidus, and thus determine the different etiologies of this disorder.
Methods
This study was conducted using SPSS including patients who had been diagnozed with diabetes insipidus, hospitalized between 2012 and 2020 in the Endocrinology Department of Hedi Chaker university hospital, Sfax, Tunisia.
Results
A total of 20 patients were included in this study. The average age was 60 years old. 13 of them were women and 7 were men. All of our patients had polyuria and polydipsia. Only 6 of them had signs of intracranial hypertension. No signs of dehydration was found in any of our patients. The average polyuria was quantified at 7.8 l/24 h. While average polydipsia was estimated at 7.2 l /24 h. An elevated plasma osmolarity was found in only two patients, estimated at 318 and 328 mOsm/l respectively. The average urinary osmolarity was 208 mOsm/l. Only 7 of our patients undertook a water deprivation test, it was well-tolerated in 5 of them, and poorly tolerated in 2, due to extreme thirst. The water deprivation test was in favor of central diabetes insipidus in 4 patients and inconclusive in 3 others. Central diabetes insipidus was found in 19 patients, while nephrogenic diabetes insipidus was found in only one patient. A lack of posterior pituitary hyperintensity on sagittal T1-weighted imaging was found in 7 out of the 19 cases of central diabetes insipidus. Neuro-surgery was the most common cause of central diabetes insipidus, found in 10 patients, while empty sella syndrome was found in 3 patients, head trauma in 2 patients, craniopharyngioma in 1 patient, and idiopathic central diabetes insipidus in 3 patients. While the nephrogenic diabetes insipidus was linked to lithium.
Conclusion
The patient history, MRI scan and water deprivation test usually suffice to establish the cause of diabetes insipidus, but some situations remain unclear and not devoid of discrepancy. Copeptin test may offer a promising accuracy regarding diagnosing the etiologies of diabetes inspidus.

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EP160

A pituitary TSH and GH co-secreting adenoma presenting with thyrotoxicosis, but no symptoms of acromegaly: a case report

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TSH producing pituitary adenomas are a rare cause of thyrotoxicosis. These tumors account for only 1–2% of the pituitary adenomas. Co-secretion occurs in 30% of thyrotropinomas and requires careful investigation and subsequent follow up.
A 43-year-old male presented with hand tremor and tachycardia. He was found to have elevated TSH, free T4 (FT4) and free T3 (FT3), but did not get treatment for years. In 2019 he developed atrial fibrillation. TSH was 7.65 mIU/l (0.55–4.78 mIU/l), FT4 was 28.5 pmol/l (11.5–22.7 pmol/l), FT3 was 13.69 pmol/l (3.5–6.5 pmol/l). In early 2020 he underwent an MRI of the brain, which showed a 25×18×18 mm pituitary macroadenoma. Basal growth hormone (GH) level was 0.99 ng/ml, and during an oral glucose tolerance test it remained 0.48 ng/ml at 60 min and decreased below 0.4 ng/ml at the other time points. In May 2020 he had transsphenoidal surgery. Histology showed plurihormonal hypophysis adenoma with extensive GH and focal prolactin (PRL) and TSH expression with immunohistochemistry, consistent with type 3 plurihormonal adenoma. Following the surgery he continued to have elevated TSH and FT3 levels and required beta-blocker therapy for symptom control. Thiamazole therapy was also attempted, but the patient did not tolerate it. Somatostatin analog therapy was also considered, but was not started. He continued to have heat intolerance, palpitations, anxiety and generalized weakness. On the 4-month postoperative sella MRI there was no significant change in the size of the pituitary tumor (25×16×15 mm). His TSH, FT4 and FT3 level increased to 9.4 mIU/l (0.27–4.2 mIU/l), 33.0 pmol/l (12.0–22.0 pmol/l) and 14.7 pmol/l (3.1–6.8 pmol/l) respectively. Basal GH level was 0.48 ng/ml, and during an oral glucose tolerance test it decreased below 0.4 ng/ml at all time points. In December

2020 he had a reoperation of the persistent tumor. Histology revealed GH immunohistochemistry positive hypophysis adenoma, but TSH positivity could not be verified. 6 days after surgery his TSH decreased to 0.03 mIU/l, FT3 to 3.0 pmol/l and FT4 to 18.6 pmol/l. One month after the surgery his TSH level was 0.81 mIU/l, FT3 was 2.6 pmol/l and FT4 was 6.3 pmol/l, therefore he was started on thyroid hormone supplementation. No other pituitary hormonal derangements were observed. First-line treatment of thyroptopinomas is pituitary adenomectomy followed by irradiation in the case of surgical failure. Our case highlights the importance of attempting definitive cure by removal of the tumor to avoid long-term effects of pituitary irradiation.

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EP161

Predictive factors of macroprolactinoma aggressiveness: case report and review of literature

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Introduction
Prolactinomas are the most frequent pituitary tumors. They are usually benign with a good response to conventional medical treatment by dopaminergic agonists (DA). However in some cases, prolactinomas are defined as invasive or aggressive according to clinical, radiological, biological and histopatholgical arguments. The aim of our case report is to discuss potential predictors of aggressiveness in prolactine secreting pituitary tumors.
Case report
A 56 year-old female patient, was admitted in hospital for a giant pituitary adenoma revealed by opto-chiasmatic syndrome. MRI showed a giant macroadenoma measuring 54 × 50 × 54 mm with latero supra and infrasellaire extension and lytic lesions of sphenoid bone and clivus. Hormonal explorations showed a hyperprolactinemia of 48 658 ng/ml (monomeric prolactin represented 95% of total prolactin ruling out a macroprolactinemia) with a secondary gonadal and corticotropic defiencency. Partial transcranial adenomectomy was performed then cabergoline was started at 1 mg/week. Histological assessment confirmed a macroadenoma with a Ki67 of 5%. Follow up imaging and biological assessement are in progress.
Discussion
Aggressive pituitary tumors (APTs) are defined as radiologically invasive tumors with an unusually rapid tumor growth rate, or relevant tumor growth despite optimal standard therapies. The World Health Organization 2017 classification of pituitary tumors abandoned the previous term 'atypical pituitary adenoma' and categorizes prolactinomas into PRL-producing adenomas and APTs or carcinomas in case of metastases. Invasiveness alone is insufficient to define APTs, but is still considered as a key component of aggressiveness. APTs typically evolve from macroadenomas with lactotroph and corticotroph tumors predominating. In our case, the giant prolactinoma with invasive radiological signs and lytic bone lesions were suggestive of aggressiveness. However, radiological and biological evolution after surgical and correctly conducted medical treatment will settle the diagnosis.
Conclusion
Prolactinomas are the most frequent secreting pituitary tumors. Their treatment is well established due to their good response to DA. However, some cases can be invasive with a rapid growth pattern. Predictive factors of aggressiveness are not well defined but tumor size, early radiological signs of invasiveness as well as histological assessement may be suggestive of such entity.

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EP162

Pituitary macroadenoma and Covid-19 infection

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Introduction
SARS-CoV-2 is a novel coronavirus rapidly spread throughout the world.. As it is already known, several endocrine organs do express ACE2, namely, pancreas, thyroid, testis, ovary, adrenal glands, and pituitary We report a patient diagnosed with pituitary incidentaloma and Covid-19. We would like to introduce our experience in treating patient with pituitary incidentaloma and covid-19.
Materials and methods
A 71-yowoman with a history of pituitary macroadenoma was admitted to Heraci University hospital with bilateral pneumonia related to coronaviral infection. According to the patient at the age of 43 after the second delivery (she had 2 pregnancies, 2 deliveries) an olfactory disorder was developed and then 2 years later she was treated by neurologists for trigeminities for many years. In March 2020 she had severe headaches, abrupt deterioration of vision, diplopia,. Brain MRI was performed and it revealed pituitarycystic macroadenoma with compression of chiasmus opticus, spread to cavernous sinuses. Lab results revealed TSH = 10.05 µIU/ml (*n* 0.27–4.2), FT4 = 0.780 ng/dl (*n* 0.93–1.7), level of cortisol, ACTH, prolactin were in normal laboratory ranges, as well as HbA1C, glucose and blood electrolites, Pituitary macroadenoma (incidentaloma) and primary hypothyroidism were diagnosed and L-thyroxin 50 mkg together with cabergolin 0.5 mg twice a week (before surgery) were prescribed. In October 2020 patient had following complaints- high temperature, general weakness, shortness of breath. SARS COV-2 PCR test positive. She got treatment at home by GP -Levofloxacin 500 mg 7 days, Dexamethasone 6 mg 4 days, Enoxaparin, Ibuprofen. She was admitted to the hospital on the 12th day of the illness with BMI = 25.3, SpO2 85%(O2-), 96%(O2 +), BP = 120/80 mmHg, Ps = 85 bpm, T = 38.5°C. Chest CT-bilateral pneumonia with a typical viral etiology, mild lesions up to 15%.

	Result	*n*
Lymphocytes	0.62%	(1.00–3.70)
ESR	41Mm/hr	(2–15)
CRP	6.234 mg/dl	(< 0.5)
AST	65.9 mmol/l	(< 35)
ALT	86.5 mmol/l	(< 40)
glucose	8.9–7.0–6.2 mmol/l	(4.2–6.1)
Prolactin	0.860 ng/ml	(6–29.9)
TSH	2.43 µIU/ml	(0.27–4.2)
FT4	1.11 ng/dl	(0.93–1.7)

Treatment underwent – infusion therapy, Dexamethasone 12 mg with dose decrease to 4 mg, Heparin 10000 U daily, Aspirin, Quamatel, Spironolactone, Galvus 50 mg, L-thyroxin 50 mkg, Oxigen
Results.
The patient improved on treatment. She has no temperature since the 2nd day. Saturation without oxygen was 90% from the 6th day. The patient was advised to continue L-thyroxine therapy with the same dose, remove cabergoline and check prolactin in 6 weeks. Monitoring of glucose level was recommended. After stabilization, surgical treatment of macroadenoma is recommended.

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EP163

Analysis of clinical and biological features of non-functioning pituitary adenomas: A retrospective study

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Introduction
Non-functioning pituitary adenomas (NFPA) present approximately 15% to 30% of all pituitary adenomas. They are most commonly misdiagnosed, until they are large enough to lead to mass effect and hypopituitrasm. The present study was carried out with the aim of studying the clinical and biological characteristics of patients who are followed for NFA.
Patients and methods
This is a retrospective study of 35 patients presenting with NFPA, at the department of endocrinology at Hedi Chaker hospital Sfax-Tunisia, from January 2000 to December 2017.

Results
There were twenty males (57.14%) and fifteen (42.85%) females. The average age of patients was 49.23 years (16–75 years). The majority (48.57%) were aged between 40 and 60 years-old. Approximately 31.4% of patients were smokers. Headache was a major complaint for 28 patients (88%). Most of the patients reported to present moderate headache (57.14%, n = 16). Severe and mild headache were reported in 39.2% (n = 11) and 3.5% (n = 1), respectively. Holocranial headache was present in 32.1% of patients, followed by the bitemporal (35.7%) and frontal (9.5%) regions. Visual symptoms were identified in 74.28% of our study group. Blurring and progressive loss of vision were present in 53.8% and 73% of cases, respectively. Intracranial hypertension occurred in 6 cases (17.14%). Most tumors were macrodenomas, 32 (91.4%) vs 3(8.6%) microadenomas. Endocrine evaluation revealed central hypothyroidism in 34.28% of patients, presenting all a macroadenoma, with a mean level of thyroxine hormone (T4) and thyroid-stimulating hormone (TSH) of 6.95 pmol/l and 1.56 µUI/l, respectively. Adrenal insufficiency was observed in 37.65% of patients with a mean basal cortisol level of 56 µg/l. Prevalence of hypogonadotropic hypogonadism (HH) was 55% on males with a mean testosterone level of 1.12 ng/ml (range.0.02–2.8 ng/ml). On the other hand, 53.3% of the female group presented HH with an average level of oestradiol of 11.4 pg/ml (8–17.7 pg/ml). Disconnection hyperprolactinemia was found in 28.57% of patients with a mean value of 35.29 ng/ml.
Conclusion
NFPA present a heterogeneous group of pituitary tumors that range from being totally asymptomatic to inducing visual disorders and pituitary dysfunction secondary to mass effect. While NFPA are benign tumors, their management require treatment and regular monitoring and follow up.

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EP164

Is hypoprolactinemia also associated with sexual dysfunction?

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Our knowledge about sexual dysfunction during the treatment of patients with prolactinoma is limited. The sexual dysfunction may not improve or turn out a different form as in our patient. Delayed ejeculation (DE) is a complex form of male sexual dysfuntion, characterized by a considerable delay in ejaculation or an inability to complete ejaculation. Both organic and psychogenic etiologies can cause DE, however the pathophysiology is indefinite. In this case, we present a male patient who had developed delayed ejeculation during his follow-up period. A 33-year-old male patient was admitted to our outpatient clinic with complaints of loss of libido, impotence and premature ejaculation. His hormone profile showed hyperprolactinemia, prolactin level was determined as > 200 ng/ml and magnetic resonance imaging (MRI) of the pituitary revealed a macroadenoma. The patient diagnosed as a prolactinoma and cabergoline was started 1 mg per week. Four months after cabergolin, prolactin level was 0.63 ng/ml (2.64–13.13). The patient's loss of libido regressed, but initially described delayed ejaculation rather than pre-existing premature ejaculation. He presented with different patterns of sexual dysfunction in his follow-up period. The effects of prolactin on the male reproductive system have not been clearly elucidated yet. Hyperprolactinemia disrupts the pulsatile secretion of GnRH and cause sexual dysfuntion. Recovery of sexual dysfunction is expected after treatment with dopamine agonists. However, the long-term suppression of the stimulating pathways in the hypothalamus and the psychological reasons caused by the initial complaints in the patients may be effective in persisting sexual dysfunction. Delayed ejeculation is a multifactorial condition that can be both organic and psychogenic, and the pathophysiology is unclear. Hypoprolactinemia was found to be associated with metabolic syndrome and worse glycemic and lipid control. In a study a higher prevalence of erectile dysfunction was found in patients with hypoprolactinemia, but no difference was found in the prevalence of DE. As a conclusion, there isn't enough data in the literature regarding sexual dysfunction in patients with prolactinoma during the follow-up period. In our patient, the psychological reasons caused by the initial complaints may also lead to development of delayed ejaculation. With this case presentation, we aimed to highlight the need to increase the number of studies on sexual dysfunction in the follow-up of patients with prolactinoma.

Key words: Prolactinoma, erectil dysfunction, sexual dysfunction, delayed ejeculation, cabergolin

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EP165

Hypopituitarism in young patients: clinical aspects and diagnosis

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Introduction
Hypopituitarism is the partial or complete loss of anterior pituitary function that can result from acquired or congenital causes. Understanding its clinical aspects in children could lead to early diagnosis and therefore better outcome.
Objective
The aim of this study is to evaluate the characteristics of presentation, and etiology of Hypopituitarism in children.
Methods
This descriptive retrospective database study was conducted at the Hedi Chaker university hospital, Sfax, Tunisia after collecting medical records of patients having in common anterior hypopituitarism.
Results
We collected the data of 20 patients with an average age of 10 years (between 1 and 18 years), SR was 4. In 70% of the cases, the discovery circumstance was other physicians suspecting the disease and therefore referring the patients to us. Family history showed an autoimmune disease in 10% of the cases and only 5% had a family member with hypopituitarism. 35% of our subjects had fetal distress, 5% had neonatal hypoglycemia, 10% had micropenis and 10% had a history of head trauma. Up to 75% of the individuals of our study group had growth retardation, 25% had puberty delay and 10% presented intellectual deficiency. The mean BMI was 20 ± 3.8 kg/m^2 and the mean height Standard Deviation was 1.5 ± 1.6. For those with growth retardation the mean age of the growth curve abruptness was 5 ± 2 years. The physical examination revealed that 25% of the individuals had dysmorphic appearance, 15% had depigmentation. The most common deficiency found was GH deficiency (80%) as well as gonadotropic deficiency (70%) whereas corticotropic deficiency was present in only 20% of the cases and thyrotropin deficiency in 15%. PRL was low in 10% of the cases, and high in 25%. No global hypopituitarism was found in our study group however 15% had partial hypopituitarism, the rest had only one pituitary hormone deficiency. MRI was conducted in 19 patients and was abnormal in 55% of the cases showing hypoplasic pituitary (15.7%), pituitary interruption syndrome (15.7%), hyperplasic pituitary (5.2%), primary empty sella syndrome (5.2%) and hypophysitis (10.5%). The most common causes of hypopituitarism found in our database were congenital causes (66.7%) followed by hypophisitis (11.1%) and hyperplasic pituitary (5%).
Conclusion
Diagnosis of hypopituitarism is important, because unrecognized pituitary dysfunction significantly affects the physical and psychological well-being of people.

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EP166

Acromegaly: clinical and para-clinical study by gender

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Gender is a factor in clinical presentation, biological and morphological characteristics in certain types of pituitary adenomas. Concerning acromegaly, this influence is not well known. In our retrospective study of 32 patients, 12 women and 20 men, hospitalized in our department from 2002 to 2019, we have realized a comparative clinical, para-clinical, therapeutic and prognosis. The median age of women is 47 years, the same as that of men. The average duration of disease progression is similar in both sexes (2.8 years). Extremity hypertrophy affects 88% of women vs. 80% of men, dysmorphic syndrome: 100% vs 95%, arthralgias: 83% vs. 63%, sleep apnea: 85% vs. 60%, organomegaly: 75% vs. 56%, diabetes mellitus: 41% vs. 45%, hypertension: 58% vs. 40%, hypertrophy of the left ventricle: 54% vs. 42%. We found microadenomas in 10% of men, macroadenomas: 100% vs. 89%. Acromegaly was associated with hyperprolactinemia in 54% of woman vs 11% of men, and complicated by corticotroph insufficiency in 66% vs 87%, thyreotropic and gonadotropic insufficiency were slightly the same in both sexe. Complications are slightly similar in both sexes except

for microadenomas which seems to be less frequent in the woman group and hyperprolactinemia which is more frequent in this group.

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EP167

Delayed diagnosis of acromegaly: a two-year journey

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Aims
To present the case of a 69 year-old female patient who was diagnosed with acromegaly two years following the initial onset of facial and acral symptoms, having already developed colonic hyperplastic polyps, one of the complications associated with acromegaly, one year prior to diagnosis.
Material
Case report and literature review.
Method
Acromegaly was diagnosed based on clinical suspicion, raised IGF-1 level, absence of GH suppression following OGTT, brain MRI and histology.
Results
After recognition of phenotypical, particularly facial and acral, features of acromegaly, IGF-1 level was elevated at 624 nmol/l, OGTT failed to suppress GH nadir levels, and brain MRI showed a pituitary macroadenoma which was identified histologically as a mixed, sparsely granulated somatotroph and lactotroph adenoma.
Conclusion
The onset of acromegaly can be insidious in older patients leading to complications and delayed diagnosis. Early diagnosis of acromegaly and effective screening and monitoring for its complications decrease morbidity and mortality and improve overall prognostic outcomes and quality of life.

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EP168

Acromegaly and discoid lupus: a case report

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Introduction
Acromegaly is an acquired endocrine pathology associated with the overproduction secondary to hypersecretion of growth hormone, by a somatotropic pituitary adenoma in more than 90% of cases, the symptoms of which may concern various organs (eye, heart, colon, etc.). skin….). Occasionally, it can present itself in association with skin changes which in some cases are very rare. We report the observation of a patient followed for acromegaly and discoid lupus
Presentation of the case
his is a 43-year-old patient, followed for acromegaly since 2014, held in front of a facial dysmorphia and on a paraclinical level on an IGF-1 level at 337 ng/ml (80–271) × 1.49 normal and pituitary MRI: pituitary macroadenoma of 24 × 17 × 27 mm somatotropic on anathomopathological examination operated twice in 2014 then resumption of surgery in February 2017 by the transphenoid route, complicated by an anterior pituitary thyreotropic and gonadotropic insufficiency started on treatment substitute Levothyrox 75 µg/d; Trisequens, with surgical failure then put on somatostatin analogues. On skin and mucous membrane examination: presence of two atrophic lesions with irregular borders surmounted by scales on both cheeks suggesting discoid lupus. At skin biopsy: Appearance compatible with lupus. The anti native DNA and antinuclear antibodies are negative.
Conclusion
The association of discoid lupus and acromegaly is exceptional, one can observe during acromegaly hypertrichosis, multiple pendulum molluscums, diffuse melanoderma or acanthosis nigricans, frontal skin signs and scalp and therefore know these associated skin lesions. at acromegaly can facilitate its diagnosis.

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EP169

Multiple endocrine neoplasia type 1: clinical features, diagnostics

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Background
In medical practice, there occurs an increasingly common pathology of various endocrine and not only these organs, which is known as multiple endocrine neoplasia – MEN syndrome, which, depending on the affected organs, is classified as MEN type 1, MEN type 2 and MEN type 3. Multiple endocrine neoplasia type 1 (MEN-1, Wermer syndrome) is a rare hereditary disease with an autosomal dominant type of inheritance characterised by high penetrance and the presence of hyperplasia and neoplasia in at least two different endocrine organs. The purpose of the study is to to investigate the features of diagnosis and treatment tactics of the MEN syndrome type 1 based on a clinical case.
Materials and methods
We examined Patient K. born in 1979. Diagnostics methods used in this case were: laboratory – determination of the level of prolactin, vasoactive intestinal peptide, calcitonin, vitamin D3 (25-OH) D, parathormone, calcium, aldosterone, chromatographic A; and instrumental – ultrasound, CT, PET/CT.
Results
The peculiarity of this case is that the disease started with persistently recurrent prolactinoma, which was characterised by the resistance not only to therapeutic but also to surgical treatment. Treatment with radiolabeled somatostatin analogues is a new promising treatment for patients with inoperable or metastatic neuroendocrine tumors.
Conclusions
The difficulty of diagnosis of patients with combined pathology is that by fixing on one disease, you can miss the beginning of the other diseases. In this particular case, by concentrating on a tumor of the pancreas, it was possible to omit the recurrence of prolactinoma.

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EP170

Gonadotropic pituitary adenomas

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Introduction
Gonadotropin-secreting adenomas occupy nowadays the third or fourth place of all pituitary adenomas (12 to 17% of pituitary adenomas operated on), after prolactinomas, somatotropic adenomas and corticotropic adenomas. They can be either accompanied by hypersecretion of gonadotropins or their dosable subunits in plasma recognized only by immunocytochemistry. Gonadotropic adenomas are not uncommon. They are often misknown because they lack any particular clinical expression. Indeed, they are most often revealed at the macro adenoma stage by a tumor syndrome or signs of anterior pituitary insufficiency. The objective of our work is to describe the epidemiological, diagnostic and therapeutic aspects of gonadotropic adenomas.
Material and methods
This is a retrospective study that focused on the cases of pituitary adenomas, collected at the Endocrinology – Diabetology and Nutrition Department of Mohammed VI University Hospital in Oujda, over a period of 6 years and a half. The data were collected from medical records and the analysis was done by SPSS version 21 software.
Results
The gonadotropic adenoma represents 4% of all pituitary adenomas. The average age of our patients was 44.6 years, mostly present in women (sex ratio: 2/1). The reason of consultation was a pituitary tumor syndrome with a decrease in visual acuity in the majority of cases. The average body mass index was 28.2 ± 5.01 kg/m^2. All of our patients had a macro adenoma with signs of ophthalmologic and neurological impact. In our series, all the patients were symptomatic and showed at least one endocrine sign; the most common one being hypogonadism in 66.6% of cases and isolated amenorrhea in 33.3% of the cases. Regarding biological assessments, only one patient had a high level of FSH and LH gonadotropins with low estradiol and a high level of subunits, while the rest of the patients had hypogonadotropic hypogonadism. All our patients benefited from a partial removal of the macro adenoma using endoscopic transsphenoidal surgery, with simple post-operative care. A revision surgery was noted in one patient

and all our patients had a corticotropic and thyroid hormone substitution postoperatively.
Discussion/conclusion
Gonadotropic pituitary adenomas, now recognized with greater frequency with the progress of immunocytochemistry, have become an important chapter in pituitary pathology. A better analysis of the secretion of gonadotropins and their free subunits, with the help of stimulation tests if necessary, allows a significant number of these adenomas to be recognized.
Keywords: gonadotropic pituitary adenoma, diagnosis
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EP171

Acromegaly in the elderly: about 3 cases
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Introduction
Somatotropic adenomas in the elderly are rare, and characterized by diagnostic delay and non-specific clinical signs. We report three cases of acromegaly discovered at a late age.
Observation
They are three women aged 66, 68 and 77 respectively. The circumstance of discovery of acromegaly was goiter in the first case (P1), poorly controlled diabetes in the second case (P2) and dysmorphic syndrome in the third case (P3). The level of IGF1 was respectively for P1 and P2, 1084 ng/ml and 1700 ng/ml. P1 had hyperprolactinemia with gonadotropic insufficiency. The pituitary axis was intact for P2 while P3 had panhypopituitarism. All the patients were diabetic and had joint involvement. P1 and P3 were hypertensive with left ventricular hypertrophy. It was a macroadenoma with invasion of the optic chiasm in all three cases. P1 presents with progressive acromegaly despite surgery twice with a preparation with somatostatin analogues. P2 was cured by the combination of surgery, radiotherapy and somatostatin analogues while P3 was lost to follow-up after surgery.
Discussion and conclusion
Acromegaly in the elderly is frequently associated with diabetes and hypertension. Surgery remains the treatment of choice. If it is contraindicated in the face of fragile conditions in the elderly, treatment with somatostatin analogues should be considered as a first-line treatment. The prognosis of acromegalic patients is inversely correlated with the patient's age.
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EP172

Recurrence of hypercortisolism after long-term post-transsphenoidal surgery remission in a patient with Cushing disease
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Selective transsphenoidal resection of the pituitary adenoma is the initial treatment of choice for Cushing disease. Although the achievement of low cortisol levels following transsphenoidal surgery for Cushing disease is associated with surgical success, recurrence can still occur.
Case presentation
A 38 years old female patient, known with Cushing disease, secondary hypertension, type 2 diabetes and osteopenia, is admitted to our clinic in march 2019, after the second transsphenoidal surgery with symptoms suggesting a cortisol deficiency (nausea, vomiting, fatigue). The patient had her first transsphenoidal surgery in 2010, after which she also presented cortisol deficiency with the recovery of the hypothalamic–pituitary–adrenal axis after 1 year and maintenance of remission for several years.

	10.2010	01.2011	06.2011	09.2011	01.2017	07.2017	02.2019	03.2019
Cortisol 8^{00} (*n* 4.8–19.5 µg/dl)	33.77	0.78	2.70	6.25	10.54	12.09	17.5	0.37
ACTH 8^{00} (*n* 4–66 pg/ml)	68.42	–	11.22	18.68	36.35	49.95	39.83	8.3
Cortisol after DXM 2×2	17.56	–	–	–	2.78	2.6	4.39	–
Urinary free cortisol (n = 21–111 µg/24 h)	–	–	–	–	108.64	98.28	–	–
Imagistic exam (pituitary adenoma dimensions on CT or MRI)	0.8/0.69 cm	0.38/0.25 cm	–	–	0.7/0.4 cm	–	0.6/0.5 cm	0.37/0.27 cm
Secondary comorbidities					Newly diagnosed hypertension (maximal value 220/110 mmHg)		Newly diagnosed diabetes (HbA1c = 7.2%, a jeun glycemia = 138 mg/dl) and hypercholesterolemia	
		⇧ First TS Surgery					⇧ Second TS Surgery	

Clinical exam
BP = 140/80 mmHg, HR = 80 bpm, cushingoid facial features, axillary acanthosis nigricans, no headache, no visual field disturbance, central redistribution of obesity, reduction of muscle strength, no new stretch marks, old, whitish stretch marks with loss of substance on the lower abdomen, hyperpigmented areolas, regular menses.
Biochemical tests
secondary adrenocortical insufficiency, normal gonadotrophin levels, normal thyroid function
Treatment
Prednisone 5 mg per day was started and follow-up after 3 months was recommended
Conclusion and discussion
Patient diagnosed with Cushing disease 10 years ago, who seemed in remission after the first TS surgery, returned after 5 years with newly diagnosed hypertension, without any other clinical signs of Cushing and a non-suppressible cortisol value, but a normal urinary free cortisol. We recommended the patient to come for reassessment after 3 months, but she did not comply and returned after 2 years with newly diagnosed diabetes, Cushing phenotype and greater hypercortisolism**.** Even if the patient with Cushing disease seems to evolve favorably post-TS surgery, the long-term follow-up for the possibility of recurrence is needed.
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EP173

The psychogenic polydipsia: clinical and biological profiles
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Introduction
Psychogenic polydipsia (PPD), also known as self-induced water intoxication, is mostly seen in psychiatric populations. PPD can lead to life threatening complications and may even be lethal if not diagnosed and treated early. The aim of this study is to determine the clinical and biological features of PPD.
Patients and methods
A retrospective study including 11 patients consulting for polydipsia at the department of endocrinology at Hedi Chaker-hospital Sfax-Tunisia, between 2000 and 2020.
Results
Mean age was 39.6 years old, with no sex predilection (6 males and 5 females).
Family history of diabetes mellitus was observed in 6 patients. A history of psychiatric illness was found in 33.5% of patients. Average duration of symptoms was 2.6 years (range:5 months-5 years). Polydipsia was abruptly onset in 4 cases. The anamnesis revealed a pituitary tumor syndrome in 4 patients. On examination, none of our patients showed signs of dehydration. The natraemia varied between 136 and 141 mmol/l. No cases of hypokalemia, hypercalcemia, diabetes, or renal failure were found. The mean quantified diuresis was 5.8 l/24 h with a maximum of 9.5 l/24 h. The mean urine specific gravity was 1003. The mean urinary osmolality was 177.3 mOsmol/kg. All patients underwent an indirect water deprivation test (WDT) combined with the administration of desmopressin that concluded to PPD in all cases. Magnetic resonance imaging of the hypothalamic–pituitary

region was performed in 6 patients and showed microadenoma in 2 cases and partial empty sella in one patient.
Conclusion
PPD is common in patients with psychiatric personality and psychosis such as schizophrenia and psychotic depression. Though no specific treatment has been established for PPD, its management includes water restriction cognitive behavioral therapy.

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EP174

Acromegaly and cardiovascular risk factors

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Introduction
Acromegaly is a rare chronic disorder caused by GH hypersecretion. It's associated with an elevated morbidity and mortality rate. Cardiovascular diseases' complications are the first cause of mortality in patients. In this study we conducted an assessement of cardivascular risk factors in patients with acromegaly.
Patients and methods
A retrospective evaluative study of 32 patients followed for acromegaly from 2002 to 2019 in the department of Endocrinology, University Hospital La Rabta.
Results
Patients were 63% male and 37% female, sex ratio was 1.7. The mean age was 47.9 ± 13.2, six (19%) female patients were older than 50 years and five (16%) male patients were older than 60. Nine patients (28%) were active smokers and 17 (54%) were obese. Diabetes was present in 14 patients (44%) and glucose intolerance in 6 (18%). Hypertension was diagnosed in 15 patients (47%). Ten (21%) patients had dyslipidemia in which 7 had hypercholesterolemia and 9 had hypertriglyceridemia. Two patients had no CV risk factors, four had only one factor, 11 patients (34%) had two factors and 15 (47%) had three or more CV risk factors.
Conclusion
Incidence of cardiovascular risk factors in patients with acromegaly is higher than general population. This is explained by the insulinoresistance caused by the excess of growth hormone. Thus to reduce cadiovacular morbidity and mortality, it is necessary to diagnose and treat the acromegaly and the associated cardiovascular risks as early as possible.

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Reproductive and Developmental Endocrinology

EP175

Gynecomastia: a descriptive analysis

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Introduction
Gynecomastia is the most common breast condition in men. The aim of our study is to describe clinical and therapeutic characteristics of patients with gynecomastia.
Methods
A descriptive retrospective study was conducted in the department of endocrinology at the Hedi Chaker hospital, Sfax, Tunisia.
Results
We collected the data of 28 patients with an average age of 37 years (extreme: 6 and 76 years) when having gynecomastia. Most patients presented spontaneously at the endocrinology office (53.3%). The rest were referred by other specialists. Five patients had a personal history of diabetes (17.9%), 3 had psychiatric disorder (10.7%).2 had a history of sterility (7.1%).1 had a renal failure, 1 was treated for hyperthyroidism, 1 had a bladder cancer and 1 subject had a Klinefelter disease. Symptoms associated with gynecomastia were hypogonadism in 39.3%, pituitary tumor syndrome in 3.6% and weight loss in 3.6%. The mean BMI was 29.4 ± 4.4 kg/m^2. Overweight and obesity were objected in 14.3% and 25% of patients respectively. Gynecomastia was bilateral for 18 patients (64.3%) and unilateral for 10 patients (35.7%) (left in 28.6% and right in 7.1%). No one in our group presented nipple discharge and only 2 had a painful gynecomastia. Gonadal examination was performed in 19 patients, and it was normal in 78.9% of them. Ectopic testicles were noted in 21.1% of cases. Laboratory tests showed hypergonadotropic hypogonadism in 35.5% of cases, hypogonadotropic hypogonadism in 14.3% and elevated PRL in 21.7%. Breast ultrasonography was performed in 35.7% of cases. The etiology was identified in 25 patients. The most common cause was physiological gynecomastia in 32% of cases, followed by drug induced gynecomastia in 24% (the drugs mostly incriminated were spironolactone, anti-depressants, omeprazole, chemotherapy). Treatment was conducted in only 10.7% of cases. The follow up of 22 of these patients showed a reduction in the volume of gynecomastia in 33.6% of cases and its disappearance in 66.7%.
Conclusion
Whereas in almost all the cases, gynecomastia has benign causes, it shouldn't be ignored because it can hide life threatening diseases.

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EP176

The coexistence of triple A syndrome and congenital hypogonadotropic hypogonadism

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Introduction
Triple-A syndrome (AS) is a rare autosomal recessive disorder, defined by the coexistence of primary adrenal insufficiency (PAI), alacrimia and achalasia cardia. The association to other endocrine has so far not been reported in the literature. Herein, we describe the coexistence of AS and congenital hypogonadotropic hypogonadism in two cases.
Case presentation 1
An 18-year-old patient, child of a consanguineous family, was admitted for short stature, delayed puberty and gynecomastia. He had a medical history of triple AS: alacrimia, PAI was revealed at the age of 5 by recurrent convulsive seizures secondary to hypoglycemia, achalasia cardia diagnosed one year later and treated by Heller myotomy. Examination showed obesity, a height of 142 cm; his stature age = 11 years while his bone age = 13 years. Tanner stage G1P1A1. Growth hormone (GH) secretion was normal after stimulation. The testosterone serum level was low (0.14 nmol/l), basal LH level = 0.18 mU/ml and basal FSH level = 1.6 mU/ml. The positive response to the GnRH test indicates a hypothalamic origin of the gonadotropin deficiency. Hypothalamic pituitary MRI was normal. The karyotype was normal. A homozygous splice-donor site mutation (IVS14 + 1G > A) was found in the AAAS gene.
Case presentation 2
A 5-years-old male with a medical history of alacrimia, first consulted at the age of 5 for dysphagia, regurgitations and growth delay. Esophageal manometry confirmed the diagnosis of achalasia. And the low levels of serum cortisol at 28 nmol/l confirmed the diagnosis of PAI. A replacement therapy with hydrocortisone was started, and the patient underwent a myotomy at the age of 6. The patient's younger sister was also being treated in the same pediatric hospital for AS. He was referred to our department at the age of 23 for acute adrenal insufficiency. Examination showed a stature delay (height = 141 cm) and a normal development of secondary sex characteristics. His bone age corresponded to that of 14 years. Further investigation revealed a GH deficiency (L-Dopa test), and a hypogonadotropic hypogonadism (testosterone = 1.26 ng/ml, FSH = 3.3 mU/ml and LH = 3.97 mU/ml) resulting in osteoporosis. Pituitary MRI showed no abnormalities. Mutation screening is not yet performed.
Conclusions
To our knowledge, the association of AS to Hypogonadotropic Hypogonadism was never reported outside of our department. In absence of achalasia and alacrimia, PAI and hypogonadotropic hypogonadism in a male would point towards X-linked adrenal hypoplasia congenita. Nevertheless, AS diagnosis in these two cases was evident.

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EP177

Marfan syndrome: a case report

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Introduction
Marfan syndrome is a rare autosomal dominant genetic disease resulting from a mutation in the gene encoding type 1 fibrillin (FBN1), which is a glycoprotein in the composition of elastic fibers in connective tissue. It mainly affects the cardiovascular, musculoskeletal and ocular systems.
Case presentation
We report the case of a 14-year-old girl, with no particular history, referred to an endocrinology consultation for exploration of gigantism. At the clinical examination we immediately note her tall size: 185 cm which corresponds to more 3DS compared to the normal and to more 4 S.D. compared to the target size. Ligament hyperlaxity was objectified (wrist and thumb sign) associated with skeletal deformities such as pectus carinatum, arachnodactyly, hallux valgus of both feet, clawed toes and dorsal scoliosis. The hormonal tests shows an IGF1 level at 428 ng/ml (normal for the age and the pubertal stage (S4, P4)), in front of the strong suspicion of Marfan Syndrome a cardiac MRI was done, objectified a dilation of the sinus segment of the thoracic aorta, with a CMD on the left.
Discussion
marfan syndrome is the most likely diagnosis in front of a height increase associated with a dysmorphic syndrome, according to the criteria of GHENT (revised 2010): in the case of no family history of Marfan syndrome, the association of dilation of the ascending aorta to a systemic score > 7 (which = 9 in our patient) confirms the diagnosis.
Conclusion
Marfan syndrome is a disease that affects the connective tissue of several systems, hence the need for long-term multidisciplinary management in order to treat or even better prevent complications, specially cardiovascular complications.

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EP178

Precocious puberty: two siblings, two diagnosis

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8-year-old girl is referred to a Pediatric Endocrinologist for the appearance of thelarche, first noted at 6.5 years. She had a relevant clinical history of a neonatal meningitis, requiring prolonged hospitalization and the need for ventriculoperitoneal shunt. On physical examination, she had breast development and dark, coarse pubic hair compatible with Tanner stage 3. She weighed 32.3 kg (percentile – Pc- 75–90), her height was 128 cm (Pc 50) and her annual growth rate was 11 cm (> Pc 87). Clinical work-up was performed. Among the analytical study, evidence of central precocious puberty (CPP) was shown by an increase in gonadotropins and estradiol (LH 2.78 mUI/ml, FSH 3.58 mUI/ml, estradiol 53.7 pg/ml). The remaining analytical study showed no further alterations, namely a normal 17-hydroxyprogesterone value (17-OHP). The wrist X-ray revealed an advance of 3.5 years in bone age. The gynecological ultrasound showed characteristics compatible with the pubertal stage. Cerebral MRI revealed: 'Clastic area sequelae in the frontal region, correlating with antecedents. No other relevant lesions with a sure pathological significance in the rest of the brain parenchyma.' She was diagnosed with CPP and treatment with triptorelin was started. Months later, the patient's brother, aged 7 years and 9 months, is referred to a Pediatric Endocrinologist because of precocious pubarche. He had Wolff-Parkinson-White syndrome and no usual medication. On physical examination, he showed pubic hair compatible with a Tanner stage 2 and a testicular volume of about 2 ml. He weighed 25.5 kg (Pc 50–75), his height was 131.5 cm (Pc 75–90) and his annual growth rate was 7.9 cm (> Pc97). Among his clinical work-up, his high 17-OHP stood out (12.92 ng/ml), whilst gonadotropins' and testosterone' values were adequate for his age. His wrist X-ray showed a 2 years advance in bone age. The patient was diagnosed with non-classical congenital adrenal hyperplasia (CAH), treatment with hydrocortisone was initiated and genetic study is being performed. In view of the brother's diagnosis, it was decided to perform the Synachten test on the girl. The final 17-OHP value was 3.95 ng/ml, excluding CAH. Although the sister was previously diagnosed with Central Precocious Puberty and the brother a Precocious Pubarche, it was hypothesized that the girl might have a Pseudo Precocious Puberty, taking into account the boy's diagnosis. The coexistence of two different disorders with impact in puberty in the same family is noteworthy. The timely recognition and treatment of the different pathologies allowed a good clinical outcome.

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EP179

A difficult diagnosis: menstruation-related periodic hypersomnia

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Introduction
Kleine-Levin syndrome, also called recurrent hypersomnia is a rare sleep disorder characterized by recurrent episodes of severe hypersomnia associated with cognitive and behavioral disturbances such as confusion, derealization, apathy, compulsive eating and hypersexuality. Menstrual-related hypersomnia is classified as a subtype of syndrome Levin-Kleine consisting of recurrent hypersomnia that is temporally linked with menses.
Case presentation
An unusual case of an 15-year-old girl with repeated episodes of hypersomnia, bradymenorrhea, behavioral disturbances similar to psychotic episodes including visual hallucinations (spiders) and anxiety. The sleep periods occurred in connection with ovulatory menstrual cycles and it was observed the absence of hallucinatory episodes during menstrual supression. Various pharmacological options have been proposed to reduce symptoms during the episodes, including anti-psychotics (haloperidol, risperidone), anti-depressants (sertraline, lorazepame), but with little amelioration on the patient's symptoms. Her physical examinations revealed no abnormalities and on mental status examination, she appeared to be very distressed due to her symptoms. Investigation of the menstrual cycle failed to document any striking hormonal abnormality. Serum levels of follicle stimulating hormone, luteinizing hormone, estradiol and progesterone were normal. The thyroid function tests showed Hashimoto's thyroiditis with normal thyroid hormone levels. Hormone evaluation also indicated minimal hyperprolactinemia secondary to psychiatric treatment. CSF levels of hypocretin-1, a hypothalamic peptide that has been shown to be deficient in narcolepsy was less < 30 pg/ml. A magnetic resonance imaging scan was performed and showed no cerebral abnormality. Nocturnal polysomnogram and multiple sleep latency testing were positive for narcolepsy and central sleep apnea.
Conclusion
Symptoms similarities between menstrual-related hypersomnia and other psychiatric disorders make effective diagnosis challenging. Consequently, additional clinical features and ineffective psychiatric treatment mandate further diagnoses. Sex hormones play a role in the menstrual cycle and frequently in the regulation of daily sleep-wake rhytm in women. The patient's treatment proposed was combined oral contraceptive treatment: chlormadinone acetate and ethinylestradiol. This case underlines the importance of multidisciplinary evaluation and treatment in unusual cases.

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EP180

The clinical, biological and etiological aspects of hirsutism

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Objective
To determine the clinical, biological and etiological aspects of hirsutism.
Material
A retrospective study from 2009 to 2017 included 51 patients explored and followed for hirsutism in the endocrinology department of the Rabta hospital.
Results
The mean age of hirsute patients was 29 years, their average age of menarche was 12 years old. Hirsutism appeared before puberty in 2%, during the puberty in 49% and after puberty for 49%, It appeared progressively in 97% and abruptly in 3% of the cases. The degree of hirsutism according to the Ferriman and Gallway score was minimal in 48%, moderate in 41% and finally severe in 11%. It was associated with cycle disorders in 52% of the cases. Signs of hyperandrogenism were found in 6.5% of our patient. 62% of them were obese and 30% were overweight. An arterial hypertension was

found in 18%, diabetes in 22%, glucose intolerance in 2% and dyslipidemia in 29% of the cases. Testosteronemia was increased in 31% of cases. The etiologic investigation showed polycystic ovary syndrome (PCOS) in 30 patients (59.2%) associated with obesity in 19 cases and eleven patients had metabolic syndrome. Idiopathic hirsutism was found in 13 patients (25%), congenital adrenal hyperplasia in 10% with only one case of ovarian tumor and two cases of cushing syndrome (1.6%).
Discussion
Hirsutism is a frequent endocrinopathy. It may be associated with a metabolic syndrome. A rigorous etiological investigation is required before the treatment. The total testosterone assay is recommended for this etiologic survey in first intention.

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EP181

Polycystic ovarian syndrome and metabolic syndrome

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Patients with polycystic ovary syndrome (PCOS) have features of the metabolic syndrome, including insulin resistance, obesity, and dyslipidemia, suggesting an increased risk for cardiovascular disease.
Objective
To assess the prevalence of metabolic syndrome in patients with a polycystic ovarian sydrome (PCOS).
Material
We conducted a retrospective study including 51 patients with secondary hirsutism. The PCOS was retained in 28 patients after elimination of other causes (Rotterdam2003) and the definition of metabolic syndrome was based on the following criteria of IDF 2005.
Results
The mean age of patients was 28 years, hirsutism was mild in 49%, moderate in 42% and severe in 9% of the cases, it was associated with cycle disorders in 60% of cases. Mean testosteronemia level was 0.92 ng/ml. Diabetes was found in 21.6% of our patients, arterial hypertension in 17.6% of them, waist circumference was > 80 cm in 66.7%, triglycerid levels were > 1.5 g/l in 12%, HDLc < 0.5 g/l in 69% of the cases. The metabolic syndrome was retained in 40.6% of our patients according to the IDF criteria. A low-calorie diet and metformin were instituted in 24.5% of our patients. Cyproterone acetate was added in 61% of the cases. The evolution was marked by weight loss and improvement in their metabolic profile.
Conclusion
The prevalence of the metabolic syndrome in patients with a PCOS was high, hence the importance of screening and treatment in order to prevent cardiovascular diseases.

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EP182

Anthropometric parameters vary slightly but sexual maturation rating and bone age delay and reproductive hormones reduce significantly in patients with delayed puberty

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Puberty, a crucial biological process, ends up in sexual maturation, reproductive capability and adult body size. It is controlled by hypothalamo–pituitary–gonadal axis (HPG), where hypothalamus synthesizes and secretes gonadotropin releasing hormone, which stimulates the adenohypophysis to produce follicle stimulating hormone (FSH) and luteinizing hormone (LH). FSH causes formation of sperms and LH stimulates production of testosterone (T). Puberty needs an intact HPG axis and any interruption in this axis may result in short-term or long lasting dysfunction of reproductive axis. Delayed puberty in boys is typically described by the deficiency of masculinization and reduced volume of testes (< 4 ml) in combination with absent or low sperm count until 14 years of age. The current investigation determined anthropometric parameters (height, weight, BMI), bone age, sexual maturation rating (SMR) and plasma levels of FSH, LH and T through respective ELISA systems in 37 sporadic cases of male delayed puberty and 55 age matched controls of 14 to 23 years of age visiting Pakistan Institute of Medical Sciences, Islamabad, Shifa International Hospital, Islamabad and Military Hospital, Rawalpindi. SMR was assessed by measuring penile length, testicular volume, pubic hair and facial hair stage. Interpretation of results was carried out by employing Student's *t*-test and ANOVA. The results revealed that the height of delayed puberty patients was lower than controls between 14 and 23 years of age, whereas weight of delayed puberty patients was slightly higher as compared to controls. Most of delayed puberty patients were in over-weight category of BMI. Bone age of most of delayed puberty patients was also delayed than chronological age. SMR of delayed puberty patients indicated that all patients had significantly lower penile length, testicular volume, pubic hair stage and facial hair stage than controls. The hormonal analysis displayed significantly decreased plasma FSH, LH and T levels in patients with pubertal delay as compared to controls. In conclusion, our investigation demonstrates a slight difference in anthropometric parameters of controls and delayed puberty patients during later stages of puberty while sexual maturation rating and hormonal parameters were significantly decreased in delayed puberty patients as compared to controls throughout the pubertal period.

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EP183

Interventions affecting blood pressure and anxiety in women with mild preeclampsia: a narrative review

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Introduction
Preeclampsia (PE) accounts for approximately 2–5% of pregnancies, leading to several maternal-fetal complications. The present study aimed to review types of interventions affecting blood pressure and anxiety in women suffering from mild PE.
Materials and methods
This study was a narrative review based on keywords determined by the MeSH terms. For this purpose, the databases of PubMed, Scopus, Google Scholar, Scientific Information Database (SID), and Magiran were searched using the keywords of 'preeclampsia, intervention, blood pressure, anxiety, EPH-gestosis, pregnancy toxemia, and toxemia of pregnancy' in Persian and English for relevant articles published from 1980 to 2020. The inclusion criteria were all randomized clinical trials (RCTs) associated with interventions affecting blood pressure and anxiety in cases with mild PE.
Results
a total number of 16 RCTs were reviewed in this study. After reviewing, 12 articles were recruited for developing this study and the non-relevant cases were excluded. Accordingly, interventions affecting blood pressure and anxiety in women with mild PE were classified into four groups: Group 1: psychological–educational interventions, Group 2: complementary medicine interventions, Group 3: pharmacological interventions, and Group 4: others.
Conclusion
Health care providers are suggested to reflect on these interventions and make use of this classification of interventions in accordance with patients' conditions when hospitalizing women with mild PE.
Keywords
Mild Preeclampsia, Intervention, Anxiety, Blood Pressure, Review
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EP184

The SARS-CoV-2 infection and PCOS: what we know nowadays?

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Introduction
The novel COVID-19 has been rapidly expanding and causing many deaths all over the world, since December 2019. The health condition and the coexistence of other diseases may affect the severity of SARS-CoV-2 infection.
The state of the art
PCOS is a common endocrine and metabolic disorder, afflicting females of reproductive age, with an incidence up to 10%. It is a heterogeneous clinical syndrome, characterized by hyperandrogenism, menstrual irregularity and hyperinsulinaemia, in which both genetic and environmental factors are thought to play a role. Women with PCOS are considered to belong to an age and sex group which is at lower risk for severe COVID-19. However, the possible pathophysiological mechanisms regarding PCOS and more severe COVID-19 have been hypothesized. Insulin resistance and hyperinsulinaemia result in enhanced hyperandrogenism. Androgens may drive clinical results in COVID-19. First, sexual hormones affect the immune system and testosterone suppresses it. Second, SARS-CoV-2 gains entry to target cells via the angiotensin-converting enzyme 2 (ACE-2) receptor and male hormones are effective in the ACE-2 passageway and simplify SARS-CoV-2 entry into cells. Finally, the lung expression of TMPRSS2 (transmembrane protease, serine 2), a cellular co-receptor necessary for SARS-CoV-2 infection, is associated with an androgen-regulated gene. What is more, Renin-Angiotensin-System (RAS) overactivity has been described in type 2 diabetes and obesity, the conditions markedly frequent in PCOS, which are known to be the factors increasing the risk of severe COVID-19. Moreover, the overactivity of the RAS system has been also proven in PCOS. Thus PCOS may predispose these women to more severe SARS-CoV-2 infection. Vitamin D deficiency, identified as a global public health matter, may be another important factor, potentially involved in the increased risk of developing severe forms of COVID-19 in PCOS women. It has been reported that poor vitamin D status can affect a variety of diseases, including SARS-CoV-2 infection, because of its crucial role in the functioning of the immune system. Vitamin D is also a negative endocrine RAS modulator and inhibits renin expression and generation. Hypercytokinemia, presented in obesity as well as in PCOS, may be another risk factor for severe SARS-CoV-2 infection in PCOS women.
Conclusions
The complexity of PCOS, including the coexistence of many metabolic disorders as well as hormonal and cytokine disturbances, may increase the susceptibility of severe COVID-19 in PCOS women. Further studies are needed to clarify the link between severe COVID-19 and PCOS, to provide the optimal management.

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EP185

Growth retardation: epidemiological, clinical and etiological aspects

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Introduction
Growth retardation (GR) is a frequent complaint in pediatrics. A clear and rapid diagnostic process is essential in order to improve the prognosis for height. The aim of our study was to review the epidemiological, clinical and etiological aspects of GR and to assess the height gain particularly after treatment for Growth hormone (GH) deficiency.
Methodology
This is a retrospective study of 27 consulting patients for GR at the endocrinology department of the Military Hospital of Tunis between January 2000 and December 2019.
Results
Our population was predominately male (sex ratio = 2). The mean chronological age (CA) at the time of diagnosis was 13.8 ± 3.8 years. The mean linear growth retardation was −3.02 ± 0.73 standard derivation (S.D.). Fifteen patients (62%) had severe GR (≤−3S.D.). The mean bone age (BA) was 10.23 ± 2.49 years, with a mean delay (CA-BA) of 3.5 ± 2.06 years. Dysmorphia was found in 11% of cases. Delayed puberty was associated in 62% of cases. GH deficiency was found in 56% of cases; 71% had total GH deficiency and 29% had partial GH deficiency. They were treated with somatotropin. The height gain after treatment for GH deficiency was 20.62 ± 14.32 cm. The other causes were celiac disease (8%), constitutional GR (8%), genetic and malformative diseases (14%), 1 case of type 1 diabetes, 1 case of peripheral hypothyroidism and 1 case of GR secondary to a small size from birth.
Conclusion
Monitoring growth should be systematic and regular in all children. By an early diagnosis of GR, serious diseases can be detected and an appropriate treatment can be started at an early stage.

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EP186

Testicular regression syndrome, a case study

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Introduction
XY testicular agenesis is a very rare disease. The phenotype of persons suffering is variable depending when the gonadic regression in utero occurs.
Observation
We have reported a 26 years old patient case, without particular history, monitored for puberty delay from the age of 17 years. The clinical examination reveals a very tall patient: 1m92, with macroskelia, a penis of normal size, a classified P2 pubic pilosity, absence of axillary pilosity as well as at the level of face, no gynecomastia nor spontaneous or induced galactorrhea. Absence of palpable gonads in intrabotal or inguinal position. Morphological exploration did not visualize testes in normal or ectopic position with a hypoplastic prostate. The hormonal assessment found a hypogonadism, hypergonadotropic, negative HCG test. The karyotype is normal: 46 XY eliminating a Klinefelter syndrome. The exploratory laparotomy did not find a gonad in the abdominopelvic position.
Discussion
The TRS is a rare etiology, of unknown cause, it is an elimination diagnosis, at the end of a negative etiological investigation without objectifying morphological or hormonal stigma of gonad within our patient, we completed a TRS in the absence of Mullerian structure and the normality of the external genitalia. The patient received hormone replacement therapy with a good clinical course without improving the fertility prognosis.
TRS: testicular regression syndrome.

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EP187

Gynecomastia – what is behind the curtain?

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Introduction
Although addressability for breast pathology is much lower in men than in women, the underlying causes of the initial complaints are often much more spectacular. Gynecomastia is one of the principal reasons for addressing the endocrinologist and next to the important psychosocial impact, sometimes it seems to be only the tip of the iceberg, revealing important underlying medical conditions.
Case reports
We present the cases of two male patients who addressed our clinic for gynecomastia. The first case is of a male patient, aged 40, who addressed our service for a painful right breast nodule, appeared 2 weeks prior to the presentation. The patient reported having two other similar episodes in Maroc, 7 years ago and 1 year ago, considered to be infectious mastitis and treated by antibiotics. Only regular blood tests were performed during the previous episodes, with no hormonal profile and no imaging or histopathological studies. The physical evaluation at the current presentation revealed a painful nodule in the upper external quadrant of the right breast. Laboratory evaluation revealed important hyperprolactinemia and hypogonadotropic hypogonadism, with normal liver, renal and thyroid tests. The ultrasound revealed bilateral gynecomastia, with no tumoral process. The testicular ultrasound was normal. The pituitary MRI revealed a microadenoma measuring 6.3/5/6 mm. The patient was initiated on dopamine-agonist therapy and the prolactin level returned to normal within 2 months. The second case is of a male patient, aged 65, who was hospitalized for atypical chest pain. The physical examination revealed bilateral gynecomastia, reported by the patient as being present from his early 20s. After complete cardiac evaluation, he was addressed to us. The laboratory evaluation revealed hypergonadotropic hypogonadism. The ultrasound revealed bilateral gynecomastia with an ACR4 area of 11.5/9.5/10 mm in the left breast, with no pathological

adenopathy. The percutaneous biopsy performed showed discrete fibrocystic dysplasia. The testicular ultrasound found small, hypervascularised testes with microcalcifications. The karyotype performed showed a Klinefelter syndrome mosaicism 46, XX/47, XXY. The osteodensitometry revealed femoral osteopenia. The patient was initiated on testosterone substitutive therapy and vitamin D and calcium supplementation.
Conclusion
Although in more than 50% of cases gynecomastia is idiopathic, complete clinical, biochemical and imaging assessment is required in order to exclude rare or life-threatening conditions. Initiation of adequate treatment, when needed, will have a high impact on patient satisfaction and on the outcome, preventing possible serious complication, as those associated with hypogonadism, neoplasia, liver or renal diseases.

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Thyroid

EP188

ANCA vasculitis: a rare and serious complication of Benzylthiouracil

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Introduction
Vasculitis with antineutrophilic cytoplasmic antibodies (ANCA) has been reported in patients treated with anti-thyroid drugs, especially Propylthiouracil and exceptionally with benzylthiouracil (BTU). We present here a case of ANCA-anti-MPO-associated vasculitis related to BTU.
Case presentation
A 46 old women was treated with BTU during 18 months for Basedow's disease. She showed abruptly an alteration of the general state with fever, hepatosplenomegaly, cytopenia with microcytic anemia at 6.8 g/dl and leucolymphopenia at 2500, proteinuria between 0.4 and 0.8 g/24 h with normal kidney function and biological inflammatory syndrome. A chest-abdominal-pelvic CT showed hepatosplenomegaly with splenic infarction. The p- ANCA assay was positive with anti-myeloperoxidase specificity. The benzylthiouracil was discontinued. The patient was treated with bolus of solumedrol relayed by corticosteroids at a dose of 1 mg/kg per day with disappearance of bicytopenia and regression of hepatosplenomegaly. She reconsults few weeks later for respiratory failure, with crackling rattles in pulmonary auscultation, anemia at 5.4 g/dl and images of alveolar condensation to chest radiography. The diagnosis of intra-alveolar hemorrhage was retained. She was treated with solumedrol bolus. One month later, she developed a high-abundance hemoptysis with hemodynamic failure and death.
Conclusion
Because of the gravity of this complication, clinical monitoring is recommended in patients taking benzylthiouracil. If vasculitis develops, the anti-thyroid drug should be discontinued and corticosteroid treatment, with immunosuppressors in some cases, is initiated. Prognosis is less severe than primary ANCA vasculitis, and death due to anti-thyroid therapy-induced AAV as our case is exceptional, related generally to severe alveolar hemorrhage.

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EP189

Papillary carcinoma arising in retrosternal ectopic thyroid tissue. A case report

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Introduction
Ectopic thyroid tissue is a rare clinical entity, with a prevalence of 1: 300 000 in the general population. The ectopic tissue may be located anywhere from the base of the tongue to the diaphragm, the most frequent sites being lingual, thyroglossal, laryngotracheal, and lateral cervical regions. It may also occur in less frequent sites such as the esophagus, mediastinum, heart, adrenal glands, and pancreas. The mediastinum is the most frequent location after the neck. Malignant transformation of ectopic thyroid is uncommon; but even rarer is the development of papillary carcinoma in it. We report the case of papillary carcinoma arising in retrosternal ectopic thyroid tissue in association with an oncocytic variant of papillary carcinoma arising from the thyroid gland.
Case
A 50 years old female patient was presented to the medical consultation with 6 months history of neck swelling. Her medical and family histories were non-specific. The physical examination found a slight anterior cervical painless swelling. The neck ultrasonography was performed revealed 2 nodules of 4×9 mm and 4×3 mm classified Tirads 5. Besides, a nodule of 4 cm in size was identified in the superior mediastinum on the right. The USG-guided fine needle aspiration cytology performed on the retrosternal mass was reported to be in favor of ectopic thyroid tissue with malignant nature. Thyroid functional tests, calcitonin, and thyroid antibodies were within normal limits. A total thyroidectomy was scheduled for the patient. During the surgical exploration, the retrosternal ectopic thyroid mass of 4 cm was identified and removed. The histopathological examination was in favor of a retrosternal ectopic papillary thyroid carcinoma and a multifocal oncocytic variant of papillary carcinoma arising from the thyroid gland. The patient then underwent radioiodine ablation therapy (100 mCi) and was put on Levothyroxine suppression therapy.
Discussion and conclusion
Ectopic thyroid tissue results from abnormal embryologic development and migration of the thyroid gland. True malignant transformation in ectopic thyroid tissue is extremely rare and is always diagnosed after surgical excision of the lesion by pathology examinations. There are well-documented cases of ectopic thyroid cancer while primary tumoral lesion occurs in the orthotopic thyroid as described in our case. However, it is not always possible to detect the presence of these anomalies, during the preoperative examinations of the patients who will undergo thyroid surgeries; therefore, one must be careful about these types of anomalies in the perioperative examinations.

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EP190

A case of primary hyperparathyroidism associated with papillary thyroid carcinoma

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Introduction
The association between parathyroid and thyroid diseases is not uncommon; however concurrent presence of parathyroid adenoma and thyroid cancer is rare (1). As a natural consequence, preoperative imaging studies for diagnosis and localization of parathyroid adenomas may result with the detection of thyroid incidentalomas and most of these thyroid nodules should be evaluated by fine-needle aspiration biopsy before parathyroid surgery (1). We have recently encountered a case of papillary thyroid carcinoma (PTC) associated with primary hyperparathyroidism (PHPT).
Methods
We describe the clinical findings, thyroid and parathyroid function tests, and imaging data of a patient presenting with hypercalcemia and thyroid nodule.
Results
A 56-year-old female with chronic epigastric pain, was referred to our department after discovery of hypercalcemia. In the routine laboratory tests, we noticed to a serum calcium of 11.1 mg/dl [8.2–10.2]. Further evaluation, confirmed a low serum phosphorus and a high serum parathyroid hormone (126 pg/ml), low vitamin D while renal functions tests, and thyroid test levels was within normal range. Patients had not history of treatment with calcium or vitamin D supplements. Cervical ultrasound showed 4 parathyroid glands increased in size and a 3.5 cm thyroid nodule in the lower right pole classified EU-TIRADS 5. 99 Tc-sestamibi scanning revealed features of parathyroid adenoma adjoining the lower pole of right thyroid lobe. A conducted aspiration biopsy of thyroid nodule was indicative of PTC. The patient was referred to the otorhinolaryngology department for surgery.
Conclusion
Concomitant PTC and PHPT are rare. The underlying mechanisms are not yet established and may be coincidental. Goitrogenic and carcinogenic factors have been implicated in the pathogenesis with no conclusive evidence. Shared embryological origin, genes and transcription factors, high parathyroid hormone (PTH), low vitamin D and hypercalcemia could result in high levels of angiogenic growth factors (2).

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EP191

Place of surgery in Basedow's disease 'About 100 cases'

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Introduction
Graves' disease is an autoimmune thyroid disease manifested by hyperthyroidism, homogeneous goiter and sometimes ophthalmopathy. The frequency of the disease is less than 1% with a female predominance of 5–10/1 male. Its treatment is difficult because of the evolving vagaries of this disease. We report the results of surgery for Graves' disease through a retrospective study.
Material and methods
100 files of patients operated on for Graves' disease (MB) either as first-line after preparation for medical treatment (average duration of less than 6 months) in 9 or after failure of medical treatment in 91%.
Results
Average age: between (20–60 years)
Female predominance
Reason for consultation: goiter + signs of hyperthyroidism): 79%
Basedowian ophthalmopathy 69%.
Palpation of the neck: goiter type 2: 74 (firm, elastic, vascular in 70%)
The thyroid hormone balance: TSHus slowed down in all cases (avg: 0.12 U/ml) associated with an increase in peripheral hormones FT3 and/or FT4.
The autoimmunity assessment
Anti TPO Ab: 13% positive, Anti TSHus receptor TSI 20% positive, TG Ab 3% positive
Surgery results
65% of patients (P) underwent a total thyroidectomy.
35% (P): subtotal thyroidectomy
Histology
82% of patients: Typical basal disease
17% (P) Graves' disease associated with cell variants
• Oncocytic metaplasia
• Functional hyperplasia
1% (P) papillary microcarcinoma + MB.
Conclusion
The management of Graves' disease requires a precise diagnosis as well as an appropriate treatment. Follow-up depends on the speed of the response and the occurrence of recurrence. The medical treatment for Graves' disease takes a long time. It imposes physical and economic constraints with a high rate of relapses. If remission does not occur radical treatment is indicated by radioiodine or surgery.

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EP192

DeQuervain's subacute thyroiditis

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Introduction
DeQuervain's subacute thyroiditis (DST) is a rare pathology, defined by the involvement of the thyroid gland by an inflammatory process probably of viral origin, not suppurative and not autoimmune. In this context, we report 4 cases of TSD followed up in the endocrinology department over a period of 23 years, to highlight diagnostic and therapeutic particularities.
Results
The average age was 38.5 years with extremes ranging from 31 to 46 years. The sex ratio was equal to 0.33. A family history of goiter existed in one patient. The reason for consultation was anterior cervicalgia occurring as a result of influenza-like illness with a biological inflammatory syndrome in all patients. A goiter was found in all 4 patients, compressive and painful in three of them. One patient had hypothyroidism, the other 3 had hyperthyroidism. The anti-thyroperoxydase antibodies were positive in 2 patients. The scintigraphy was white in all 4 patients. Beta-blockers were considered in 2 patients, associated with corticosteroids in the first and non-steroidal anti-inflammatory drugs (NSAIDs) in the second patient. Therapeutic abstention was indicated for the third case. L-thyroxine was prescribed in patient with deep hypothyroidism. The evolution was favorable with return to euthyroidia in 3 patients but the fourth was lost sight of.
Conclusion
DST is an easy-to-diagnose pathology, usually of favourable evolution. The use of NSAIDs or corticosteroids may be necessary. Cases of definitive hypothyroidia are possible.

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EP193

Depression among patients with autoimmune thyroiditis

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Introduction
Today, it is well recognized that disturbances in thyroid function may significantly affect mental status including emotion and cognition. Several studies have demonstrated the existence of a relationship between depression and hypothyroidism, although there is still no clear explanation of the pathophysiology that causes this association.
Objectives
To assess whether there is a higher prevalence of depression among patients with hypothyroidism and whether it is correlated with laboratory parameters such as TSH, free T4 or the levels of anti-peroxidase (TPO) and anti-thyroglobulin antibodies.
Methods
We collected the medical and psychiatric history and laboratory tests of 200 patients with autoimmune hypothyroidism treated in our hospital (Hospital Clínico Lozano Blesa, in Zaragoza; Spain). Student's T test was used for statistical analysis.
Results
A high prevalence of depression was observed among patients with autoimmune hypothyroidism (46.5%), in addition, higher mean values of anti-TPO antibodies have been obtained in patients with depression (552.87 IU/ml versus 337.12 IU/ml, $P = 0.015$), as well as anti-thyroglobulin antibodies (371.52 IU/ml vs. 135.27 IU/ml, $P = 0.034$) and TSH (20.55 mU/l vs. 9.31 mU/l $P = 0.012$). There were no differences between the FT4 values of both groups.
Discussion and conclusion
There is a significant prevalence of depressive symptoms among hypothyroid patients, being present in almost half of the individuals studied, as well as higher levels of TSH and anti-TPO and antithyroglobulin antibodies in subjects diagnosed with depression, all of that according to the published data in previous studies. Therefore, it could be interesting to quantify thyroid hormones in those patients who present with symptoms of depression, especially those who are more refractory to antidepressant treatment. However, the mechanisms underlying the interaction between thyroid function and depression remain to be clarified and a causal relationship between the two cannot be established yet, so more studies are needed to clarify the specific reason for this association. Moreover, further studies are required to determine if thyroid-related genes can influence well-being in subjects that are not on thyroid hormone replacement and if thyroid hormones may be beneficial in these subjects if they are not responding to standard antidepressant therapies.

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EP194

Problems in the diagnosis of thyroid orbitopathy

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Thyroid orbitopathy (TO) is an autoimmune inflammatory disease of retroocular tissues. Mostly, TO is associated with Graves' hyperthyroidism. The development of TO is accompanied by pathological changes in the soft tissues of the orbit with damage to the optic nerve and cornea, the accessory apparatus of the eye. Despite the presence of specific symptoms, the diagnosis of TO causes problems for doctors. A 61-year-old man complained of discomfort in the eyes, double vision, lacrimation, dryness and redness of the eyes, swelling under the eyes, palpitations, which first appeared in June 2020. At first, the patient did not go to the doctor, but decided to do an MRI of the orbit, which revealed a thickening of the lower and internal oblique muscles of the eye, more pronounced on the left, bilateral exophthalmos, edema of the lower eyelid on the left, expansion of the sheathing spaces of the optic nerves. The patient consulted an ophthalmologist after a sharp decrease in visual acuity in the right eye (diagnosis: embolism of the central retinal artery of the right eye, treatment without a pronounced positive effect, subclinical thyrotoxicosis was additionally revealed). The patient was referred to an endocrinologist, who diagnosed obesity, prescribed a diet and examination (results: TSH-0.02 mIU/ml, T4-15.76 pmol/l, T3-8.59 pmol/l). In September 2020, an ophthalmologist diagnosed the patient with reactive edema of unknown etiology in both eyes. In parallel, the patient is monitored by an endocrinologist and undergoes another additional examination: ultrasound of the thyroid gland (an increase in the volume of the thyroid gland with diffuse changes, an increase in the cervical lymph nodes), an increased titer of antibodies to TSH receptors (16.05 IU/l) was detected. However, the diagnosis was not changed, no treatment was prescribed. On physical examination: HR-98 beats per minute, the presence of spontaneous retrobulbar pain, redness and edema of the eyelids, conjunctival injection, redness and edema of the lunate fold, lacrimal meatus, chemosis. The patient was diagnosed with Grave`s disease, which was complicated by TO in both eyes, active stage, CAS 6 points. Thyroidectomy was recommended for the patient, Tyrosol 30 mg per day was prescribed, pulse therapy with Prednisolone was performed. Thus, we can say that thyroid orbitopathy is a multidisciplinary problem that requires closer interaction of ophthalmologists and endocrinologists, which will lead to early diagnosis and timely prescribed treatment, which, in turn, will improve the prognosis and quality of life of patients.

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EP195

Prevalence of double vision (diplopia) and strabismus in patient with Graves' orbitopathy

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Introduction
Graves' disease (GD) is an autoimmune thyroiditis frequently associated with development of Graves' orbitopathy (GO). Diplopia (double vision) is a major determinant of work disability in patients with GO. The aim of our study was to assess the prevalence of diplopia and strabismus in patients with GO.
Methods
This is a single-center observational study in an outpatient clinic of autoimmune endocrinopathies at a Tertiary, General, University Hospital. Patients with GO and increased levels of thyroid-stimulating immunoglobulin (*TSI > 1.75 IU/l)* were included in the study. Clinical activity score (CAS), diplopia and strabismus were evaluated by a single ophthalmologist according to the European Consensus Report. Laboratory tests for TSH, T3, FT4, TSI, TgAbs, TPOAbs, complete blood count, liver enzymes and thyroid sonography were performed in all patients.
Results
A total of 36 patients (72.2% females) with a mean age of 54 ± 11.8 years were analyzed. The median TSI levels were 9.1 IU/l (IQR 22.3), and the mean CAS score was 3.24 ± 1.4. 19.4% (7/36) of the patients had undergone total thyroidectomy, 11.1% (4/36) had thyroid cancer, 47.2% (17/36) had other autoimmunities, and 65.6% (21/32) had smoking history. Diplopia was present in 38.9% (14/36) and strabismus in 5.6% (2/36) of the patients. Diplopia was not significantly associated with gender, TSI levels, thyroidectomy, thyroid cancer, and the presence of other autoimmunities (P = NS), but patients with diplopia were older than those without (60.8 ± 11.3 vs 49.7 ± 10.1, P = 0.004).
Conclusion
The prevalence of diplopia was 38.9% in the studied group of patients with GO, whereas strabismus was much less frequent (5.6%). Diplopia was associated with older age in patients with GO.

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EP196

'Colloid leak'-An Phenomenon in thyroid surgery

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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 ± 12.1 years) had this colloid leak. Mean BMI was (22.4 ± 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 ± 12 min. Mean blood less was 10 ml ± 2.5 ml. Mean duration of stay after surgery was 48. ± 12 h. 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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EP197

Transient thyrotoxicosis after laryngeal carcinoma surgery

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Introduction
Thyrotoxicosis debuted early after thyroid lobectomy is described in approximately 54% of cases. It has also been described in a few case reports after non thyroid neck surgeries or in invasive laryngeal cancer after total laryngectomy and debulking hemithyroidectomy.

Case presentation
Patient aged 53 years old, known with laryngeal carcinoma of 37/28/40 mm located at piriform sinus, linked by the left vocal chords, with posterior invasion of cricoid cartilage, and with lysis of the left lamina of the thyroid cartilage. He is referred for surgical cure. One months before surgery the patient had normal TSH and FT4. The day after laryngectomy and debulking left thyroid lobectomy, the patient developed tachycardia (113 bpm), without other symptoms for hyperthyroidism, associated with normal TSH: 0.95 uUI/ml and increased FT4. Day 3 after surgery, TSH was undetectable with a highly increased FT4: 87 pmol/l (4 times x ULN). He received Metoprolol 100 mg/zi and no antithyroid medication. Six days post-surgery, the FT4 levels decreased to almost half 48 pmol/l (2× ULN). At day 12 after surgery, under 100 mg Metoprolol/day, the patient still had tachycardia, with no other signs of hyperthyroidism, the right thyroid lobe was not palpable, while biologically he had only a subclinical thyrotoxicosis TSH: 0.016 uUI/ml, FT4: 18.5 pmol/l (*n*: 9–19), TPOAb: 14.4 UI/ml (*n* < 5.6).
Discussion
Thyrotoxicosis debuted early after thyroid lobectomy alone or in the context of other neck surgery (eg for invasive laryngeal cancer) needs correct diagnosis and differentiation from Graves' disease. It is transient, probably due to cell destruction produced by intrasurgical manipulation of the thyroid gland, therefore requires only symptomatic, but not antithyroid drug treatment. A clue for the diagnosis is the rapid decrease of FT4 and the lack of TRAb antibodies.
Conclusion
Clinicians should be aware of the potential for a transient episode of thyrotoxicosis early after thyroid lobectomy + /– associated with other non-thyroid neck surgeries.

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EP198

Frequency and diagnostic value of Thyroid Autoantibodies

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Introduction
Thyroid autoantibodies can detected in many disorders not only at the Hosimoto autoimmune thyroiditis. Their level and frequency may vary depending on many factors both thyroidal and nonthyroidal. Anti thyroid peroxidase autoantibodies (ATPO) is one of the well known among them. We analysed frequencies of higher level of ATPO among people with different types of thyroid diseases.
Material and methods
In 94 people blood serum ATPO, TSH, T3, T4 levels were measured in the laboratory unit of the Republican Specialized Scientific Practical Medical Centre of Endocrinology and Vitamed clinic in Tashkent. Data were collected, analysed and compared by age, gender, thyroid state and diseases.
Results
High level of antiperoxidase autoantibodies were detected in 46% of observed persons, where the mean age were 42.5 ± 3.8 years old. As noted in many studies woman composed the most part of observed persons with higher ATPO level and male patients consist about 17% among them. Thyroid state were assessed by TSH, T3, T4 level. Euthyroid goiter detected in 46% of people with high ATPO, 18% of them thyrotoxicosis, 18% with hypothyroidism, and 13% cases were thyroid cancer and 22% in healthy pregnant woman.
Conclusion
ATPO is a frequent laboratory findings reflected thyroid function. Higher level of antiperoxidase autoantibodies mostly detected in middle aged people predominantly in woman, 46% cases of high ATPO were combined with euthyreosis state, 18% with hyperthyroidism, 18% of hypothyroidism, 13% cases were with cancer.

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EP199

Unmasked Graves' disease following tamoxifen withdrawal

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Introduction
The synthetic anti-oestrogen tamoxifen is the endocrine treatment modality most commonly used for therapy of hormone sensitive breastcancer. The influence of tamoxifen on thyroid function has not been fully elucidated.
Observation
A 46-year-old female patient who presented a Graves' disease diagnosed 10 years ago. She had a moderate vascular goiter and no ocular signs. She presented firstly a severe hyperthyroidism: an elevated FT4 = 82.5 pmol/l (NR = 11–21) and a suppressed TSH = 0.001 UI/l (NR = 04–4). Thyrotropin receptor antibodies (anti-rTSH) were strongly positive at 23.6 IU/l (NR < 2). The patient was treated with Benzylthiouracil for 3 years followed by voluntary interruption of treatment. The patient was later lost to follow-up. Four years later, she had a suspicious nodule in her left breast. The diagnosis of Invasive ductal carcinoma was confirmed. Tumor extension was negative. The procedure was a tumorectomy and lymph node dissection followed by adjuvant radiochemotherapy. The patient then received an antiestrogen for 5 years. The senological evolution was favourable. During these years, she was in clinical euthyroidism despite stopping all antithyroid treatment. When she stopped taking tamoxifen, she again presented a biologically confirmed severe hyperthyroidism (FT4 = 83 pmol/l, TSH = 0.001). Anti-rTSH antibodies were overtly positive (> 40). A radical treatment was indicated for our patient.
Conclusion
In conclusion, our case suggests that tamoxifen may influence thyroid hormone levels by mechanisms related to its known effect on thyroxine-binding globulin.

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EP200

Graves'disease and breast cancer: Is there a link

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Intoduction
The link between hyperthyroidism and breast cancer has been the subject of much controversy and literature in the past. It poses a daily clinical problem of information and senological follow-up of thyroid patients. We report our patient's case.
Observation
A 46-year-old female patient who presented a Graves' disease diagnosed 10 years ago. She had a moderate vascular goiter and no ocular signs. She presented firstly a severe hyperthyroidism: an elevated FT4 = 82.5 pmol/l (NR = 11–21) and a suppressed TSH = 0.001 UI/l (NR = 04–4). Thyrotropin receptor antibodies (anti-rTSH) were strongly positive at 23.6 IU/l (NR < 2). The patient was treated with Benzylthiouracil for 3 years followed by voluntary interruption of treatment. The patient was later lost to follow-up. Four years later, she had a suspicious nodule in her left breast. The diagnosis of Invasive ductal carcinoma was confirmed. Tumor extension was negative. The procedure was a tumorectomy and lymph node dissection followed by adjuvant radiochemotherapy. The patient then received an antiestrogen for 5 years. The senological evolution was favourable.
Conclusion
Women with hyperthyroidism may be at increased risk of breast cancer. This suggests that in the case of hyperthyroidism, special attention may also need to be paid to breast cancer screening.

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EP201

Encapsulated follicular tumours of uncertain biological behaviour – clinicopathological and molecular analysis

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Background
The latest WHO classification of tumours of endocrine organs defines new units of borderline thyroid tumours (BTT) of uncertain biological behaviour. The aim of our study was to evaluate ultrasonographic, cytological features, mutation profile and surgery treatment in patients with these rare tumours.
Methods
The analysis of 8 out of 487 operated patients, who underwent thyroid surgery between June 2016 and June 2020. The definitive diagnosis was made postoperatively by extensive histopathological examination. Molecular genetic analysis of genes associated with thyroid oncology (BRAF, HRAS, KRAS, NRAS, TERT, TP53, fused genes) was performed from one FNAB and 7 formalin-fixed paraffin-embedded (FFPE) samples.
Results
BTT were found in a total of 8 patients (1, 6%), with a predominance of men (6 men/2 women) in contrary to other operated patients. Preoperative cytological samples were classified in the Bethesda system as non-diagnostic (Bethesda I), benign (Bethesda II) and atypia/follicular lesions of undetermined significance (Bethesda III) in one, four and three cases, respectively. Hemithyroidectomy was performed in four cases and total thyroidectomy in four patients. The definitive histological diagnosis revealed non-invasive encapsulated follicular neoplasm with papillary-like nuclear features (NIFTP) in three patients, follicular tumour of uncertain malignant potential (FT-UMP) in three patients, well differentiated tumour of uncertain malignant potential (WDT-UMP) in one patient and hyalinizing trabecular tumour (HTT) in one case. The patients with NIFTP had mutations in HRAS - in one patient also in combination with pathogenic variant in TP53 gene and mutation in NRAS gene in two patient was detected and in HTT patient PAX8/GLIS3 fusion gene was detected from the surgically removed tissue. In remaining four cases, no somatic pathogenic mutations or fusion genes were found.
Conclusion
The surgical treatment of borderline thyroid tumours (BTT) is necessarily individual. It is influenced by preoperative clinical, ultrasonographic, cytological and molecular genetic findings, as well as the presence of other comorbidities.
Key words
borderline thyroid tumour, thyroid FNAB, molecular testing of thyroid tumours, thyroid surgery.

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EP202

Selpercatinib as an alternative therapy to Lenvatinib for metastatic medullary thyroid cancer. A case report.

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Selpercatinib is a receptor tyrosine kinase RET inhibitor for the treatment of cancers such as RET-mutant medullary thyroid cancer, demonstrating partial response and low incidence of serious adverse events. Vandetanib, a tyrosine kinase inhibitor, has shown promising results with an increase in progression-free survival and prolonged lifetime, but it causes adverse events such as hypertension, diarrhea, rash, or long QT interval. Most of them are can be even disabling for the patient, leading to discontinuation of the medication, but do not necessarily suppose a severe health risk. In this report, we describe a case of an advanced medullary thyroid carcinoma who could not stand Vandetanib therapy and who needed a change of its therapy. A 47 years-old woman asked the Digestive System Unit complaining of chronic diarrhea that worsened the last week. They performed a complete study including a blood test, abdominal ultrasound, gastroscopy, and colonoscopy. The last of them revealed an 8–10 cm polypus near to the ileocecal valve with a malignancy appearance that could not be resected by endoscopy. After that a whole-body CT scan was performed as a tumor extension study, identifying a right thyroid lobe enlargement (73 × 50 × 45 mm) with endothoracic extension that caused tracheal displacement to the left. It also evidenced several cervical, mediastinal and hilar lymphadenopathies, suggestive of metastatic spread. Eco-guided fine-needle aspiration of the right thyroid lobe suggested a medullary thyroid carcinoma (Category V of Bethesda). Endocrinology Unit performed a blood test and a 24-hour urinary fractionated metanephrines determination to rule out primary hyperparathyroidism and pheochromocytoma respectively, that were negative. One month later, a subtotal thyroidectomy and a wide lymphadenectomy was performed. Because of the incomplete resection and the tracheal compression, the colonic polypus resection needed to be delayed. A (18)F-FDG PET/TC revealed two bone metastatic lesions (T4bN1bM1). The patient started Vandetanib 300 mg diary, but six months later she suffered severe hypomagnesemia (0.5 mg/dl) that needed intravenous replacement. Also, she developed a rash and long QT interval. The hypomagnesemia persisted despite a Vandetanib dose reduction and oral magnesium replacement, because of that we decided to change ITK therapy to Selpercatinib (after positive determination of RET mutation). Three months later, she has no adverse events with the new RET inhibitor therapy. Could Selpercatinib be a better therapeutic option than Vandetanib for our patients in the next future? further studies will be necessary to answer this question.

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EP203

A rare brain metastases of papillary thyroid cancer

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Introduction
Papillary thyroid cancer (PTC) has generally good prognosis irrespective of lymph node metastases. The rate of survival in patients with distant metastases is variable, depending upon the site of metastases and radioiodine accumulation status. The median survival of patients with brain metastases is approximately one year.
Case
We present a 66 years old woman with a tumour triplicity (PTC, breast cancer and ovarian cancer). She underwent total thyroidectomy (T1bmN1bM0, stage IV A) in 2013. Radioiodine was administered twice with a cumulative dose of 7.4 GBq (300 mCi) 131-I. The other tumours were in remission. Since May 2018 there was a slight increase of thyroglobulin (0.52 µg/l). In December 2018 the thyroglobulin level was 2.24 µg/l and the ultrasound of the neck was negative. She was treated with radioiodine (100 mCi) with a negative post-radioiodine whole-body scan. During next follow-up there was further increase of thyroglobulin level (6.53 µg/l). CT scan of the whole body provided a negative result. After two months she was examined for malaise, vertigo and left hemiparesis. Brain MRI showed a solitary tumour of the frontal lobe 25 × 26 × 26 mm. The thyroglobulin level was 12.56 µg/l at that time. Extirpation of the tumour confirmed metastases of PTC. Follow-up MRI of the brain was without any residual tumour. She was treated with radioiodine (150 mCi) after administration of recombinant human TSH. The patient, two years after operation, has a stable level of thyroglobulin (0.94 µg/l), with negative brain MRI and whole-body FDG-PET scan.
Conclusion
Brain metastases of papillary thyroid cancer are very rare. Surprisingly our patient had only mild increases of thyroglobulin level, that did not allow us, in the beginning, to suspect possible brain metastases. We diagnosed the metastases only after the patient started to have neurological symptoms. There are no guidelines for the treatment of brain metastases from the thyroid cancer. Surgical resection is probably associated with prolonged survival but till now there is no evidence of survival benefit from radioiodine therapy.

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EP204

Management of papillary thyroid microcarcinomas

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Objective
The study's purpose is to describe the therapeutic management 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 2020.
Results
Our study included 8 men and 47 women. The mean age was 48.64 years with extreme ages from 24 to 73 years old. Three patients had hypothyroidism,

one patient had hyperthyroidism and two had a history of loboisthmectomy for benign nodules. No personal history of cervical irradiation or thyroid cancer in the family 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 paralysis in 3 cases. The mean size of microcarcinomas was 5 mm [1 mm–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. Its therapeutic management, which must be multidisciplinary, is still a controversial subject. It remains an entity with a good.

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EP205

Using TI-RADS classification increased accuracy of Thyroid cancer diagnosis

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Introduction
Problems with thyroid cancer and its diagnosis are one of the current issues in modern endocrinology. Ultrasound examination detects thyroid nodules in 19-67%of the population, whereas the new classification of thyroid ultrasound examination proposed by the American Association of Thyroidologists – the use of TI-RADS in the diagnosis of thyroid cancer increases the diagnostic accuracy of this test by 91–95%. The aim of our study was to assess the importance of laboratory-instrumental, cytological examination methods and TI-RADS classification in the early diagnosis of patients with thyroid cancer.
Material and methods
In 34 patients with operative treatment at Republican Specialized Scientific Practical Medical Centre Endocrinology and Vitamed Clinic with a diagnosis of thyroid cancer and 10 healthy subjects observed. The blood serum level of TSH, T4, calcitonin, Anti-TPO, Anti-TG, CEA titers were determined. Results of laryngoscopy, scintigraphy, as well as fine-needle aspiration biopsy (FNAB), express histology compared. Thyroid ultrasound examination performed according to the traditional and newly proposed TI-RADS classifications.
Results
Thyroid cancer diagnosed in 6.5 times more often in women than in men. The mean age of observed patients were 43 ± 1.2 years. 50%of patients were found to be obese and 13%were found to have a hereditary predisposition to thyroid cancer. The amount of TSH in the blood were in 13.3% ($P < 0.05$) higher than in healthy subjects. The results of blood biochemistry were not significantly differ from healthy subjects. Whereas diagnosis of thyroid cancer by traditional ultrasound examination were 23%of patients, by before surgery FNAB in 64%, while diagnosis accuracy increased by 80%with TI-RADS classification. Thyroid cancer confirmed by histology after surgery in 100%by using of TI-RADS classification, whereas in 80%in those observed by traditional ultrasound.
Conclusion
The incidence of thyroid cancer was higher in women than in men and affected middle-aged (mean 43-year-olds) patients. Thyroid cancer diagnosis confirmed in 23%cases by conventional ultrasound examination, in 64%by FNABs, and 80%by ultrasound using TI-RADS classification. After surgery histology confirmed diagnosis in 80%by traditional ultrasound and in 100%by using TI-RADS classification and prevented unnecessary thyroidectomy.

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EP206

The impact of clinicopathological characteristics of differentiated thyroid cancer on free-disease survival

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Introduction
Differentiated thyroid cancer (DTC) is a rare disease (1%), and usually has good prognosis if well treated. However, the percentage of mortality due to this cancer is about 0.5%. Moreover, 5 to 27%of patients treated for DTC suffer from regional recurrence. Therefore, many research tried to identify predective factors for the survival, relapse and progression of this cancer.
Purpose
The aim of our study was to identify the histopathologic characteristics considered as bad prognosis signs.
Methods
This is a descriptive retrospective study for patients who had DTC and were treated either in the nuclear medicine departement or the ear, nose and throat (ENT) departement in Hbib Bourguiba hospital, Sfax, Tunisia.
Results
A total of 115 consecutive cases of DTC were reported. The median age at diagnosis was 40 years (13-83 years). Sex ratio was 5.38 (97/18). The cases included classical papillary thyroid cancer (PTC) in 88.7% and follicular thyroid cancer (FTC) in 11.3%. Total thyroidectomy was performed on all our patients : central and/or lateral neck dissection in 95.7%of patients, and radioactive iodine ablation in all the cases. Additional therapies were administered to 10 patients. A 10-year period follow-up, showed that 78.4%of patients had excellent response. Disease-free survival (DFS) was described in 81.1% of PTC and 58.3%of FTC, but differences were not statistically significant ($P = 0.075$). Unique tumor had better prognosis than multiple tumors : 84.9% versus 68.6%. A more than 4 cm tumor size had statistically more risk of relapse with $P = 0.006$. Patients with intact tumor capsule had 87.4%of DFS versus 67%in case of tumor capsule invasion ($P = 0.039$). In small tumors limited to the thyroid, the pourcentage of DFS was 83.3%versus 31.1%in tumors with extrathyroidal invasion. Tumor necrosis was significantly associated with bad prognosis with DFS pourcentage of 42% ($P = 0.013$). Finally, we noted that patients with more than 5 nod lymph involvement had a very bad prognosis ($P < 0.0001$). However, the affected lymph node territory had no statistically significant difference ($P = 0.112$).
Conclusion
Differentiated thyroid cancers account for 0.5–1% of all cancers and are usually of good prognosis. It depends on a number of factors. Some of these factors are of controversial therapeutic importance. As a result, several prognostic evaluation systems have been developed (EORTC, AMES). But not all of these factors are unanimously accepted and no international scores have been adopted.

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EP207

Patients with differentiated thyroid cancer treated with low iodine dose: clinical results

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Introduction and objectives
Thyroid cancer treatment tends to be individualized based on risk stratification and increasingly less aggressive for low-risk tumors, as recent studies have shown that low doses of I-131 are just as effective than higher doses with excellent remission rates. The objective of our study was to evaluate the response after 1 year of treatment with 30 mCi of I-131 in patients with differentiated thyroid cancer.
Material and methods
Retrospective observational study. 13 patients were included with a mean age of 49.8 ± 10.4 years (61%women). All of them underwent total thyroidectomy followed by a 30 mCi dose of I-131. To evaluate the response at one year, TSH and thyroglobulin levels, cervical ultrasound and total body scan were performed. At each visit, dynamic risk staging was performed, classifying them into: excellent response, incomplete biochemical and/or structural response, and indeterminate response. Statistical analysis was performed using the SPSS program (SPSS, inc, v 15.0)

Results
The pathological study showed 76.9%papillary thyroid carcinoma, 58.3%high risk variants (38%classic variant, 15.4%follicular pattern, 15.4%minimally invasive encapsulation, 7.7%tall cells, 7.7%columnar cells, 7.7%oncocytic features). 92%of the patients were classified as low risk or stage I, according to the TNM system. The mean MACIS value was 4.79 ± 0.87. Mean TSH at follow-up 0.84 ± 1.59 µIU/ml. 69.2%presented an excellent response, 23.1%an indeterminate response, and 7.7%an incomplete structural response.
Conclusions
In our experience, patients appropriately selected to receive low doses of iodine have a good response and tolerance to treatment. Dynamic risk staging is an effective follow-up tool, allowing individualization of the therapeutic strategy to reduce the risk of recurrence.

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EP208

Lymph node metastasis in thyroid papillary microcarcinoma

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Introduction
Thyroid papillary carcinoma is the most common type of thyroid cancer. Thyroid papillary microcarcinoma is a subtype of papillary carcinoma that includes tumors with 10 mm or less diameter. As a result of diagnostic methods improvement, prevalence of this tumor is increasing. In this study, we reviewed lymph node metastasis characteristics among patients with papillary microcarcinoma.
Methods
A retrospective study about 55 patients operated for a papillary microcarcinoma, at our institution, from 2000 to 2020.
Results
The average age of our patients was 48 years. The sex-ratio (H/F) was 0.17. The circumstances of the discovery were a metastatic cervical adenopathy in 5 cases, incidental on histological examination in 45 cases, on an echoguided fine needle aspiration in 5 cases. We performed a total thyroidectomy without lymph node dissection in 3 cases. A total thyroidectomy with central lymph node dissection was done in 39 cases, lateral and central lymph node dissection were performed in 5 cases. It was a two-stage thyroidectomy in 15 cases. Lobo-isthmectomy was performed in 6 cases, and a lobectomy (totalization) in 2 cases. Lymph node metastasis was diagnosed on the anatomopathological examination in 15 cases: 10 of them presented central lymph nodes metastasis, 5 of them presented central and lateral lymph nodes metastasis. Among those patients, the mean papillary microcarcinoma size was 8 mm. It was multifocal in 1 case, non-encapsulated in 8 cases, infiltrating perithyroid tissue in 10 cases. All patients, having lymph node metastasis, had radioactive iodine. No cases of recurrence or distant metastasis have been reported.
Conclusion
Papillary microcarcinoma has a benign behavior with excellent prognosis in most cases however lymph nodes metastases are frequent and seem to be correlated with tumor size, capsule, and multifocality.

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EP209

Differentiated thyroid carcinoma with metastatic presentation

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Introduction
Follicular thyroid carcinoma (FTC) has metastasis in 10-15%; papillary thyroid carcinoma (PTC) rarely metastasizes. Bone metastasis are rare and can cause pain, fractures and spinal cord compression.
Case-1
72 year-old male referred to the hospital with lower back pain. Imaging examination revealed lytic lumbar lesions. Thoracic-abdominal-pelvic-CT showed trachea compression by a multinodular right thyroid lobe. Thyroid-US revealed a 35 mm nodule in that lobe – FNAC: Bethesda IV. Biopsy of one lytic lesion showed thyroid carcinoma metastasis. Total thyroidectomy was performed – histology: PTC. Therapy with ^{131}I took place; post-treatment ^{131}I-scintigraphy revealed low back hyperfixation. During follow-up, he maintained signs of bone metastases, confirmed by FDG-PET-CT. Heunderwent radiotherapy and further ^{131}I treatment. The disease progressed with bone and pulmonar lesions and eventually he lost his mobility. He declined TKI treatment and died 4 years after diagnosis.
Case-2
59-year-old female referred to the hospital, in 2011, with inferior limb pain. Pelvic-CT revealed lesions around the left iliac bone: biopsy revealed FTC metastasis. A thyroid-US showed a 32 mm left lobe nodule – FNAC: Bethesda V. She underwent total thyroidectomy (histology: FTC) and ^{131}I; post-treatment ^{131}I-scintigraphy showed hyperfixation of ileum, sacrum and scapula. Before any further treatment, she died with generalized bone metastatic disease.
Case-3
76-year-old female (prior history of right hemithyroidectomy in 2014, for benign nodular goiter) sent to neurosurgery in 2018, with occipital headache. Brain-MRI showed lytic lesions of the occipital bone: biopsy revealed FTC metastasis. Thyroid-US showed 2 nodules on the remaining thyroid (18 mm; 7 mm) – FNAC: Bethesda IV. Totalization of thyroidectomy was performed – histology: NIFTP. She underwent ^{131}I therapy. Post-treatment ^{131}I-scintigraphy revealed hyperfixation of the thyroid bed, occipital bone (confirmed by brain-MRI), right ribs and lung. After another ^{131}I therapy, scintigraphy showed persistent disease. Radiotherapy is on demand.
Case-4
In 2015, a 82 year-old female was admitted to the hospital with thoracic pain. Thoracic-CT showed a 38 mm pulmonary nodule and sternum lytic lesion (histology compatible with FTC metastasis). Thyroid–US revealed a 22 mm left lobe nodule – FNAC: Bethesda VI. Total thyroidectomy took place in 2016 – histology: FTC. ^{131}I therapy was proposed. Post-treatment ^{131}I-scintigraphy revealed hyperfixation of the thyroid bed, sternum and lungs, confirmed by thoracic-CT. The patient underwent a second ^{131}I therapy, but the disease progressed. She refused further treatment and died 1 year later.
Conclusion
These cases show rare presentations of differentiated thyroid carcinoma. We must pay attention to osteartícular complains, especially in the presence of thyroid nodules or previous thyroid surgery.

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EP210

Epithelioid hemangioendothelioma with thyroid involvement – case report

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Epithelioid hemangioendotheliomas (EHE) are rare vascular tumors that are typically low to intermediate grade, but they can also have an aggressive behaviour. Mortality rate is dependent on the tumor location. It is frequently a solitary lesion located in the superficial or deep soft tissues, but they can be found in liver, lungs (normally multifocal), pleura, bones, lymph nodes and rarely in the thyroid gland. We describe a case of metastatic EHE with involvement of the thyroid gland, liver and lungs (probably primary tumor) and aggressive behaviour. A 73-year-old woman was admitted to our hospital due to progressive tiredness, pleuritic pain and episodic cough. Thorax CT scan showed diffuse lung nodularity and micronodularity suggestive of metastatic disease. SARS COV2 infection was excluded. An abdominopelvic CT showed multiple hepatic lesions suggestive of metastases. She underwent lung and liver biopsy both suggestive of EHE (cells with little atypia, round nucleus and rare mitosis, vascular lumens with hemosiderin pigment, CD34+, CD31+). She was also submitted to ultrasound-guided thyroid fine needle aspiration cytology due to a hypoecogenic macronodule, detected on thorax CT, located on the right lobe and isthmus of the thyroid gland, that exceeded the limits of the ultrasonographic image. Thyroid cytology showed moderate cell atypia, CD34+, with features similar to the other biopsy results. She was discharged and referred to Portuguese Oncology Institute. Few days after discharge, she presented at the ER with liquid and solid dysphagia and dyspnea. Neck CT showed a substernal goiter with the right lobe measuring 50 × 65 × 95 mm and mass effect on the larynx, trachea and esophagus, causing an important reduction of laryngeal air column. After a multidisciplinary approach it was decided to perform surgical tracheostomy. During this procedure a biopsy

of the cervical mass was performed and showed a malignant epitheliod neoplasm, without vascular differentiation but also areas with features of EHE, co-expression of CK AE1/3 and CD34, expression INI1. Few days later the patient presented with acute respiratory insufficiency and died. Although rare, EHE can have several locations and mimic many other malignant and non-malignant diseases. Involvement of the thyroid gland is very uncommon. Clinicians should be aware of this diagnosis and include it in the differential diagnosis of a cervical mass. Surgery is the usually the treatment of choice in case of primary EHE of the thyroid gland. Our case of metastatic disease had a very bad prognostic and showed an aggressive course.

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EP211

Therapeutic and evolutive aspects of cardiothyreosis in adult population of southern tunisia

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Introduction
Cardiothyreosis is associated with higher morbidity and mortality than other forms of hyperthyroidism. The aim of our study was to identify its therapeutic and evolutive aspects in an adult population of southern Tunisia.
Methods
Retrospective study including all cases of cardiothyreosis followed in our department during a period of 20 years.
Results
100 cases of cardiothyreosis were collected. To treat the hyperthyroidism, the association of antithyroid drugs and radioactive iodine was used in 52%of patients. Thyroidectomy was performed in 9%of cases. For the cardiothyreosis, 90%of patients went under ß-blockers. All patients with congestive heart failure (CHF) were treated with diuretics. Patients with atrial fibrillation have received anticoagulants. The most used molecule was acenocoumarol (86%). The evolution of cardiothyreosis was favorable in 64.4%of cases while 9%of patients died. In our study, the association of atrial fibrillation and CHF in the same patient, and the elevation of the end-systolic and end-diastolic diameters of the left ventricular were significantly associated with higher risk of mortality ($P < 0.05$).
Conclusion
While its diagnosis is often easy, the management of cardiothyreosis remains difficult. The prognosis of this disease may be ameliorated by an early and efficient treatment.

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EP212

Ectopic thyroid tissue: about 2 cases

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Introduction
Accessory thyroid is defined as the presence of thyroid tissue in locations other than the normal anterior neck region between the second and fourth tracheal cartilages. It is a congenital disease caused by the abnormal migration of thyroid tissue in the embryonic stage. Lingual thyroid is the most common form of ectopic thyroid, extra lingual thyroid tissue is commonly located in the anterior cervical area, along the path of the thyroglossal duct.
Case report
Through a review of 2 different cases, the etiopathogenetic, clinical-diagnostic, and therapeutic aspects of ectopic thyroid tissue are here in discussed to highlight the main presentations of this polymorphous disease. The first case involved an ectopic thyroid gland in the submandibular region with no normally positioned thyroid in a male child of 9 years old with congenital hypothyroidism without mental retardation. The child was put on thyroid hormone treatment and the thyroid hormone level was restored. The second case involved a 40-year-old woman, presenting 3 months after total thyroidectomy, two right lateral cervical masses with moderate signs of compression and without signs of inflammation or thyroid dysfunction. The Cervical tomodensitometry revealed the presence of three tissue formations above the hyoid bone 7.6 × 7 mm, pre hyoid 16 × 12 mm and para hyoid 40 × 31.5 mm compatible with accessory thyroid with empty thyroid lodge.
Conclusion
The ectopic thyroid is classified under the category of congenital hypothyroidism, and it is one of the top causes of thyroid dysgenesis. The first case illustrate the importance of newborn screening and identification of congenital hypothyroidism which is the commonest treatable cause of mental retardation.
Key-Words
Ectopic –Accessory-Thyroid-Hypothyroidism

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EP213

Coexistence of Hodgkin lymphoma and papillary thyroid carcinoma: 3 years follow up of a case report.

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Introduction
Thyroid cancers account for about 2.9%of all cancers. Although it is reported that the risk of developing PTC as the second primary cancer increases after treatment of Hodgkin lymphoma (HL), concomitant PTC and HL are quite rare and to the best of our knowledge we found only three cases in the literature. This case report presents the treatment management and three-year course of a male patient with simultaneous diagnosis of PTC and HL.
Case
A 26-year-old male presented with a complaint of neck swelling. On physical examination, 3 cm mobile, painless, stiff lymphadenopathy (LAP) was detected in the right cervical region. He did not have fever, night sweats or weight loss. The ultrasonography revealed 6 mm, hypoechoic nodule with irregular boundries and microcalcifications and several hypoechoic LAPs with asymmetric cortical thickness. FNAB was applied to the 6 mm nodule in the right thyroid lobe. Since FNAB reported as suspicious cytomorphological findings for malignancy, patient went on total thyroidectomy and lymph node dissection. Pathology revealed three foci of PTC with sizes of 7 mm, 0.5 mm and 0.75 mm in the right lobe. The first focus was 7 mm in size, with minimal extrathyroidal extension and adjacent to the surgical border posteriorly and no lymphovascular invasion. According to the ATA guidelines, the case was intermediate risk. Nodular lymphocyte predominant Hodgkin lymphoma was detected in the lymph nodes, removed from the right cervical region. On postoperative 1st month, ^{18}F-FDG whole body positron emission tomography (PET) revealed pathological involvements in the right jugulodigastric and right cervical chain. The patient was diagnosed with low-risk, stage IA lymphocyte predominant Hodgkin lymphoma. In the second postoperative month, conventional radiotherapy (RT) was applied to the neck region. Radioactive iodine was given at the postoperative 5th month. Whole body scan showed an activity in thyroid bed. The patient was then followed up with TSH suppression. Whole body scan with recombinant human TSH, 1.5 years after RAI treatment was normal. The patient, who is currently at the 36th month of his follow-up, is in remission for lymphoma and PTC.
Discussion
Cases with simultaneous diagnosis of PTC with HL are very rare. In these cases it is important to decide which cancer to treat first. It is thought that therapeutical time interval does not affect mortality and morbidity in the treatment of differentiated thyroid cancer. Therefore, as we did in our case, we recommend giving priority to lymphoma treatment.

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EP214

Disorders of carbohydrate metabolism in hyperthyroidism in children and adolescent

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Relevance
Excess thyroid hormone as a result of thyroid hyperstimulation affects all types of metabolism, including carbohydrate metabolism

Purpose
To assess the incidence of carbohydrate metabolism disorders in children and adolescents with hyperthyroidism.
Materials and methods
Hormonal analysis of thyroid status (TSH, free and total T3, free and total T4, TSHRAb, TPOAb), and biochemical studies (glycemia, glycated haemoglobin, total cholesterol, urea, creatinine, hepatic transaminases) in 79 children and adolescents who received inpatient and outpatient treatment at the RSSPMC after Ya. Kh. Turakulovin the period from 2007 to 2020.
Results
In the period from 2007 to 2020, we examined 73 children with hyperthyroidism in the active phase at the age of 2–18 years, the control group consisted of 21 children of the same age without endocrine pathology, living in the Republic of Uzbekistan. The mean serum level of sugar, creatinine, ALT, AST in the group with hyperthyroidism was significantly higher than in the control group, the mean values of urea did not have a significant difference, the mean total cholesterol level in the group with hyperthyroidism was significantly lower than in the control group (Table 1). Among children and adolescents with hyperthyroidism, 6.85%(5) were simultaneously diagnosed with type 1 diabetes mellitus. In 11%(8) adolescents, fasting hyperglycemia and impaired glucose tolerance were revealed.

Table 1. Indicators of glycemia and some biochemical tests in the study groups

	Sugar	Total cholesterol	Urea	Creatinine	ALT	AST
Hyperthyroidism	6.0 ± 0.4	2.7 ± 0.1	4.75 ± 0.1	65.7 ± 2.6	33.4 ± 1.9	34.3 ± 1.8
The control	4.2 ± 0.3	4.2 ± 0.2	4.3 ± 0.4	57.9 ± 2.4	13.0 ± 1.4	16.6 ± 2.5
p	0.0004	0.0003	0.27	0.04	0.001	0.002

In 56 children and adolescents with hyperthyroidism, we analyzed the correlation between glycemic and other biochemical tests and thyroid status. A weak negative correlation between TSH and creatinine ($r = 0.3$, $P < 0.05$) and a direct correlation with fT4 ($r = 0.3$, $P < 0.05$), a high correlation of fT3 and glycemia ($r = 0.8$, $P < 0.05$) and weak with AST ($r = 0.3$, $P < 0.01$), as well as the level of fT4 with glycemia ($r = 0.4$, $P < 0.05$), ALT ($r = 0.4$, $P < 0.01$), AST ($r = 0.4$, $P < 0.01$) and creatinine ($r = 0.3$, $P < 0.05$). A weak direct correlation between TSHRAb and AST level was revealed ($r = 0.4$, $P < 0.05$).
Conclusions
This study shows the presence of carbohydrate metabolism disorders in hyperthyroidism in children and adolescents, demonstrated by diabetes mellitus (6.85%), fasting hyperglycemia and impaired tolerance to glucose (11%). A direct correlation was found between thyroid hormones and blood sugar.

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EP215

A neck mass revealing thyroid hemiagenesis in an adolescent girl with euthyroidism.

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Introduction
Thyroid hemiagenesis is defined as the absence of one lobe of the thyroid gland. It represents a rare congenital abnormality with a prevalence of 0.05 to 0.2%. The left lobe is more commonly affected than the right lobe. Thyroid hemiagenesis is incidentally found during a routine thyroid screen. Herein, we report a thyroid hemiagenesis revealed by a compensatory hypertrophy of the contralateral thyroid lobe in an adolescent girl with euthyroidism.
Observation
A 16-year-old girl was referred to our department for an anterior right neck mass. Her past medical history was unremarkable. On physical examination, she had a large right thyroid lobe with a complete absence of the left lobe. On biological investigations, she had a TSH level of 1.07 mIU/l (nr: 0.35–4.95) and a FT4 level of 1.09 ng/dl (nr: 0.70–1.50). Cervical ultrasound showed a complete absence of the left lobe of the thyroid and a large heterogeneous right lobe with hypervascularity. Scintigraphy confirmed the hemiagenesis of the left lobe of the thyroid gland and showed a diffuse enlargement of the right lobe with a high and uniform accumulation of the tracer. No ectopic thyroid tissue was noted. Anti-thyroperoxydase antibodies and anti-TSH receptor antibodies were negative. The patient remained euthyroid over the course of follow-up.
Conclusion
Thyroid hemiagenesis is commonly asymptomatic and thyroid function is usually normal. However, patient may present a goiter resulting from the development of a compensatory hypertrophy of the contralateral lobe as in our case.

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EP216

A case of Hashimoto's thyroiditis following Graves'disease

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Introduction
Graves' disease is typically characterized by the presence of circulating autoantibodies that stimulate the TSH receptor, inducing hyperthyroidism and goiter. Hashimoto's thyroiditis is an autoimmune disease leading to thyroid tissue destruction by cell and antibody-mediated immune processes. The development of Hashimoto's thyroiditis following Graves' disease is rarely reported. Its pathogenesis is not confirmed. Herein, we report a case of Hashimoto's thyroiditis following Graves'disease treated with radioactive iodine.
Observation
A 40-year-old woman was referred to our department for thyrotoxicosis. She presented with a weight loss, palpitations, excessive sweating, tremor, and nervousness. On physical examination, she had a regular pulse of 112 beats/mn, a diffusely enlarged thyroid gland, and a tremor in both hands. Laboratory tests revealed overt hyperthyroidism with free thyroxine (FT4) level of 6 ng/ml (normal range: 0.7-1.48) and thyroid stimulating hormone (TSH) level of 0.001 µIU/ml (normal range: 0.35-4.94). Thyroid scintigraphy showed an enlarged gland with diffusely increased tracer uptake, confirming the diagnosis of Graves's disease. The patient was treated with propranolol and thiamazole. Two months later, she received a radioactive iodine therapy. Three years and 9 months later, the patient had a TSH level of 8.787 µIU/ml with a very high level of thyroperoxydase antibodies (2208 IU/ml; nr: < 35 IU/ml) consisting with the diagnosis of Hashimoto's thyroiditis. She was treated with levothyroxine.
Discussion and conclusion
In the early stage of Hashimoto' thyroiditis, a mild and transitory hyperthyroidism may occur as a result of thyroid cells destruction and the releasing of thyroid hormones into circulation. In our patient, based on the severity of hyperthyroidism and the scintigraphic feature, we concluded that the etiology of the initial thyrotoxicosis was Graves' disease. The occurrence of hypothyroidism could be secondary to radioiodine therapy. However, the very high level of thyroperoxydase antibodies is consisting with the diagnosis of Hashimoto' thyroiditis. In 10 to 15%of Graves' disease, Hashimoto's thyroiditis may occur after remission. The precise mechanisms are not known.

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EP217

Thyroid dysfunction associated with immune checkpoint inhibitors therapy

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Introduction
Prospective and retrospective trials report the incidence of endocrine adverse events provoked by immune checkpoint inhibitors (ICI) up to 30%. PD-1/PDL inhibitors have a higher incidence of thyroid dysfunction: hypothyroidism 5%-14%, transient hyperthyroidism – 3%-5%.
The aim of the study was to assess thyroid function in PD-1/PDL treated patients.
Materials and methods
69 patients were included in the study: 27 melanoma patients and 42 non-small cell lung cancer patients. 46 patients were treated with nivolumab,

10 – with pembrolizumab, 9 – with atezolizumab and 4 – consistently with nivolumab and pembrolizumab or atezolizumab. TSH, free T4 and freeT3 were assessed before ICI therapy (visit 0) and every time before the next administration of the drug. The minimum period of observation was 3 months, so we report results obtained at this point in the study.
Results
Before starting ICI 6 patients had TSH and thyroid hormones levels beyond the limits of the reference range: subclinical hyperthyroidism – 2 cases, subclinical hypothyroidism – 1 case, overt hyperthyroidism – 2 cases, overt hypothyroidism – 1 case. In 5 cases we found low T3 (euthyroid sick syndrome). After 3 months of therapy 9 new cases of low T3, 2 cases of persistent hyperthyroidism, 2 cases of subclinical hyperthyroidism and 2 cases of destructive thyroiditis with two phases were revealed.
Conclusions
ICI therapy induced thyroid dysfunction in 21.7%of patients during 3 month after it's initiation, however endocrine related adverse events were not considered as an indication for discontinuation of treatment.

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EP218

A rare case of Graves' disease development from Hashimoto thyroiditis

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The conversion of Hashimoto thyroiditis (HT) to hypothyroidism is frequently observed in daily clinical practice, but the development of Grave's disease (GD) after long-standing hypothyroidism is rare and intriguing. A 70-year-old woman visited an endocrinologist, complaining of increased heart rate, anxiety, and a feeling of discomfort in the neck. Past medical history revealed HT with hypothyroidism. Laboratory tests showed significantly increased thyroid-stimulating hormone (TSH) and positive anti-thyroid peroxidase antibodies. Replacement therapy with levothyroxine 100 µg daily was initiated and implemented for approximately ten years. During the annual follow-up, thyroid hormones were found to be in the normal range. The recent physical examination revealed a firm and slightly enlarged thyroid. TSH suppression was detected, the peripheral thyroid hormone concentration and thyroid-stimulating hormone receptor antibodies (TRAB) were seen to have increased. Neck ultrasound showed slight thyroid hypoechogenicity and non-homogeneity due to multiple hypoechogenic zones. Sonographically, the thyroid lesions were indicative of chronic thyroiditis. Overactive thyroid was suspected. Therefore, levothyroxine was gradually withdrawn. Six months later, hyperthyroidism was seen to have persisted and, ultimately, required anti-thyroid treatment. This case demonstrates a rare case of HT converting to GD. We suggest that the possibility of conversion from hypothyroidism to hyperthyroidism should be considered even if there is long-standing hypothyroidism. We propose measuring TRAB in suspected cases. Further studies are needed to confirm this proposal.

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EP219

The influence of age-related androgen deficiency on risk factors for cardiovascular diseases in men with hypothyriodism

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The long-term androgen deficiency (AD) in men with hypothyroidism is an important problem due to the fact that it leads to concomitant cardiac pathology, which remains the leading cause of mortality in the world. The presence of different points of view on the problem of AD and its effect on the risk factors for cardiovascular disease in patients with hypothyroidismattracts attention. The aim of the study is to assess the clinical signs of age-related androgen deficiency and their association with cardiovascular risk factors in men with hypothyroidism. 84 patients were examined, 38 of them - with hypothyroidism and age-related androgen deficiency, 46 patients with hypothyroidism and normal testosterone levels. The control group was formed of 20 men without hypothyroidism. The lipid and carbohydrate metabolism status, the presence and type of obesity, the level of depression, daily blood pressure monitoring were determined. AD was verified by decrease the total testosterone concentration in serum (< 12 nmol/l). The level of total testosterone and sex hormone binding globulin in serum were determined by radioimmunoassay analysis. The decrease of testosterone level in men with hypothyroidism is accompanied by an increase in the frequency of abdominal obesity, triglycerides and glucoseescape, and is associated with subclinical depression. In men with hypothyroidism and AD, the average blood pressure in the daytime significantly exceeds the similar rates in patients with hypothyroidism and normal levels of testosterone. AD was verified by decrease the total testosterone concentration in serum (< 12 nmol/l). The level of total testosterone and sex hormone binding globulin in serum were determined by radioimmunoassay analysis. The presence of androgen deficiency negatively affects the risk factors of cardiovascular disease in men with hypothyroidism.

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EP220

Thyrotoxic periodic paralysis presenting in an adult male from Cambodia: a case report

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Introduction
Thyrotoxic periodic paralysis (TPP) is a rare complication of hyperthyroidism characterized by the sudden onset of hypokalemia and muscle paralysis. This rare but possible clinical presentation of thyrotoxicosis is significantly more predominant in males of asian descent. The mechanisms of hypokalemia are incompletely understood. The prevailing theories include increased Na-K ATPase pump activity and mutations in genes encoding Kir channels in skeletal muscle. Common factors triggering attacks of periodic paralysis include the consumption of carbohydrate-rich foods, strenuous physical activity, high salt/sodium intake, stresses (surgical, infectious, psychological), trauma, and drugs.
Case presentation
We describe a case of a 52 years-old asian-french male who presented to the emergency department with complaints of acute onset of bilateral lower extremity weakness. He also endorsed a history of weight loss, palpitations, heat intolerance and tremors. Physical examination revealed a slightly enlarged thyroid gland. No exophtalmus or skin changes were present. Laboratory assessment showed severe hypokalemia with serum potassium level 1.5 mmol/l, low serum Thyroid Stimulating Hormone (TSH) (< 0.01 mUI/l) and increased both serum free triiodothyronine (27.3 pmol/l) and free thyroxine (63 pmol/l). TSH receptor antibodies were identified (4.2 IU/l). Hence, the patient was diagnosed as having thyrotoxic periodic hypokalemic paralysis associated with Graves' thyrotoxicosis. Treatment with antithyroid drugs and potassium supplements reversed the symptoms and the episodes of acute muscular weakness did not reappear.
Take-away lesson
TPP is a rare and reversible cause of paralysis. Thus, in cases of acute muscle paralysis, it is important to consider thyrotoxicosis as one of the possible causes, and take measures accordingly. Correction of hypokalemia improves acute presentation, but the patient will remain at risk for paralysis until euthyroid state is achieved.

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EP221

NIvolumab induced grade 3 hypothyroidism – case series

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Introduction
Immunological side effects related with use of immune checkpoint inhibitors (ICIs) are named as immune-related adverse events (irAEs). irAEs include clinical pictures such as autoimmune thyroiditis, hypophysitis, primary adrenal insufficiency and autoimmune diabetes mellitus. Nivolumab is an

anti-PD-1 (anti-programmed cell death-1) monoclonal antibody approved for the treatment of malignant melanoma, advanced non-small cell lung cancer and advanced renal cell carcinoma. In the literature, Nivolumab was reported for causing thyroid dysfunction in some patients treated for cancer. The incidence of Nivolumab-induced grade 3 hypothyroidism is reported as 0.12%. Here, we present two cases of overt hypothyroidism after nivolumab treatment.
Case-1
A 49-year-old male patient with a diagnosis of metastatic malignant melanoma has a treatment history for 9 cycles of nivolumab. The patient has no known thyroid disease and no history of thyroidectomy or longitudinal radiotherapy. TSH (Thyroid stimulating hormone) and FT4 levels were checked 3 months before Nivolumab therapy and were measured as 1.43 mIU/l (normal range) and 1.21 ng/dl (normal range), respectively. Overt hypothyroidism was detected in the workup performed due to the headache complaint of patient 2.5 months after the last nivolumab treatment. Result of biochemical workup was as follows: TSH>47.9 mIU/l (high), FT4:0.27 ng/dl (low), FT3: 2.71 ng/dl (low), anti-TPO(Anti-thyroid peroxidase): 0.6 IU/ml (negative), anti-TG (Anti-thyroglobulin):1651 IU/ml (positive). Performed neck ultrasound was compatible with chronic thyroiditis. Patient started receiving levothyroxine treatment and was followed up.
Case-2
A 65-year-old female patient with a diagnosis of metastatic breast cancer received 11 cycles of nivolumab treatment, and the last cure was 1 month ago. The patient has no known thyroid disease and no history of thyroid surgery or longitudinal radiotherapy. TSH measured 2 years ago was.6 mIU/l and patient was euthyroid. Overt hypothyroidism was detected in the patient's workup: (TSH> 47.9 mIU/l (high) FT4: 0.2 ng/dl (low) FT3: 1.07 ng/l (low) anti-TPO: 0.5 IU/ml (negative), anti-TG: 680 IU/ml (positive)). Patient was started on levothyroxine treatment.
Conclusion
Although there was no known history of thyroid disease; anti-TPO was negative and anti-thyroglobulin was positive at high titer and overt hypothyroidism was identified in both patients who received Nivolumab. Since there are no thyroid autoantibody tests before the treatment, it is not known whether the anti-thyroglobulin positivity alone is due to the treatment. Performing thyroid autoantibody and thyroid ultrasound before treatment would guide the follow-up of patient's thyroid function tests.

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EP222

Difficulties in differential diagnosis of thyrotoxicosis: case report

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Thyrotoxicosis (T) develops as a result of persistent excess of thyroid hormones (TH). There are two groups of diseases that are fundamentally different in pathogenesis. The first group includes those in which the production of TH increases. Diseases of the second group are accompanied by T caused by destruction of the thyroid gland tissue. Therapeutic approaches for different types of T are different, therefore, a careful differential diagnosis of T is necessary, even if at first glance the diagnosis seems obvious. A 35-year-old patient presents with complaints of weakness, weight loss (11 kg in 1.5 months), tremors, palpitations, which first appeared about a month ago. On examination: BMI = 24 kg/m^2, HR = 100 bpm, BP = 115/80 mmHg, the thyroid gland is no larger than the distal phalanx of the subject's thumb. Laboratory examination: TSH < 0.0083 mU/l, free T4 = 28.29 pmol/l (9.0-19.05). Ultrasound of the thyroid gland: signs of diffuse changes in tissue, the total volume = 16.8 ml^3. For differential diagnosis of T, antibodies to TSH receptors were determined, the titer of which turned out to be slightly increased 1.43 IU/l (< 1). A diagnosis of Graves' disease (GD) was made, and treatment was prescribed (Tyrozol 30 mg, Bisoprolol 2.5 mg per day). After 3 weeks, the patient noted an improvement in well-being, but weakness, tremor, an increase in free T4 (23.33 pmol/l) and total T3 (3.26 nmol/l at a rate of 0.98–2.33) remained. The lack of achievement of the target values of TH levels was regarded as inadequacy of the received dose of Tyrozol, in connection with which it was decided to increase the dose to 40 mg per day. After 2 weeks: free T4-27.26 pmol/l and total T3-3.84 nmol/l. The lack of positive dynamics called into question the diagnosis of GD. With a more thorough collection of anamnesis, it was found that 1.5 years ago, the patient took amiodarone for 6 months. In this connection, to establish the cause of T, scintigraphy was performed: a weak accumulation of a radiopharmaceutical with diffuse uneven distribution. Thus, amiodarone-induced T type 2 was verified. Treatment was corrected: Tyrosol withdrawal and Prednisolone administration, 40 mg/day with positive dynamics from treatment. It is important to carefully collect the patient's history and follow the algorithms for differential diagnosis. Errors in diagnosis lead to improperly prescribed treatment, an increase in the duration of symptoms, which affects not only the patient's quality of life, but also reduces the level of his trust in medical workers.

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EP223

Prominent multinodular goiter in a patient with Williams-Beuren Syndrome

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Objective
Presentation of multinodular goiter as an unusual feature in a patient with Williams-Beuren Syndrome.
Methods
Review of the patient's clinical records and of the relevant literature.
Introduction
The Williams-Beuren Syndrome is a multisystem disorder caused by a microdeletion of 1.5–1.8 megabase pairs on chromosome 7q11-123, with loss of 26–28 genes centered around ELN, which codifies elastin. The partial loss of elastin is the cause of cardiovascular abnormalities, particularly supravalvular aortic stenosis and other arterial stenoses. Most patients are hypertensive, and prone to stroke and sudden death. The phenotype of Williams-Beuren patients includes growth failure with adult short stature, a characteristic facial appearance, and mental retardation with a friendly, sociable character. The endocrine manifestations include precocious puberty, partial GH deficiency, hypercalcemia, osteopenia/osteoporosis, glucose intolerance or type 2 diabetes mellitus. Up to Cof Williams-Beuren patients develop subclinical or overt hypothyroidism, often not requiring treatment; in some cases the hypothyroidism is congenital with associated thyroid hypoplasia. Antithyroid antibodies are usually negative. Goiter is, however, not included in the usual descriptions of the syndrome.
Case description
A 45 year old male patient had been diagnosed with Williams-Beuren syndrome, and had the characteristic facies (short nose with upturned tip, small chin) and mild mental retardation. A cardiology workup had shown hypertension, systolic murmur, supravalvular aortic stenosis and mild mitral regurgitation, with preserved ventricular function; normal sinus rhythm with isolated ventricular extrasystoles. He was on treatment with delapril, manidipine, atenolol and hydrochlorothiazide. He had complained of an indolent cervical lump in the last year, without symptoms of thyroid dysfunction or local compression and was referred to our Endocrinology Clinic. Physical examination showed: Height 161 cm, Weight 75 kg, BMI 28.9 kg/m^2, diffusely enlarged thyroid gland, non-painful, without adherence, increased consistency, palpable nodules or adenopathies. Lab tests showed: Blood glucose 129 mg/dl, HbA_{1C} 6.2%, LDL-cholesterol 117 mg/dl; TSH 1.89 µU/ml, negative antithyroid antibodies. Cervical ultrasonography showed an enlarged thyroid gland with 6.5 cm (left lobe) and 6.2 cm (right lobe) craniocaudal diameter, and multiple subcentimeter colloid cysts, not susceptible of FNAC. Thyroid scintigraphy showed diffuse hyperplasia. The additional diagnoses were micronodular euthyroid goiter, overweight, type 2 diabetes mellitus and dyslipidemia.
Conclusions
Although mild hypothyroidism is common in patients with Williams-Beuren syndrome, goiter is not usually described. Its presence in our patient might be coincidental, but cervical ultrasonography for goiter screening may be considered.

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EP224

Acute myocaditis : a rare complication in the Graves disease

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Introduction
Graves' disease is an autoimmune disorder that has multiple cardiac repercussions including arrhythmias and heart failure. Acute myocarditis is a rarely described complication. In this context, we report a case illustrating this association.
Case presentation
A 23-year-old man has been followed for Graves' disease that had been suspected by weight loss, tachycardia and bilateral and asymetric proptosis. The diagnosis had been confirmed with an fT4 at 27 pmol/l (1.42 times the normal), TSH at 0.04 IU/l (*n*:0.35-4), anti-TSH receptor antibodies positive at 40 IU/l and on thyroid ultrasound a hypervascular and enlarged thyroid gland. The patient was treated with carbimazole 30 mg per day and propranolol 60 mg per day. One year later, he was seen for oppressive chest pain, with an ECG showing an inferolateral elevated ST segment and an anteroseptal ST segment depression. The troponin level was 21.627 ng/l. Acute coronary syndrome has been suspected. The patient was put on dual antiaggregant and anticoagulation. He had a coronarography showing normal coronary arteries. Transthoracic ultrasound showed hypokinesia of the mid and basal segments of the anterolateral and inferior walls with an ejection fraction at 50%. A myocardial magnetic resonance imaging was then practiced and showed an aspect of myocarditis. Since the patient was apyretic, did not present arthromyalgia and there was no biological inflammatory syndrome, the viral origin was eliminated. The diagnosis of autoimmune myocarditis was then retained. Therapeutically, he was kept on a beta blocker and received radioiodine therapy twice. The evolution was marked by post radioiodine hypothyroidism which was then substituted with L-thyroxin and by the absence of recurrence of chest pain.
Conclusion
Acute myocarditis is an unusual affection in Graves' disease. The mechanism is different from of the cardiothyreosis which is linked to a direct effect of thyroid hormones on the heart. An autoimmune mechanism has been implicated in this entity which can be confirmed histologically by the presence of anti TSH receptor antibodies in cardiomyocytes. Hence the importance of careful cardiac exploration in Graves' disease.

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EP225

Pancytopenia in Grave's disease: due to ATD or other autoimmune disease ?

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Introduction
Grave's disease is an autoimmune disease characterized by hyperthyroidism. It is in some cases associated to more autoimmune organs dysfunction. The antithyroid drugs are the first line treatement, and sometimes they are responsible for severe adverse effects.
Observation
We report the case of a 34 year-old man, treated for his grave's disease with thiamazol for two years. Two weeks after interrupting his treatment of his own volition, then reintroducing it, he consulted for asthenia, fever at 40°C and a poor state of health, the blood count revealed a severe pancytopenia with agranulocytosis (Hemoglobin 4.5 g/dl, WBC 760/µl, Neutrophils 320/µl, Platelets 23 000/µl). In front of this emergency, the antibiotherapy was started, and the thiamazol was immediately interrupted, but there was no noticeable amelioration in the blood count, so we suspected the presence of another factor such as the pernicious anemia, and a low level of vitamine B12 was indeed found (46 pg/ml). The anti intrinsic factor was positive at 80 RU/ml, and the gastric tissue biopsy showed a non active chronic gastritis with severe atrophia and moderate intestinal metaplasia confirming the diagnosis of the Biermer disease. The procedure to follow was to treat the patient with intra-muscular injection of vitamine B12 and his condition as well as his blood count improved within two weeks (Hemoglobin 9.6 g/dl, WBC 2330/µl, Neutrophils 1150/µl, Plateles 151 000/µl). As for his Grave's disease, he received a radioactive iodine therapy. The severe pancytopenia was in this case due to two factors ; the allergic reaction to the antithyroid drug and the insidious presence of Biermer's disease. This association of these two diseases is called autoimmune polyendocrine syndrome type 3B which is a group of rare diseases.
Conclusion
Pancytopenia with agranulocytosis is a rare adverse effect of the antithyroid drugs. Blood count must be evaluated before and after initiation. Moreover, the autoimmune thyroid disease may be associated to other autoimmune disorders, hence the importance of screening for other autoimmune diseases in front of new symptoms.

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EP226

Assessment of clinical burden and practice patterns in patients with chronic hypoparathyroidism in the United States (US): A claims data analysis using a surgery-based approach

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Objectives
There is a paucity of real-world studies on the clinical burden and practice patterns associated with chronic hypoparathyroidism (cHP). This study assesses the comorbidities, treatment and lab testing patterns in cHP patients identified using surgery-based criteria.
Methods
This was a retrospective study conducted using a large (130 million individuals) US claims database (HealthVerity Closed Payer Claim Medical and Pharmacy database (Private Source 20) from Oct 2014 to Dec 2019. The patients were eligible if they had a procedure claim of either parathyroidectomy, complete or partial thyroidectomy, or neck dissection, followed by a HP diagnosis claim (6–15 months apart), with a subsequent second HP diagnosis claim at any time point. Patients also had to be continuously enrolled for 15 months before the index date (the date of the first qualifying HP diagnosis claim) and □6 months after. Patients were followed one year before the surgery and up to two years after the index date. Demographics, comorbidities, lab tests and treatment patterns were analyzed.
Results
1406 patients met the eligibility criteria and 1184 patients had complete data for 1-year follow-up. The mean age was 52.1 ± 16.4 (S.D.) years, and 83.2%were females. The mean time between surgery and qualifying HP diagnosis claim was 8.7 ± 2.3 (S.D.) months, and 115 patients (8.2%) had a HP diagnosis prior to surgery. During the 1-year follow-up, the most common comorbidities were cancer (54.2%, of which 49%were thyroid cancers), hypertension (49.7%), hypocalcemia (47.1%), chronic pulmonary disease (21.9%), diabetes (21.7%), cardiac arrhythmias (18.4%), CKD stage 3-5 (11.3%), osteoporosis (9.8%), and neuropsychiatric disorders, including anxiety (23.9%), depressive disorders (21.8%), and sleep-wake disorders (20.9%). Lab tests ordered during the 1-year follow-up included serum calcium (93.2%), eGFR/creatinine (86.2%), 25-Hydroxy Vitamin D (66.5%), intact PTH (63.0%), serum magnesium (40.9%), serum phosphorous (38.4%), bone mineral density (9.8%), and 24 h-urine calcium (8.4%). During the same period, 66.9%of patients had a prescription claim for thyroid replacement therapy, 51.6%for calcitriol, 13.3%for ergocalciferol, and 5.5%for PTH.
Conclusion
This large cohort of cHP patients, identified using surgery-based criteria, was recently diagnosed and had a substantial comorbidity burden that was aligned with the lab testing patterns. Already at this early stage of cHP, kidney function appears to be a key concern, and may be important when considering therapeutic intervention. These data are consistent with our findings from a larger cHP population identified in the same database using a diagnosis-based approach.

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EP227

Limitations for the use of ultrasound ablation of thyroid nodules

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High-intensity focused ultrasound ablation (HIFU) was used in the treatment of thyroid nodules using the device "Echopulse" (Theraclion, France). The therapeutic sensor is represented by a piezoelectric lens with a diameter of 12 cm, with a variable radiation frequency from 0.8 to 1.6 MHz. The treatment was carried out automatically after preliminary planning. The impact zone (ablation focus) was marked automatically on the device screen. The limitations for using HIFU were evaluated. It was found that the localization of the thyroid node is important. Optimal is the presence of a layer of healthy thyroid tissue between the treatment area and the adjacent structures and organs of the neck. The most favorable is the central location of the node and the size of 15–25 mm in diameter. Of the local constraints, the following are marked. There are limitations in performing HIFU in people with short, thick necks and partially retrosternal nodules (cervical-mediastinal goiter) due to the complex and time-consuming positioning of the lens. HIFU application in the event that the thyroid node contour is located close to the trachea, carotid artery and esophagus is difficult, the HIFU program will automatically exclude this area from the ablation zone. With HIFU, the distance to the carotid artery should be more than 4.5 mm (especially if the carotid artery is behind the focal point), and the distance to the trachea should be more than 5 mm (if the trachea is behind the focal point, then more than 10 mm). There are also restrictions for HIFU subcapsular nodes: the depth of the leading edge of the node should not be less than 5.0 mm, the depth of the trailing edge of the node should not be more than 26.7 mm. When selecting patients, the volume of the liquid component was taken into account, HIFU is ineffective in cystic nodules, since the ultrasound energy is not focused in the liquid. A contraindication is the detection of calcifications of various sizes. Macrocalcinosis interferes with the effect of HIFU. There are also limitations in identifying large hyperechoic areas with reduced vascularization (signs of a pronounced fibrous component). Common contraindications for performing HIFU that are not related to thyroid pathology are: Mental instability of the patient. Pacemakers and pacemakers are installed. Recurrent neural abnormalities on the opposite side of the HIFU exposure side. The presence of scars and pigmented nevi in the area of placement of the therapeutic lens.

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EP228

Case report of a female patient with primary hyperparathyreoidism and acute pancreatitis

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A 65-year-old patient was hospitalized three times over a two-year period for severe acute pancreatitis. After the first hospitalization, cholecystectomy was performed. During the second hospitalization she was treated in the ICU because of the development of necrotizing emphysematous pancreatitis with the development of sepsis. During the third hospitalization the patient presents clinically with general weakness, agitation, visual hallucinations, disorientation and damaged cognitive-mnemonic functions. While being treated, elevated blood calcium levels were detected (Ca 3.35 mmol/l), and additional laboratory tests were performed (PTH 9.55 pmol/l, total Ca 2.80 mmol/l, vitamin D 8.53 mmol/l, anorganic phosphate 0.98 mmol/l). Ultrasound examination of the neck reveals a solid-cystic formation behind the left lobe of the thyroid gland. Cytological finding of the puncture formation indicates hyperplasia of the thyroid gland, and scintigraphy with Tc-99m MIBI indicates pathological accumulation of radiopharmaceuticals in the left thyroid lobe and hyper functional parathyroid gland tissue behind the left thyroid lobe. Initially she was treated with pamidronate, followed by a left thyroid lobectomy and parathyroidectomy of the left parathyroid glands. Pathohistological diagnosis indicates a parathyroid adenoma. Postoperative calcium values were normal (Ca 2.27 mmol/l) with marginally elevated TSH (TSH 5.12 mIU/l, fT4 14.03 pmol/l). Low-dose levothyroxine substitution was prescribed. Three years after the development of pancreatitis and thyroid lobectomy with parathyroidectomy, the patient was hospitalized for a new verified type 2 diabetes (FPG 19.0 mmol/l, HbA1c 13.7%) without developed micro and macrovascular complications of the disease. Insulin therapy was started, according to basal- bolus protocol (insulin aspart with human insulin) and glycaemic control was achieved.

Conclusion

Hypercalcemia was an etiopathogenetic basis for recurrent acute pancreatitis.

Key words

hypercalcemia, acute pancreatitis, primary hyperparathyroidism

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EP229

Prifictive factors of malignancy in thyroid nodules: About 304 cases

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Background

The thyroid nodule is a common presentation. Its prevalence is estimated to be 5%. Surgical treatment could not be systematic. It requires structured diagnostic approach to ascertain the risk of malignancy and determine appropriate management.

Aim

To evaluate potential role of epidemiological, clinical and para clinical criteria as preoperative indcators of malignancy in thyroid nodules.

Methods

This is a retrospective analytical study of 304 cases of patients who undergone surgery for thyroid nodule in ENT Departement of Farhat Hached Hospital from 2012 to 2019.

Results

The median age at diagnosis was 44, 73 years. It is more common in women with sex-ratio (M/F) is 0.1. Cancer risk is 36%in men versus 25.1%in women. The mean delay of consultation was 12 months(extrêmes de 1 à 276 moths). Family history of thyroid disorders were present in 10.2%of cases. Personal history of goiter was found 12 patients (3.9%). de compressive symtomps were detected in 22.7%of cases. Cervical lymph nodes were présentes in 36 patients (11.8%of cases). Hard consistency was found in 44 patients (14.5%). Le nodule was fixed in 38 patients (12.5%). Margins were irregular in 23 patients (7.6%). Several US features have been found to be indicative of malignant potential. Microcalcifications(33.6%, p), irregular limits(46 Patient, 15.1%), or microlobulated margins(28 patients (9.2%), hypoechogenicity (95 pateinst, 31.3), taller-than-wide shape(70 patents, 23%), and increased intranodular vascularity(118 patients, 39%) were found to be independent risk factors for malignancy. Scintigraphy with technétium99 was performed in 15.9%of cases and FNA in 16%of cases. An analatycal study was concucted in order to determnates pedictive factors of malignancy:family history of thyroid disorder, personal history of thyroitidis, goiter, hard consistency ($P < 0.001$), fixity ($P < 0.001$), irregular limits ($P = 0.002$, cervical lymph nodes($P < 0.001$), and flush syndrome ($P = 0.007$), hypoecgogenecity ($P < 0.001$), blurred margins($P < 0.001$), taller-than-wide shape ($P = 0.002$), microcalcifications ($P < 0.001$),, intranodular vascularisation ($P = 0.003$) and the score EUTIRADS V ($P < 0.001$).

Conclusion

The risk stratification based on clinical features and US findings is useful to determinate the convenient management of thyroid nodules.

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EP230

Exceptional thyroid cancer: a challenging diagnosis

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Introduction

Thyroid carcinoma is the most common type of endocrine malignancy and the cancer with the largest annual increase in incidence in recent decades. They are classified as primary or metastatic. The most common thyroid cancer subtypes include papillary, follicular, medullary, and anaplastic. We aim to present 11 cases of exceptional thyroid malignancies managed in our department.

Materiel and methods

A retrospective study of 11 cases of exceptional thyroid cancer was performed in ENT and neck surgery department Farhat Hached hospital Sousse Tunisia.

Results

Our study included: six cases of lymphomas, a case of insular carcinoma, two cases of thyroid metastasis of lung cancer, a case of neuroendocrine thyroid carcinoma and two sarcomas. On cervical examination, a multinodular thyroid gland was noted in the 6 cases of lymphomas. Cervical lymph node involvement was present in 6 cases associated with laryngeal nerve

palsy in 3 cases. Ultrasound demonstrated a multinodular thyroid gland in all cases associated with microcalcifications in one case. CT scan showed lung metastasis in two cases (angiosarcoma and mantle cell lymphoma). A gastroscopy confirmed the stomach localization in a mantle cell lymphoma. A total thyroidectomy was performed in 4 cases. A bilateral lateral lymph nodes dissection was performed in 2 cases. an emergency tracheotomy was performed for 4 patients who presented with dyspnea. Chemotherapy was administrated in 5 cases. The evolution was fatal in 6 cases.
Conclusion
An accurate diagnosis is important despite the immense difficulties. The management remains challenging. The ideal treatment modality should be determined considering the presence or absence of metastases, the patient's general condition, and the presence or absence of local symptoms.

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Late Breaking

EP231

What is the most cost-effective model of screening for type 2 diabetes in the Republic of Uzbekistan

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Background
Epidemiological studies revealed up to 5-6 undiagnosed cases of type 2 diabetes mellitus (DM2) per 1 registered patient. The late diagnosis of DM2 presents a medical and socio-economic problem.
The aim of the study to identify the most cost-effective, easy-to-use method for regular screening for DM2 in primary care settings in the Republic of Uzbekistan.
Materials and methods
4 diabetes screening scenarios differing in the inclusion criteria (age 45 vs age 45 plus arterial hypertension plus obesity), and screening methods (testing for glycemia and/or HbA1c) were studied in urban and rural primary care polyclinics among 2430 people.
Results
In primary health care real clinical practice, the most cost-effective and easy-to-follow strategy for active screening for DM2 is testing for random glycemia using a certified glucometer, in any resident aged 45 or older visiting his/her GP for any reason. If test results are intermediate, the person is called again the next day for fasting glycemia testing to confirm the diagnosis. If the test results are normal, the person is given recommendations of healthy lifestyle and re-testing in 1 year. If the test result corresponds to DM, the person is referred to a local endocrinologist.
Key words
diabetes mellitus, prediabetes, screening

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EP232

Evaluation of awareness about requirement of anti-obesity pharmacotheraphy before weight loss surgery in a tertiary outpatient Endocrine Clinic in Turkey

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Background
Obesity is an increasing public health problem all around the world. It plays role in the pathogenesis of many diseases, especially diabetes, hypertension, hyperlipidemia, cardiovascular diseases and cancer. The prevalence of weight-loss surgery is increasing as a result of developments of surgical techniques. In parallel with these developments, more patients admit for weight-loss surgery. Pharmacotherapy is one of the most important component of interventions before surgery. In this paper we aimed to evaluate patients' awareness towards receiving pharmacotherapy before admission to surgery.
Method
Patients who had been referred from general surgery department to our clinic for endocrinological evaluation were included to our study. 47 patients were evaluated.
Results
21%(*n*: 10) of the patients were male and 79%(*n*: 37) were female. 17%of the patients (*n*: 8) had type-2 diabetes. Mean body mass index (BMI) was found to 44.1 kg/m^2. 80%(*n*: 38) of the patients had not received any pharmacological treatment before and directly preferred surgery as an anti-obesity treatment modality. None of these patients were aware of the importance and requirement of pharmacotherapy before surgery. Liraglutide was started in 4%(*n*: 2) patients, exenatide 17%(*n*: 8) diabetic patients and orlistat in 19%(*n*: 9) patients, respectively. Lifestyle changes were recommended to 60%(*n*: 28) patients and evaluation for pharmacotherapy planned for the next visit.
Discussion
Pharmacotherapy and behavioral modification are major interventions before weight loss surgery. Incompatibility with pharmocotherapy and behavioral modification is one of the contraindications for bariatric surgery. Besides, pharmacotherapy increases the success of weight loss surgery. To conclude, increasing awareness among patients to apply for pharmocotherapy and behavioral modification before surgical procedures may help us to achieve meaningful weight loss in long term.

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EP233

Reduction in medication of multidrug hypersensitive patient by bariatric surgery

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Introduction
Type 2 diabetes and hyperlipidemia are primarily managed with lifestyle modifications, self-monitoring of blood glucose, and medication. Patients who are obese and cannot achieve normal blood glucose levels despite diet, exercise, and multiple medications may be considered for bariatric surgery. Many diabetic patients with very high triglyceride levels are at high risk for ASCVD and therefore after triglyceride levels are controlled the patient should be evaluated for cardiovascular disease risk. Bariatric surgery is more effective at inducing weight loss than either diet or medications. Baratric surgrey is alsow associated more robust decrease in serum triglyceride levels and increase in HDL-C levels. Here we describe a bariatric surgery results of obese multidrug hypersensitive patient with a high level of serum triglyceride.
Case
44 years old woman, had Type-2 Diabetes Mellitus and hyperlipidemia for at least 3 years. She had no medication due to multidrug hypersensitive. Her BMI was 39.9, fasting glucose, serum triglyceride, VLDL, HDL, HbA1C are: 166 mg/dl, 2166 mg/dl, 433 mg/dl, 32 mg/dl, 60 mmol/mol respectively. İn addition to Initial treatment of very low-fat diet, we immediately started medication to reduce triglyceride levels into a safe range to prevent triglyceride-induced pancreatitis. After 10 day of receiving fenofibrate and dapagloflozin she had an generalized acute urticaria need hospitalization and first treated with antihistamine drugs. Here serum triglyceride level was 1906 that force us to continue medication tratment with antihistamine drug. After 4 mounth of treatment and weight loss (10 kg) we didn't reach therapy goals of hyperlipidemıa. The patient had a bariatric surgrey after mutidisplanary consensur. After surgrey she stoped medication and her serum triglyceride measure was 240 mg/dl.
Conclusion
We report a case of generalized urticaria probable or very probable induced by fenofibrate underwent bariatric surgery. Approximately 60-70%of patients with obesity are dyslipidemic. The Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy have been shown to improve A1C, reduce weight, and reduce the number of medications patients need for diabetes management. Comorbidities such as hyperlipidemia and hypertension also

may improve. A reduction in medication of hypersensitive patients can be considered an additional benefit of bariatric surgery.

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EP234

Short-term carbohydrate and lipid restriction impact on obese gerbil

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The control of obesity and the regulation of its components are strongly linked to nutrition. Thus, low calorie diets restricted in carbohydrates and lipids are becoming increasingly suitable for combating the complications of obesity. In the present work, we propose to report the short-term repercussions of dietary carbohydrate and lipid restriction on the weight parameters of the obese gerbil. Our experiment was undertaken on a species of gerbil (Gerbillus tarabuli) and lasted 5 months. Gerbil is a wild animal from the Algerian desert. In captivity, this rodent subjected to a high carbohydrate high fat diet, develops metabolic disorders which are characterized by visceral obesity. The obese animals were subjected to carbohydrate and lipid restriction for 8 weeks. Gerbils submitted to carbohydrate and lipid restriction diet show a significant decrease in body masse (approximately 10%), in subcutaneous and epididymal adipose tissues weight (approximately 50%) compared to obese animals. However, no significant difference was recorded for mesenteric adipose tissue weight for the two groups. In conclusion, our results demonstrate that short-term carbohydrate and lipid restriction diet decreases body weight and reduces adiposity in obese gerbils.

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EP235

Double diabetes mellitus: a case report

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Introduction
Type 1 diabetes mellitus (T1DM) is an autoimmune disease in which pancreatic Cells are destroyed, generating an incapacity to maintain appropriate insulin and glucose concentration. On the other hand, type 2 diabetes mellitus (T2DM) is associated with varying degrees of insulin resistance (IR) and relative insulin deficiency. The association of T1DM and the clinical features of T2DM as obesity, hypertension, dyslipidemia, or metabolic syndrome (MS) is called “double-diabetes” and has been associated with an increased rate of chronic complications and cardiovascular diseases in patients with T1DM.
Case
A 46 years old female patient had had diabetes mellitus for 8 years, under premixed insulin (1.2 U/kg) and 2 g of metformin due to her glycemic imbalance (Hba1c: 14%) with a history of a few episodes of diabetic ketoacidosis (DKA), hypertension, weight gain under insulin, adult-onset diabetes in maternal grandfather, mother, brother, and sister. She was considered T2DM due to her clinical presentation that included a BMI of 30 kg/m^2, a waist circumference of 97 cm, acanthosis nigricans around her neck, and significant family history of diabetes. During her last hospitalization for glycemic imbalance, the biological assessment revealed positive antibodies to glutamic acid decarboxylase (GAD) over 2000 U/ml. The patient was diagnosed with T1DM and put under insulin in a basal/bolus regimen associated with 2 g of metformin to counter insulin resistance.
Discussion and conclusion
Double-diabetes (DD) was a term coined to describe individuals with type 1 diabetes showing clinical features compatible with type 2 diabetes. It has been variably used in literature, to describe both individuals with obesity and other insulin resistance (IR) characteristics. The mechanisms involved in the development of IR in patients with T1D remain unknown. Some studies have proposed that obesity due to a non-healthy lifestyle and over-insulinization in addition to the genetic background are its main cause. Meanwhile, others have reported that IR is present in patients with T1D even in the absence of obesity. Definition of a strict intermediate subtype between both types of diabetes is difficult, therefore this grey zone between them behaves more like a continuum according to current evidence.

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EP236

Carney complex: a case report

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Introduction
Carney complex (CNC) is an extremely rare genetic syndrome of pigmented skin lesions, endocrine hyper-function and myxoma. Given its diverse clinical manifestations, CNC is often misdiagnosed. Recognition of some special clinical manifestations and imaging features may help with the diagnosis. We report the case of CNC with endocrine and cutaneous tumors.
Case
A 50 years old female patient followed for acromegaly for 10 years, had undergone transsphenoidal surgery. She has a history of thyroidectomy for goiter, operated twice for melanotic schwannoma of the neck and multiple lipomas. There was no similar case in her family. The diagnosis of CNC was retained. Screening of PRKAR1A is ongoing.
Discussion and conclusion
Carney complex (CNC) is a very rare disease which is often misdiagnosed because of its diverse clinical characteristics. It was first described in 1985 by J Aidan Carney, and its main clinical features are spotty pigmentation, endocrine overactivity, and myxoma. The regulatory subunit (R1A) of the protein kinase A(PRKAR1A) gene is implicated in its causation. The PRKAR1A mutations causing CNC have been identified in 70%of the total cases reported worldwide. The exact prevalence of Carney complex is unknown. Around 750 cases from many ethnicities have been reported worldwide since 1985. The prevalence can be underestimated because the diagnosis is challenging, and the awareness of this rare and complex disorder is insufficient among the medical community.

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EP237

An elderly woman with vitiligo and memory deficits

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Introduction
Pernicious anemia is an autoimmune cause of Vitamin B12 deficiency, that can occur as part of polyglandular adenopathy Type 3. According to one prospective serial study, it’s incidence was 2.3%in people ≥ 60 years of age, being more common in women than men. A case of polyglandular syndrome, most likely PGA-3, is being described. She had Type 1 diabetes, Hashimoto’s thyroiditis, vitiligo & pernicious anemia.
Clinical case
63 years old post-menopausal lady with Type 1 DM>15 years, Primary Hypothyroidism, Dyslipidemia, Vitiligo & Minimal NPDR. She was worked up previously for evolving cognitive defects e.g. short term memory lapses & was found to have Vit. B12 deficiency(B12-69 pmol/l, S. folate NA). Was treated e Inj. B12 replacement and got somewhat improved. Family Hx insignificant. Systemic review: NAD(No GI symptoms, candidiasis). Drug Hx: Metformin 1 gBD, Novorapid(10-10-6 units), Lantus, 16 units PM, Levothyroxine100 µg/d, Aspirin, 81 mg/d, Inj. Methyl Cobalamin-1 mg/monthly, Ferrous-folic-once daily, Refresh eye drops. Exam: Vitally stable e no postural instability. Wt 62.6(62 kgs in 2017), BMI-27.85 kg/m^2 Vitiligo+ mouth, hands & feet. No hyperpigmentation. Otherwise General and Systemic exams unremarkable. Labs: HbA1c 9.8%(was 8.5%before), CBC-Hb%11.8 g/l, MCV 82.2 fl, ACR 7.68 mg/gm, Lipids(T. Cholesterol-5.91 mmols/l, LDL-3.41 mmols/l, TGs 0.95 mmols/l, HDL 2.07 mmols/l), Corrected Ca++ 2.43 mmols/l. TFTs(TSH 3.7 mIU/l, FT4 19.1 pmol/l). Rest WNL. Other Investigations: CT scan brain-normal, Short Synecthen Test negative(ACTH 4.8 pmol/l), Anti-gastric parietal cell & Anti-Intrinsic factor Antibodies strongly positive(Anti-parietal ;47.4 units-normal: 020), Anti-Intrinsic factor Abs-69.2 units-normal0-1.1 units). ECG & CXR-unremarkable. Anti-Islet cell Abs-Negative, Anti-GAD-65 Abs Highly Positive-5504.1 U/ml(0.0-5.0), S. Gastrin-30 pg/ml(0115). Anti-thyroid Abs: Anti TPO-1761 units(0-100), Anti TG-278.34 units (< 0.6

units-negative). Elective surveillance upper GI endoscopy: unremarkable apart from the finding of a 3 mms, whitish nodule in the gastric antrum. Gastric histopathology: (4 specimens). Specimen from the gastric nodule revealed mild to moderate inactive gastritis, gastric atrophy & intestinal metaplasia. Antral Bx-positive for H. pylori like organisms. Otherwise biopsies from incisura & body of stomach showed mild to moderate inactive gastritis. Gastroenterology follow-up was still awaited.
Conclusions
–Vitamin B12 deficiency should always be ruled out in people, esp. the elderly, having cognitive disturbances.
–In the presence of other autoimmune disorders like Type1 diabetes, vitiligo etc, Vitamin B12 deficiency is most likely due to pernicious anemia, which can be proven by checking anti-gastric parietal & anti-intrinsic factor antibodies.

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EP238

Prostate cancer metastasis to cervical node chain-an unusual clinic

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Introduction
While cervical lymph nodes are the region where head and neck malignancies frequently metastasize, prostate carcinoma rarely metastasizes to this area. Here, we will present a case with papillary thyroid microcarcinoma whose pathological lymph node cytology in the cervical region was found to be prostate carcinoma metastasis.
Case
Since thyroid fine needle aspiration cytology (FNAC) results were non-diagnostic 3 times, an 64-year old male patient underwent bilateral total thyroidectomy. His pathological examination was compatible with papillary microcarcinoma, and was given 100 mci radioactive iodine (RAI) treatment. While post-ablation whole body scan (WBS) revealed the activity involvement compatible with residual tissue in the right lobe region, the diagnostic WBS was found to be normal (TSH, Tg and Anti Tg values are shown in Table 1). In PET-CT, pathological increased activity uptake was detected in the bilateral level IV lymph node area. Neck ultrasonography showed a lymph node with pathological appearance and 8.5 × 8.7 × 11 mm in size at left level IV. Cytological examination of this lymph node was compatible with carcinoma metastasis. Also, another pathological looking lymph node on the left level IV with 7.7 × 9.4 × 10.8 mm in size was found to be compatible with malignant cytology, carcinoma metastasis (Table 1). An immunohistochemical study of the prostate and thyroid origin (PSA, TTF1) has been conducted in cytology, but a definitive clue for the origin of the tumor has not been obtained. Thereupon, the FNAC was repeated from the level IV lymph node (8.5 × 8.7 × 11 mm) of the patient and non-diagnostic cytology was found, afterall the cell block was applied. Finally, left level IV lymph node cytology was reported to be compatible with prostate adenocarcinoma metastasis.

Table-1

	TSH(ıu/ml)	Tg (ng/ml)	Anti-Tg (u/ml)	Tg washout
Post-ablation WBS	73	27.3	19	
Diagnostic WBS	41.4	25.5	18	
Left level IV (8.5 × 8.7 × 11 mm)		4		0.89
Left level IV (7.7 × 9.4 × 10.8 mm)		4		0.3

TSH; thyroid stimulating hormone, Tg; thyroglobulin, Anti-Tg; anti- thyroglobulin, WBS; whole body scan, RAI; radioactive iodine

Conclusion
Metastatic prostate adenocarcinoma (PAC) to cervical lymph nodes is rare. If the history is unknown, cases may be misdiagnosed as metastases from cervical neoplasms. Findings showing metastatic PAC to the cervical lymph nodes in FNAC are; the involvement of left-sided cervical lymph nodes and cellular smears consisting of flat layers with granular cytoplasm and uniform polygonal cells arranged in the acini, fuzzy cell borders, and round-oval nuclei with prominent nucleoli.

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EP239

A rare cause of levothyroxine malabsorption: İleostomy

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Introduction
It is recommended to determine levothyroxine (LT4) dose individually in patients with hypothyroidism. However, higher doses of LT4 therapy are required to achieve target TSH levels in significant number of patients. Oral LT4 absorption occurs in the small intestine, especially in the jejunum and proximal ileum, while a small amount is absorbed in duodenum. Causes of LT4 malabsorption include helicobacter pylori infection, chronic atrophic gastritis, celiac disease, lactose intolerance, pancreatic insufficiency, cirrhosis, nephrotic syndrome, gastrointestinal malabsorptive surgical procedures, short bowel syndrome, drug and diet-related interactions. Here, we present a case of ileostomy with multiple small intestine resection, which is a rare cause of LT4 malabsorption.
Case
A 59-year-old male patient was consulted to our endocrinology clinic due to high TSH levels before ileostomy closure from the gastrosurgery clinic. The patient underwent total thyroidectomy in 2009 due to medical recurrence Graves disease and had postoperative hypothyroidism, he was euthyroid with levothyroxine treatment of 175 µg/day. With the diagnosis of rectal cancer in January 2020, the patient underwent a low anterior resection and colostomy. Pathology reported as moderately differentiated adenocarcinoma, followed by chemotherapy and radiotherapy. In October and November 2020, segmental small bowel resection due to radiation ileitis, ileus was performed. Ileostomy was performed in November 2020 for the patient whose colostomy did not work for a long time. Despite medical treatment, ileostomy was planned to be closed after 8 weeks due to the daily discharge of 14 times from ileostomy. It was consulted preoperatively in January 2021 due to TSH:66 mU/l. The oral levothyroxine dose was gradually increased from 150 µg/day to 350 µg/day due to increase in TSH to 80 mU/l, despite appropriate replacement of levothyroxine. When his TSH level was 37 mU/l, free T4 and T3 were normal with 350 µg/day oral levothyroxine, ileostomy was closed in February 2021. The patient's free T4 and T3 values started to increase in 3 days after ileostomy closure, and levothyroxine dose was gradually decreased. The patient has been followed euthyroid with levothyroxine döşe of 150 µg/day.
Conclusion
Intestinal absorption problems may cause high-dose LT4 therapy. The decrease of the intestinal absorption surface and the shortening of the intestinal transit time can be considered among malabsorption mechanisms. Further research should be conducted in the presence of increased serum TSH levels despite high dose LT4 therapy.

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Assesment of serum TSH concentrations in hypothyroid elderly patients (aged 75 and above) under levothyroxine treatment

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Background
Hypothyroidism is a common disorder in elderly. Management of elderly population requires special attention since both undertreatment and overtreatment leads to increased mortality and morbidity. Normal ranges of TSH differs as patients get older and it is recommended as 4-6 mIU/l in patients older than 70–80 years. In this study we aimed to evaluate the TSH concentrations of elderly patients (75 years of age and older) who are under levothyroxine treatment

Method
We retrospectively evaluated elderly patients, aged 75 years and older, who applied to endocrinology clinic for hypothyroidism between March 2018 and November 2020. TSH values of patients who were under levothyroxine treatment were analysed
Results
57 hypothyroid patients who were under levothyroxine treatment were included in the study. 8 patients were male (14%), 49 (86%), were female. The mean age of patients' was found as 79.0. Only 4 (7%) of 57 patients TSH concentration was between 4-6 (mIU/l) ; 23 (40.4%) patients TSH concentration was below 4 mIU/l and even 9 patients' TSH concentration (15.8%) was below 0.5 (mIU/l). 21 (36.8%) patients' TSH concentration was above 6 (mIU/l).
Discussion
Our study showed that few patients stay in the recommended range during their treatment process for hypothyroidism. Elderly patients are more prone to adverse effects related to cardiovascular system with both undertreatment and overtreatment. Furthermore, overtreatment may lead to osteoporosis and fractures. Therefore, careful titration of levothyroxine treatment and monitoring of TSH values are especially important in elderly patients.
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Author Index

A. Ben Abdelkarim AEP355
A, Fathallah AEP355
A. Sheenam AEP386
A. Yaakoub AEP355
Aarella, V AEP646
Aarella, VG AEP699, AEP386
Abadlia, S **PEP2.5**
Abawi, O **AEP235**
Abballe, L OC5.5
Abdallah, Al Salameh PEP13.2
Abdelgader, Y **AEP386**, **AEP699**, **AEP646**
Abdelhedi, F AEP616
Abdelkafi, M EP230, EP68, AEP371, EP117, AEP781
Abdellaoui, W AEP452, AEP455, AEP535, EP139, EP82, EP170
Abdelmoumen, A AEP235
Abdelnour, E AEP565
Abderrahmane, AY AEP348
Abdessalam, H AEP209
Abdesslem, H EP47
Abdul Manaf, R AEP895
Abdulla, E AEP559
Abdullakhodjaeva, N AEP207
Abecassis, F EP210
Abegão Matias, A AEP199
Abellán Galiana, P EP154
Abeyaratne, D AEP842
Abid, M EP192, AEP616, AEP707, AEP361, AEP762, EP211, AEP72, AEP363, AEP197, EP87, EP188, EP7, AEP238, EP56, EP133, EP66, AEP584, EP50, EP91
Abid, S **AEP831,** EP180, **AEP57, AEP71,** AEP58
Abilov, Z **AEP483**
Abir, D AEP654, AEP628, **AEP24**, AEP99, **AEP485**
Abir, EA PEP2.5
Abir, E AEP754
Abir, M AEP355, **AEP691,** EP229
Abir, T **EP82,** AEP341, AEP364, AEP378
Aboobakuru, AA AEP701
Abraham, P AEP533, YI4
Abramova, N PEP10.4, **AEP327**, AEP614, AEP313, AEP656
Abrams, P PEP9.3
Absatarova, Y EP19
Abuín Fernández, J **AEP700**
Abushady, M AEP720
Abushanab, D **AEP17**, **AEP33**
Acarer, D AEP505
Acciai, G AEP861
Ach, K EP141, EP16, AEP771, AEP12, AEP645
Acharya, J AEP439
Acharya N, H **AEP391**
Achour, A AEP602
Achwak, M **EP104**, **EP106**, AEP365, EP58
Açıkbaş, İ AEP192
Acosta-Calero, C AEP174, AEP431, PEP7.2, PEP15.8, AEP800
Adamczewska, K PEP10.8
Adamczewski, Z PEP10.8
Adamidou, F AEP87
Adamidou, L AEP804, AEP274
Adamska, A **AEP390**
Adaway, J AEP6, PEP1.1
Adaway, JE PEP1.5
Adel, M AEP720, AEP41, AEP718, AEP393, EP176
Ademi, Z AEP17, AEP33
Ademoglu Dilekci, EN AEP581
Adhoum, C AEP602
Adimi, A AEP619
Adnan, ML **AEP860**
Afanaseva, A AEP448
Afanasieva, Z AEP155
Afonso, A AEP246, AEP180
Afşar Satiş, N AEP447
Afshan, K OC4.5, AEP594
Agapito, A AEP582, PEP2.1
Agarwal, S OC2.4
Aggeli, C AEP5, AEP63
Aggul, H AEP461, AEP498, AEP557, AEP427
Agha-Jaffar, R AEP662, AEP86
Aghajanova, E EP162
Aghayan, M **AEP335**
Agirrezabalaga Villar, R AEP186, AEP160
Agosti, E **PEP7.8**, AEP166
Agrawal, N AEP264
Aguayo Calcena, A AEP736
Agudo-Macazaga, M PEP14.5, AEP677
Aguirre Echevarria, P AEP703
Ahlquist, J AEP495, PEP1.8
Ahmadizar, F PEP2.2
Ahmadova, K AEP782, AEP884, EP239
Ahmed, Ahmed MG AEP40
Ahmed, F AEP116
Ahmed, I AEP156, OC6.6
Ahmed, N **AEP337**
Ahmed, SF OC14.5, PEP4.8
Ahmed, S EP182, OC4.2, AEP118
Ahmed Ghassane, EA AEP604
Ahn, HY AEP741
Ahn, J PEP5.8
Aimaretti, G AEP201, PEP12.6
Airaksinen, MS OC8.3
Akbaba, G OC8.5
Akcay, S **AEP27**
Akdoğan, L **EP239**, **AEP884**, **AEP799**, **AEP886**
Akdogan Kayhan, M AEP795
Åkerman, A-K AEP4
Akhanli, P AEP816, AEP873
Akın, Ş **OC10.1**, EP4
Akira, S OC8.2
Akkar, I AEP843
Akkari, I AEP358, AEP278, AEP328, **EP119**, **EP137**, **EP140**
Akker, SA AEP495
Akkoç, RF EP60
Akman, T AEP869
Akopova, A AEP299, AEP300
Akram, M **OC4.2**
Akram, M OC4.5
Akram, M **EP182**
Akram, M AEP594
Akshija, I AEP680
Aksoy Altinboga, A AEP882
Akulevich, N AEP573
Al Tawil, D PEP14.2
Al Tikriti, A AEP256
Alassane, I **AEP591**, **AEP859**
Alayci, B AEP109
Alba, R AEP490
Al-Badriyeh, D AEP17, AEP33
Albani, A OC8.1, OC13.1, **PEP13.5**
Albano, E PEP7.8
Albarel, F AEP844
Albayrak, O AEP581
Alber, AB OC5.3
Albiñana, N AEP476
Albor, C AEP122, **AEP647**, AEP111, **AEP512**, EP24, AEP141
Albu, A AEP755, AEP520
Albu, D AEP520
Alcaide-Torres, JA AEP165
Alcántara-Laguna, MD AEP241, AEP382
Aleksandrov, Y **EP227**, **AEP428**
Aleric, I PEP3.3
Alevizaki, M AEP95
Alexander, P AEP260, AEP226, AEP262, EP122
Alexandraki, K OC14.5
Alexandrescu, D AEP735, EP149
Alexis, J EP220
Alferova, P AEP407
Alfifi, S AEP785
Alfred, D AEP309
Alhambra Expósito, MªR AEP132, AEP621
Alharthi, M AEP729
Al-Hashimi, A PEP15.2
Ali, SR OC14.5, AEP116
Ali, S AEP836
Ali, T AEP164
Ali, UA **AEP565**, **AEP529**
Alice Ioana, A AEP487
Alieva, A **EP231**
Alimov, A EP231, **EP214**
Alimov, T AEP330
Alimova, F EP231
Alimova, N AEP263
Aljoied, E AEP671
Alkan, A AEP693, AEP870, AEP877
Alkundi, A EP33, AEP255

Allas, S **AEP644**, **EP226**, **OC6.5**
Allen, S PEP4.8
Aller Pardo, J AEP871
Allison, I PEP14.8
Allora, A AEP114
Almalki, A AEP78
Almaskhanova, A **AEP407**
Almeida, L **AEP395**, AEP168, PEP14.1, **EP209**, AEP48
Almeida, M AEP497
Almeida, M AEP597
Almeida, R AEP543
Almeida Ferreira, M AEP398
Almeida Ferreira, M PEP14.1, EP209
Almeida Santos, T PEP4.7
Al-Mrayat, Ma'en AEP446, AEP853
Alonso, I AEP409
Alonso Felgueroso, C EP78
Alonso Gallardo, SP **AEP250**
Alors-Perez, E AEP384, PEP9.6, OC9.3
Alsalemi, N **AEP206**
Alsancak, Y AEP798, AEP784
Al-Shaibany, A **AEP808**
Al-Sharefi, A AEP394
Altay, FP EP213, AEP688
Altieri, B **PEP1.7,** OC11.1, AEP838, AEP826
Altieri, P AEP153
Altunoglu, A AEP869
Altuntas, Y AEP498, AEP524, AEP464, AEP109
Alvarez, C V. **PL3.1,** OC3.2, OC8.3
Álvarez Escolá, C OC9.1, AEP542, AEP103, AEP531, AEP478, AEP504
Alves, H AEP395, AEP168, **PEP14.1**, EP209, AEP48
Alves, MG. PEP4.4
Alves, M AEP251
Alves, P **EP28**
Alzás Teomiro, CM **AEP382 , AEP227**
Amado, V EP129, OC9.4
Amal, M AEP368, AEP770, AEP347
Amaral, C AEP551, AEP398, AEP254
Amaral, S **PEP2.1**, AEP246, AEP115
Amat-Bou, M PEP12.4
Amatrudo, F YI1
Amayo, E AEP817
Ambawatte, S EP147, AEP320
Ambrogi, C AEP627
Ambrosio, MR PEP15.3
Ambrozaityte, L PEP5.5
Ambroziak, U PEP11.6
Ameliyanovich, M PEP15.4
Ameni, S AEP764
Amin, A AEP529
Amina, M EP18, **AEP738**
Amine, H AEP549
Amir, M AEP720
Amodeo, AL AEP412
Amodeo, R PEP14.3
Amodru, V AEP844
Amouri, W AEP777
Amrouche, C EP47, AEP209
Amzar, D-G AEP146, AEP889, AEP868
An, V AEP203
Anaforoglu, İ **AEP851**, **AEP660**
Anagnostis, P **JSC1,** AEP414, AEP652, **AEP574**, **AEP225**, **PEP6.5**
Anagnostouli, M AEP95
Anandappa, S AEP751
Anca Maria, C AEP848
Anda, D EP158
Andela, CD AEP537
Anderlová, K PEP2.3
Andersen, CY S13.2
Anderson, RA **MTE14**
Andjelkovic, M AEP404
Andoniadou, CL OC1.2
Andreadaki, E AEP49
Andreadi, A **EP64**
Andreas, S AEP838
Andreassen, M PEP13.3, PEP3.5, **AEP481,** PEP3.4
Andreea, B AEP146
Andreeva, A **AEP425**
Andrei, A EP179, AEP429
Andrei, AM **EP32**
Andreo López, MDC AEP333, **EP79**, EP207
Andrés Imaz, N AEP186, AEP160
Andrew, R OC15.1
Andric, D AEP606
Andric, J AEP102
Andújar Plata, P AEP521
Ange, D AEP604
Angelini, F PEP8.2, AEP840
Angelopoulos, T AEP823
Angelousi, A **AEP5**, **AEP49**, **OC14.4**, PEP1.7, AEP63
Anık, İ AEP506
Anis, G AEP579, AEP864
Anisia, M **AEP622**, **AEP150**
Anne-Flore, H AEP648
Anne-Sophie, H PEP6.4
Annunziata, S OC5.5
Anselmo, J AEP713
Antic, D AEP522
Antognoli, R AEP802
Antonelli, A AEP642
Antonelli, G AEP633, OC5.4, AEP641
Antonijevic, E AEP404
Antonin, L AEP859
Antonio Sampedro Núñez, M OC1.1
Antoniotti, V AEP166
Antoniou, A AEP97
Antonyuk, O **EP120**
Anwar, M **AEP265**, AEP638, AEP215, **AEP559**
Aoki, S AEP167
Apaydin, T **AEP331**, **AEP534**
Apostoloupoulou, K AEP183
Appelman-Dijkstra, N AEP116, OC6.3
Appelman-Dijkstra, NM OC14.5
Appenzeller, S OC11.1, AEP838
Arabi, M AEP453, AEP424
Aragüés, JM AEP411, AEP23, AEP749
Aramburu Calafell, M EP152
Aramburu Calafell, MT AEP703
Arana Arri, E AEP736
Arana Suarez, T AEP160, AEP186
Aranda Velazquez, G **PEP5.4**
Arapova, S AEP416
Araújo, B AEP56, AEP107
Araújo, BF AEP198, **AEP273**, **AEP247**, **AEP96**
Araújo, CA **AEP198**, AEP273, AEP247, AEP96, AEP430
Araujo Castro, M AEP499, **OC1.1,** AEP14
Araz, M AEP44
Arbouche, Z AEP619
Arcella, A PEP13.1
Archero, F AEP166
Areal, J AEP251
Aresta, C AEP9, AEP21
Argatska, A **AEP636**, **AEP719**
Argentesi, G OC1.5
Argentina, M OC14.1
Argüelles Jiménez, I AEP871
Argyropoulou, E EP35
Arhire, A Ioana **AEP813**
Arifoglu, U AEP795, AEP850
Ariza Jimenez, JA AEP396
Arizanovic, Z AEP16
Arjona-Sanchez, Á AEP384
Arlorio, M PEP7.8
Arlt, W PEP11.6, OC11.1, AEP332, OC11.5, AEP175, PEP14.8, PEP1.5, OC4.1
Armeni, E AEP236, **AEP97,** AEP90, **AEP570**
Armentia Del Pozo, AC AEP160, AEP186
Arnaldi, G PEP8.5, PEP14.7
Arnas-Leon, C AEP174, AEP800, PEP7.2, PEP15.8
Arnaud, D PEP6.4
Arnaudova, M AEP230
Arnqvist, H AEP789
Arola, J PEP9.1
Arosio, M OC6.4, AEP9, AEP21, PEP3.1, OC8.4, YI2, AEP651
Arosio, M AEP475
Arrese, M OC7.4
Arshad, MF **AEP833**
Arslan, IE AEP816, AEP873
Arteaga Ossa, MM AEP160, AEP186
Artero Fullana, A EP125
Artykbaeva, G **AEP357**
Arumugasamy, M EP67
Arvaniti, A **YI3**

Arvat, E OC10.6
Arvat, E AEP642, OC3.2
Asare, P AEP832
Asatiani, N **AEP169**
Asbar, H **AEP765**, **EP161**
Ashraf, T AEP161
Asia, M OC11.1
Askari, F **EP183**
Askitis, D **AEP769**
Asma, BA AEP368, EP171, AEP770, EP229
Asma, G EP171, AEP306, EP159
Asma, K EP185, EP23
Asonitis, N AEP49
Aspiazu Abasolo, A AEP160, AEP186
Aspichueta, P AEP252, OC7.4
Assarrar, I AEP285, AEP535, EP170, AEP303
Assié, G PEP11.5, OC1.3, OC9.5, OC13.1
Assmann, T PEP12.7
Assunção, G AEP138
Assyov, Y AEP92, AEP200
Astl, J OC10.2
Astolfi, D AEP644, EP226
Atacan, H AEP640
Atanasova, K AEP92
Athanasiou, K AEP95
Athanasouli, F PEP3.6, AEP49, OC14.4
Athanassiou, L **AEP310**, **AEP130**, AEP121, AEP68, AEP79
Athanassiou, P AEP310, AEP79, AEP130, AEP68
Atmaca, A OC3.3
Attanasio, R AEP733, OC5.2, AEP734
Auchus, R OC3.1, **PEP1.2**
Auer, M **PEP1.1**
Auer, MK AEP6
Augoulea, A AEP236, AEP90, AEP570, AEP97
Aung, T AEP94
Auriemma, RS YI1
Auvinen, A-M OC2.2
Auvinen, J OC2.2
Aversa, L PEP8.2
Ávila Rubio, V AEP211
Aviles Perez, MD EP207, AEP136
Awasthi, R AEP264
Ayala Corao, L AEP272
Ayari, S AEP625, EP3, AEP609, AEP284, EP181
Aycha, G AEP561, EP224
Aydin, C AEP884, AEP872, AEP693, AEP782, AEP870, AEP799, AEP886, AEP811, AEP865, EP238
Aydin, K OC10.1
Aydın, S EP60
Aydin Mericöz, C OC10.1
Ayechi, N AEP887
Ayedi, K AEP366
Ayhan, S AEP865
Aynetdinova, A AEP139, AEP128, YI12, AEP106, EP22, AEP124, AEP101
Ayodele, O **PEP6.8**, **PEP6.6**, **PEP6.7**
Azaiez, A AEP558
Azam, S AEP120
Aziz, A **AEP881**
Azizyan, V AEP501, AEP468, AEP566
Babaev, K AEP263
Babenko, A AEP219
Bacete Cebrián, S AEP316
Bacha, T AEP352
Bachelot, A AEP859
Baciu, I AEP659, AEP479
Baciu, IF AEP539
Baculescu, N AEP659, AEP479
Bačun, B AEP445
Bačun, T **AEP445**
Badiu, C OC3.3, AEP735, AEP2, **AEP54**, AEP757, AEP672, **PEP13.4**
Baetu, M **AEP672**
Bagci Culci, P AEP27
Bagias, C AEP127
Baha, Z AEP441, AEP373, AEP772, AEP341, AEP364, AEP378
Bahar, N **AEP31**
Bahcecioglu Mutlu, AB **AEP342**
Bahloul, Z EP188
Bais, A AEP274
Bakalov, D AEP92
Bakir, M EP54
Bakkar, S PEP6.5
Bakker, SJL OC7.1
Balacchi, C PEP11.4
Balas, M AEP550, **AEP889**
Balcere, I PEP3.7
Balciuniene, J PEP15.6
Baleanu, F EP187, EP15
Baleanu, MC **PEP1.4**
Baleiras, C EP13
Ballarino, C AEP470
Ballesteros-Pomar, M AEP837
Balsak, BOT AEP847
Baltacioglu, F AEP534
Bammou, S **AEP348**, **AEP746**
Banala, RR AEP726, AEP389
Bancos, I AEP546, OC11.5, PEP11.6
Banfi, D **OC13.4**
Bangaraiahgari, R AEP726, AEP389
Bangariahgari, R AEP389, AEP726
Bani, D PEP11.3
Banica, A AEP695
Banica, T **OC4.6**
Bantwal, G AEP264
Banwaith, T AEP439
Banys, V AEP661
Baptista, C AEP198
Barahona Constanzo, MJ AEP282
Baralić, K AEP404
Baranowska-Bik, A AEP547
Baranowski, ES. PEP1.5
Barbieri, AM PEP3.1, OC8.4
Barbosa, AP AEP876
Barbosa, D EP210, AEP311
Barbosa, M **AEP224**
Barbot, M PEP14.7
Barbuceanu, AL **EP172**
Bardet, C OC6.2
Baretić, M **AEP706**
Bargaoui, Z **AEP290**, AEP301
Bargiota, A **AEP494**, **AEP635, AEP188, AEP127, AEP379**
Barisson Villares Fragoso, MC OC1.3, OC11.5
Barmpa, E AEP494, AEP635
Barnes, C PEP1.2
Baronio, F PEP4.8
Baroukh, B OC6.2
Barrera Martín, A AEP349, AEP132
Barrio, E AEP38
Barros, A PEP4.4
Barros, L EP8, AEP107, AEP430
Bartmanska, M **PEP8.8**
Barzo, P EP160
Bas, K EP232
Baścik, B AEP151
Başçıl Tütüncü, N EP213
Basel, M AEP77
Baser, H AEP795, AEP882, AEP865, EP233
Basham, K **S22.1**
Bashari, W YI4, AEP533, OC1.5
Bashari, WA PEP3.8
Bashir, J AEP122, AEP647, AEP111, AEP512, EP24, AEP141
Basile, U PEP4.2
Basile, V OC11.4
Basinska-Lewandowska, M AEP125
Bassett, P EP54
Bastos, M AEP587, AEP18
Basyuga, I AEP678
Batalov, A AEP413
Batanero Maguregui, R AEP221
Batens, A-H YI9
Batman, A AEP524
Batool, M **EP21**, **EP67**, **AEP750**, **AEP65**
Battelino, T AEP163, PEP4.8
Baudin, E OC11.5
Baumane, K PEP15.6
Baumgartl, K PEP7.5
Bavor, P OC10.2
Bayar, I **AEP657**, **EP190,** AEP831, AEP32
Baydar, E AEP427
Bazyka, O AEP377
Bchir, N EP3, AEP625
Bearss, NR AEP177
Beccaria, M AEP835
Bechir, K EP74
Beckers, A OC3.3, AEP839
Beckert, M OC6.6
Bednarczuk, T PEP8.8
Beeharry, D **AEP118**
Behera, K **AEP593**
Beiglböck, H AEP62
Belaid, T **AEP355**, AEP691
Belaya, Z OC3.1, AEP416, OC8.2, AEP501
Belaya, Z AEP407, AEP566, PEP8.7
Belghuith, N AEP616
BelHadj Miled, H AEP781, EP117

Belkacem, S **AEP525**, **AEP435**, **EP191**, **AEP257**, **AEP526**, **AEP258**, **AEP295**
Bellahreche, Z **EP234**
Bellakhdhar, M AEP355, AEP691, AEP780, AEP766, AEP403, AEP371, AEP781, EP117, EP230, EP68
Bellary, S AEP248
Belli, S PEP15.5
Bellia, A EP64
Bellone, S AEP201, AEP166
Belousov, L AEP407
Belovalova, I AEP126
Belyakov, I AEP428
Belyi, D **AEP377**
Ben Naceur, K EP58
Ben Abdallah, B AEP771
Ben Abdelkarim, A AEP771
Ben Abdelkerim, A EP141, AEP645
Ben Abdelkrim, A EP16
Ben Ameur, W AEP771
Ben Amor, B AEP831, AEP657, EP190, **AEP32**
Ben Amor, N AEP240, AEP314
Ben Bnina, M **EP192**
Ben Boubaker, R YI5
Ben Brahim, A AEP209
Ben Brahim, R EP47
Ben Elhaj, W AEP393, EP37
Ben Hadj Ali, Z EP107, EP124
Ben Jemaa, M AEP57, **EP180**
Ben Mami, F AEP301, EP106, AEP290, EP43, AEP283, AEP275, AEP321, EP65, AEP46, AEP714, PEP2.8, AEP365, EP58, EP107, EP124
Ben Memi, F EP105
Ben Nacef, I **AEP41**, AEP561, **AEP718**, EP224, **AEP75**, EP146, AEP589, **AEP437**, **AEP438**, **AEP419**, AEP567, **AEP420**, **EP138**, AEP569, **AEP393**, AEP80, AEP747, EP29, **EP176**, EP130, EP225, AEP519, **EP37**, EP134
Ben Othman, W AEP645
Ben Rhouma, B AEP616
Ben Salah, D EP50, AEP440, AEP762, EP211, AEP764, AEP731, **AEP70**, AEP210, EP62, EP71, EP175, AEP306, EP165, EP173, EP159, AEP366, EP200, EP56, AEP253, EP7, AEP197, EP133, EP75, AEP72, EP192, AEP361, AEP362, AEP548, EP91, EP66, EP87, AEP363
Ben Salah, R **EP188**, AEP654, AEP628, AEP24, AEP99, AEP485
Ben Salem, H AEP32
Ben Teber, S **AEP762**, EP211
Ben Yakhlef, S EP99, EP44, AEP452, AEP455, **EP139**, **AEP369**, EP82, AEP53
Benabdelkrim, A AEP12
Bendlova, B OC10.2, PEP2.3, AEP181
Bengoa Rojano, N **AEP14**
Benido Silva, V EP111, **PEP5.3**, **OC10.3**
Benítez Valderrama, A AEP504, AEP478
Benítez Valderrama, AP **AEP531**
Benito Castaño, I AEP736
Ben-Joseph, R AEP242
Benlafqih, M AEP765
Benndorf, G AEP383
Bennet, W AEP833
Benothman, W **AEP12**, AEP202, **EP16**
BenSalah, D AEP584
Bensing, S AEP4
Bensmaine, F **EP220**
Benzekri, L AEP698
Berbel, I **AEP384**
Berchialla, P OC11.4, OC11.5
Bercu, B AEP695
Berdeli, M AEP482
Berg, JP OC8.6
Berger, I **OC1.2**
Berker, D OC3.3
Berkovich, G AEP108
Berlanga, P AEP81
Berman, R PEP6.6
Bernabeu Morón, I AEP521
Bernaldo Madrid, B AEP38
Bernal-Lopez, MR AEP165
Bernard, C AEP31
Bernardo, G OC7.5
Bernardo, W AEP493
Berney, D OC1.5
Berrabeh, S **AEP535**, **EP170**
Berruti, A OC11.5
Berta, E AEP410
Bertherat, J PEP8.5, PEP11.5, OC1.3, PEP1.6, OC11.5, OC9.5, PEP4.8
Besbes, G AEP558
Besrour, C **AEP727**, AEP561, EP9, EP11, AEP718, EP224, AEP75, AEP589, AEP437, AEP438, AEP567, **AEP569**, **AEP80**, **AEP747**, **EP29**, EP176, **EP130**, **EP225**, **AEP519**, **EP134**
Bessiene, L PEP11.5, OC9.5
Bestepe, N PEP15.1, AEP884, AEP846, AEP882
Betsi, G PEP10.2, AEP13
Beukhof, C AEP592
Beuschlein, F OC11.5, OC11.6, AEP8, OC14.6, OC11.2, PEP11.6
Bex, M OC3.1
Bezlepkina, O AEP721, AEP692
Bhandarkar, P AEP264
Bhatt, D AEP533, YI4
Bhattacharya, D AEP488
Bhattacharya, S AEP264
Biagetti, B **AEP490**
Bianchi, A AEP840
Bibik, E **AEP139**, **EP30**, AEP128
Bicho, M AEP409, AEP876, **AEP228**
Bichri, S **AEP514**, **AEP515**, **EP168**
Bidlingmaier, M AEP6, PEP1.1, AEP45
Biermasz, N OC13.6, PEP3.2, **PEP8.1**, PEP8.3, PEP13.6, OC6.3
Biermasz, NR OC14.5, AEP537
Biertho, L OC15.1
Bifoume Ndong, CL **AEP604**
Bilaya, V AEP377
Bilbao, J OC7.5
Bilbao Garay, I EP152, AEP703
Bilen, O AEP498, AEP557, AEP427, AEP461
Bilezikian, J AEP104
Bilginer, MC EP110, AEP326, AEP724, AEP473, AEP50, AEP343, EP73, EP4, AEP675, EP221, EP53, **AEP879**
Bilha, S AEP98
Biller, B PEP8.5, OC8.2
Bindra, J OC2.4
Bintintan, A AEP484
Bircan, BE AEP585
Bircan, MG OC8.5
Bird, N OC1.5
Birgi, HK **AEP469**
Bishouty, N AEP730
Bison, B AEP500, AEP477, OC3.5, AEP528
Bitar De Zayas-Enriquez, A **EP167**
Bitat, S PEP1.8
Bivolarska, A AEP413
Bjorvatn Sævik, Å **AEP4**
Blaggan, P PEP14.8
Blanco, J EP154
Blanco, L **AEP466**
Blanco-Acevedo, C YI8, OC9.6
Blankenstein, O PEP4.8, PEP1.3
Blanquez Martinez, D AEP136
Blázquez-Encinas, R AEP384, **OC9.3**
Bleier, J **AEP20**
Bliziotis, I AEP310, AEP79
Boccuzzi, A AEP29
Bodor, M AEP410, AEP634
Boekhoff, S AEP500, AEP462, AEP477, OC3.5, **AEP528**
Boelaert, K PEP14.8
Bogalho, P AEP115, PEP2.1
Bogavac, T EP126, AEP402
Bögl, M AEP62
Bogomilov, I **AEP810**
Bogusławska, A AEP538, **AEP399**, **AEP472**
Bohaltea, R **AEP757**
Boharoon, H **EP128**, **AEP486**

Bohyan, V PEP11.8
Bokobza, E **OC14.1**
Bolanowski, M OC3.3
Bolatova, A AEP545
Boletis, I OC14.4
Bollanti, l AEP575
Bollerslev, J AEP463, OC8.6
Bona, E AEP166
Bondar, I OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6
Bondarenko, V AEP611
Bonnar, C **AEP674**
Bonnema, S OC10.5
Bonnema, SJ **D3.1**
Bonomi, M OC4.3, PEP4.8
Borges, A EP13
Borges de Souza, P PEP15.3
Borges Duarte, D AEP88, **AEP673**, **AEP398**
Borges-Canha, M AEP69, **AEP212**
Borgwardt, S AEP527
Borissova, A-M AEP296
Borlea, A AEP889
Bornaz, E EP124, EP45, EP107
Bornstein, S OC1.2, PEP11.2
Bornstein, SR OC12.1
Borozan, S **AEP442**, AEP605, **AEP513**
Borretta, G AEP637
Borshchev, Y OC12.3
Borson-Chazot, F OC1.3
Borysewicz-Sanczyk, H AEP797
Borzan, V AEP159
Boscaro, M OC3.3
Boschetti, M PEP14.7
Boscic, D AEP102
Bosdou, J AEP574, AEP225
Bosi, E PEP2.4
Bosna, IC **OC8.5**
Bossowski, A **AEP892**, **AEP818,** AEP797
Bost, F OC14.1
Bostan, H AEP816, AEP873
Bostnavaron, M OC3.3
Bostoganashvili, N **AEP305**
Botelho, M EP151
Botella-Carreter, JI AEP14
Bothou, C **OC11.2**, **OC14.6,** AEP225
Bøtkjær, JA **S13.3**
Bottiglieri, A AEP77
Bouca, B AEP199
Bouça, B AEP246, **AEP115**
Boudaya, MS AEP715
Boudina, M **EP35**
Boufettal, H AEP615
Bougacha-Elleuch., N AEP707
Bouguerra, H **AEP619**
Bouhiya, S AEP269, EP93, EP94, AEP231, AEP350
Bouichrat, N **EP99**, **AEP117**, **AEP601**, AEP344, EP139
Boujelben, K EP121, AEP306, AEP73, EP173, EP199, AEP216, AEP307, AEP287, EP163
Boujelben, K EP192
Boujlben, K EP50
Boukhayatia, F AEP220
Bouki, K AEP13
Boukriba, S AEP123
Bouldoires, B AEP74
Boulet, N **PEP12.1**
Boulgheraief, A AEP458
Bouloumié, A PEP12.1
Boura, E AEP87
Bourdeau, I OC11.5
Bourko, I AEP891
Boutheina, C AEP202, AEP237
Boutzios, G **EP195**, **PEP10.5**, **EP34**
Bouvattier, C PEP4.8
Bouys, L OC1.3
Bouzid, A **AEP154**, **EP100**, **AEP147**, **EP38**
Boyadjieva, N AEP810
Boyanov, M **AEP92**
Bozic Antic, I AEP402, **EP126**
Bozkur, E AEP505, **AEP422**, AEP489
Bozkus, Y **EP213**, AEP688
Brac de la Perrière, A PEP4.8
Brahma, A AEP67
Brancaccio, U AEP633, OC5.4, AEP641
Brancatella, A **AEP875**, **AEP880**
Brandi, ML OC14.5
Branisteanu, DD AEP98
Bratcikoviene, N AEP661
Bravis, V EP6, AEP86
Bravo, S AEP252
Brazil, J AEP674
Brazil, J **EP54**
Breault, D AEP8
Breton, I AEP837, **MTE7**
Bretón Lesmes, I AEP834
Briansó Llort, L **EP88**
Briceño, J EP129, OC9.4
Briet, C YI5
Briet, M YI5
Briggs, A PEP6.8, PEP6.7
Brignardello, E OC10.6
Brito, D AEP749, AEP411
Britvin, T PEP11.8
Brix, K PEP15.2
Bronstein, MD **JS4.1**
Brook, A AEP842
Brooke, A AEP495
Brown, M OC1.5
Brucker, S PEP4.8
Brue, T AEP844
Brugieres, L AEP81
Brunelli, C OC5.5
Bruno, B OC10.6
Bruno, C **PEP4.2**, PEP8.2
Bruno, L AEP2
Brutskaya-Stempkovskaya, E AEP734, **AEP229**
Bryce, J **OC14.5**, AEP116
Bucci, B AEP28
Buckley, A AEP256
Buczyńska, A AEP390
Buffet, C AEP695
Bugalho, MJ YI11
Buha, A **AEP404**
Bulat, Z AEP404
Bülent, P OC11.3
Bunea, I EP197
Buque, X OC7.4, AEP252
Burak, A **EP169**, **AEP244**
Burcea, IF AEP568
Burgerhart, J AEP280
Burger-Stritt, S AEP35
Buryakina, S AEP566
Busby, M AEP175
Busca, A OC10.6
Buschmann, LK AEP462
Butz, H AEP3
Büyükkuşcu, A AEP464
Bykova, E AEP425
Byrne, S AEP191
Bystrianska, M **AEP737**
Bystriansky, A AEP737
C. Bastos, F AEP311, EP210
C. Lemos, M AEP224
Caballero, MJ AEP408
Cabeza, M **AEP450**, **OC13.2**
Cabrera Gonzalez, MI EP52
Caccioppoli, C OC2.6
Cadogan, S **AEP443,** AEP750
Cai, F OC7.6
Cai, R OC3.2
Cairoli, E OC6.4
Caixàs, A AEP476, AEP466
Cakal, E AEP873, **AEP816**
Cakir, B AEP856, AEP865, AEP799, AEP846, AEP795, AEP693, PEP15.7, AEP879, AEP814, AEP870, AEP869, AEP796, AEP884, AEP872, AEP852, AEP825, AEP782, AEP850, PEP15.1, AEP882, AEP794, AEP788, AEP886, EP239
Cakir, E AEP640
Cakir, I AEP505, AEP422
Cakır, B AEP847, AEP811, AEP877, EP238, AEP894, AEP885, EP233
Çakir, I AEP489
Calabrese, A **OC11.4**, OC11.5
Calañas Continente, AJ AEP241
Calañas-Continente, A AEP227
Calatayud, M OC9.1
Caldas, R AEP251
Çalışkan Burgucu, H AEP798, AEP784
Calle, A AEP434, EP5, AEP38
Calvo Latorre, J **PEP3.8**
Campi, I YI2
Campos Lopes, S **AEP251**, **AEP148**, **AEP189**
Camps Herrero, C EP125
Can, M AEP798, AEP784
Can Erdi, Z EP232, EP164
Canat, MM AEP524, AEP464, AEP109
Candeias, N AEP180
Cangiano, B OC4.3
Cannavaro, D AEP651
Cannavò, S AEP630
Cantini, G PEP11.3, **PEP11.1**
Canturk, Z AEP506,
Canu, L PEP11.3, PEP11.1, PEP1.7, OC11.5
Cap, J EP17, AEP129, EP203

Capatina, C AEP659, AEP479, AEP536
Capelli, R AEP19
Capitão, R AEP311
Capota, R AEP52
Cappa, M PEP4.8
Cappabianca, P YI1
Cappiello, G AEP77
Caputo, M **AEP201**, PEP12.6, AEP166
Caragheorgheopol, A AEP479, AEP482, AEP54
Caramello, V AEP29
Cardenas Salas, JJ **AEP809**
Cardona Attard, C **OC4.4**
Cardoso, C AEP409, EP210
Cardoso, H AEP254
Cardoso, MH AEP673, AEP137, AEP629, EP111, PEP5.3, AEP551
Cardoso, O EP13
Cardoso, R AEP577
Cardoso, V AEP650
Caric, B AEP517
Carine, C AEP591, AEP859
Carla, S OC3.3, OC8.2
Carlsen, S AEP4
Carneiro, F OC14.3
Caro, MT OC9.3
Caro, T PEP9.6
Caron, P PEP12.1, AEP612
Carrageta, DF **PEP4.4**
Carrasco, M AEP110, AEP768
Carrasco-Núñez, N AEP450, OC13.2
Carrasco-Valiente, J YI6
Carvalho, A OC10.3, PEP5.3, AEP756, AEP137, AEP398
Carvalho, D OC3.1, AEP69, AEP176, PEP10.6, AEP212
Carvalho, R AEP148, AEP398, AEP138
Carvalho, T PEP4.7
Casale, D AEP29
Casamitjana, L AEP476, AEP466
Casanovas Marsal, JO AEP736
Casas, L AEP282
Cassarino, MF AEP15
Castagna, MG AEP642
Castaño, JP OC9.3, EP129, AEP397, OC3.2, AEP384, OC3.4, OC9.4, YI8, OC9.6, OC9.2, AEP382
Castaño Gonzalez, L AEP736
Castedo, JL AEP176
Castelli, L AEP15
Castellini, G AEP803
Castellino, L AEP114
Castelo Fernández, B AEP871
Casteras, A AEP490, **OC9.1**
Castinetti, F AEP844, OC14.5
Castro, A **AEP110**, AEP768
Castro, E AEP110, AEP768
Castro, JJ EP86, EP76, PEP7.7
Castro-Correia, C EP178, AEP69
Catalano, R PEP3.1, OC8.4
Catalina, P EP127
Catarino, D PEP4.7, AEP430
Cavadas, S AEP148
Cavagnini, F OC3.3
Cavaletto, M AEP166
Cavnar Helvacı, B AEP894
Ceccarini, G PEP12.6
Celi, A AEP802
Celik, A OC8.5
Çelik, AM AEP480
Celine, M PEP6.4
Cellai, I AEP861
Cengiz, D **AEP581**
Cepeha, CM AEP146
Cera, G **AEP642**
Cerquetti, L AEP28
Cesareo, R AEP627, AEP104
Cetinarslan, B **AEP506,** EP145
Çetinkaya, E EP233
Ceyhan, K AEP44, OC5.6
Ceylan, AC AEP782
Ceylan, S AEP506
Chaaben, K AEP237
Chaabouni, M EP165
Chabchoub, I **AEP440**, **EP75**, **AEP210**
Chadia, Z EP185, AEP609, EP69, AEP284, EP9, EP11
Chadli, A AEP626, AEP66, AEP347, AEP359, AEP417, AEP418, AEP752, EP25, AEP670, AEP732, AEP776, AEP514, AEP515, EP168
Chadli Chaieb, M EP171
Chaeib, M AEP12, AEP771, EP16
Chai, YJ AEP741
Chaieb, M AEP645, EP141
Chaima, Z EP208, AEP753
Chainsukh Loya, A AEP383
Chaker, F EP80, EP180, AEP715, AEP220, EP23, AEP761, EP215, EP157, AEP58, EP155, AEP727, AEP558, AEP34, AEP57, AEP47, AEP71, AEP123, EP216
Chaker, M EP215
Chakhovich, T AEP667, AEP668, AEP669
Chanson, P OC1.3, PEP13.6, PEP4.8
Chantada Vázquez, MDP AEP252
Chapman, R AEP175
Charfeddine, S AEP777
Charfi, H AEP707, AEP731, **AEP25**, **EP206**, AEP339, **EP74**, **EP10**, EP89, AEP777, AEP361
Charfi, N. AEP238, EP66, AEP762, EP211, AEP764, AEP731, AEP70, EP75, AEP210, EP62, EP71, EP175, AEP306, EP165, EP159, AEP548, AEP363, AEP440, AEP584, AEP72, EP192, EP7, EP91, EP50, AEP362, AEP197, EP133
Charles, S OC6.2
Chatti, H AEP324, AEP709
Chatti, HA **AEP460**, EP150, AEP563
Chatti, H-A AEP558, EP157, AEP761
Chatti, K AEP887, AEP883
Chatzi, S EP195, PEP10.5, EP34
Chatzivasileiou, P AEP570
Chaussain, C OC6.2
Chaves, AC AEP138
Chaves, C **AEP713**, **AEP600,** AEP497, AEP597
Chawla, A AEP824
Chawla, R **AEP824**
Chawla, S AEP824
Chayma, BHS EP3, **EP185**, **EP69**, **AEP284**
Chebbi, D AEP485
Chedia, Z EP3
Chen, J-L AEP414
Chen, W PEP14.8
Chen, X **OC3.6**
Chen Ku, C OC3.1
Cheow, H OC1.5
Cherchir, F AEP47, AEP123
Cherchir, F AEP34
Chereau, N AEP695
Cherebillo, V AEP545
Chernenkov, Y PEP10.7
Chernikov, R AEP144
Chernova, A EP222
Chevalier, N OC14.1
Chiboub, M **AEP202**, **AEP237**
Chifa, D AEP24, AEP99, AEP485
Chifu, I **AEP35**
Chihaoui, M EP155
Chihaoui, M AEP57, AEP34, AEP47, EP166, EP180, AEP761, AEP220, EP80, EP157, AEP64, AEP71, EP23, AEP558, AEP123, EP174, AEP58, EP181, AEP715, AEP727, EP216
Chiheb, S EP25
Chiloiro, S **AEP840**
Chinchilla Gallo, SP AEP83
Chiocchetti, A PEP7.8
Chiodini, I OC6.4, AEP9, AEP21
Chiraz, A PEP2.5
Chitalia, N AEP367
Chmiel, J AEP151
Chondrou, A AEP570
Chong, SC **PEP7.4**, **AEP820**
Chonov, V AEP719
Choreftaki, T AEP5, AEP10, AEP63
Chorti, A AEP87
Chorti, A PEP6.5
Chortis, V OC11.1, PEP11.6

Chouchane, l **EP230**, **EP68**, **AEP766**, **EP117**, **AEP371**, **AEP781**, **AEP403**
Chouchane, L **AEP780**
Choudhary, M AEP792
Chovanec, M OC10.2
Chowen, JA **S19.1**
Chrisoulidou, A EP35
Christ-Crain, M AEP465, AEP527, AEP89, OC4.1
Chrysoulaki, M **AEP13,** PEP10.2
Chtourou, K AEP777
Chuah, M AEP787
Chukur, O **AEP682**
Chzhen, T **AEP59**
Cianga, P AEP98
Ciardi, A AEP19
Cidade-Rodrigues, C **AEP497**, **AEP597**, **AEP650**
Ciftci Dogansen, S AEP489, AEP505, AEP422
Cignarelli, A **PEP4.3**, OC2.6
Cil Sen, E AEP524, AEP464, AEP109
Cinar, N OC8.5
Cinti, S **MTEBS1**
Cipriani, S AEP803, AEP857, **AEP861,** AEP835
Ciria, R OC9.4
Ciria, R EP129
Cirmanová, V PEP2.3
Ciubotaru, GV AEP536
Cizmecioglu-Jones, FM AEP105
Claahsen-van der Grinten, HL PEP4.8
Claret, M AEP252
Clark, S OC12.6
Clarke, BL AEP84, OC6.6
Clavel, S OC14.1
Clemente-Postigo, M **AEP165**
Clemmons, D OC12.2
Cobos Palacios, L EP103, EP70
Coelho, C EP13
Coin-Araguez, L AEP165
Coisson, JD PEP7.8
Colao, A PEP4.8, AEP412, PEP14.7, YI1
Colard, M AEP31
Colasanto, A PEP7.8
Collet, S **AEP586,** AEP451
Collins, C EP54
Comeglio, P AEP861
Comninos, A AEP86
Compagnoni, C AEP19
Congiusta, N **OC12.5**
Connelly, MA OC7.1
Connolly, SP AEP728
Constantin, T AEP695
Constantine, S OC1.3
Constantinescu, D AEP98
Constanze, H **PEP11.2**, OC11.6
Conte, E PEP4.3
Conti, F AEP575
Contini, D PEP5.4
Contreras Pascual, C AEP760, **EP202**, AEP454, AEP381
Conway, GS OC4.4
Cooke, S AEP488
Cools, M PEP4.8, **JS6.3**
Coombs, N AEP140
Cooney, R PEP14.8
Cooper, C **PL5.1**
Coopmans, E **AEP839**
Coppari, R OC7.5
Copuroglu, E AEP796, AEP825
Çorapçıoğlu, D AEP342. AEP44, OC5.6
Corbetta, S **PEP6.2**, **OC6.1**, **AEP131**, AEP9, AEP21
Corchete Prats, E AEP316
Cordan, Ilker AEP798, AEP784
Cordeiro, MC AEP311
Cordero-Vazquez., E AEP490, **PEP5.7**
Cordoba-Chacon, J OC7.2
Corkery, L AEP552
Corlan, AS **AEP848**, AEP889
Corneci, C AEP672
Corno, C AEP861
Correia, R EP210
Correia, RDI AEP137
Correia, S AEP168, PEP14.1, EP209, **AEP48**
Corridoni, D YI3
Corripio, R AEP476
Cortesão, P PEP4.7
Cortese, L PEP5.4
Cos, FX **PEP2.4**
Coskun, H EP110, AEP326, AEP724, AEP473, AEP50, AEP343, EP73, EP4, AEP675, EP221, AEP291, EP53
Costa, AR AEP756
Costa, C EP178, AEP69
Costa, MM AEP311
Cota, D OC12.6
Cotoi, L **AEP146**, **AEP868**
Coutinho, J AEP115
Couto, J AEP742, AEP56, AEP743
Covelli, D YI2
Cowley, S AEP443
Cox, J AEP662, AEP86, OC1.6, PEP11.7
Cox, R YI3
Craig, S AEP488
Crepostnaia, D AEP836
Crescenzi, A AEP627
Crespo, A AEP115
Crespo Herrero, G AEP871
Crispim, D **PEP12.7**
Cristescu, I AEP134
Cristiana, C **EP127**
Cristina Taujan, G **EP187**
Critchley, H AEP414
Crotty, G AEP191
Cruces Vega, E AEP809
Cruickshank, K OC1.5
Cruz, AR AEP756
Cruz, A AEP110, **AEP768**
Cuccia, M AEP470
Cuccurullo, A AEP412
Cucu, C EP172
Cuellar Lloclla, EA **AEP396**, **AEP408, EP123**
Cuenca Cuenca, JI PEP9.8
Cuesta Hernández, M AEP434, EP5, AEP38
Cuhaci Seyrek, FN AEP886
Cuhaci Seyrek, N AEP872, AEP794
Culler, MD AEP644, EP226, **OC12.2**, OC6.5
Cultrera, A AEP29
Cuñarro, J AEP267
Cunha, F AEP650, AEP597, AEP497
Cuny, T AEP844
Cuomo, F AEP572
Currò, N YI2
Curt, AM **AEP484**
Cuzzocrea, F AEP630
Cuzzocrea, M AEP651
Cyrolyte, S AEP61
Czajka-Oraniec, I AEP547, AEP496
da Conceição, I AEP465
da Costa, M AEP137
da Cunha Oliveira, J EP210
Da Silva Lima, N OC7.4, AEP252
Dabrowska, A **AEP689**, **EP184**
Daffara, T AEP201, **PEP12.6**
Dafoulas, G AEP188
D'Agnano, S AEP637
Dahlberg, D OC8.6
Dahle, AL AEP4
Dahlqvist, P AEP4
Dahmani, Y EP234
Dakovska, L AEP296
Dalino Ciaramella, P OC6.1, PEP6.2
Dalla Mora, A PEP5.4
Daly, AF AEP839
Damak, J EP56
Damas Fuentes, M AEP346, **AEP213**, AEP293
D'Ambrosio, E AEP641, AEP633, OC5.4
Damiani, D AEP493
Dammak, J AEP366, AEP253, EP87
Dana, S AEP146, AEP868
Danchak, S EP85
Daneva, T OC15.6
Daniel, G AEP612
Daniele, N OC6.2
Danilova, LA **AEP888**
Danilova, LI AEP433, AEP261, PEP15.4, AEP891, AEP812, AEP805
Danilowicz, K **JS4.2**
Danza, G AEP861
Daraki, V AEP13, **PEP10.2**
Darashkevich, I **AEP631,** AEP631
Darda, M PEP1.8
Dardouri, T AEP781
Das, A **AEP264**
Das, A Kumar AEP822
Das, B EP156
Das, G AEP486
D'Ascanio, M PEP14.3
Daskalakis, K AEP555
Daskalova, I AEP810
Dass, N **AEP93**
Daturi, A AEP651

Daugintyte-Petrusiene, L PEP15.6
Dauksa, A AEP387, AEP61
Daukšienė, D AEP387
Davenport, C EP54
David, C AEP467
Davidenko, I EP194, AEP530, EP222, EP39
Davidson, LT AEP789
Davies, J PEP4.8
Davies, MC OC4.4
Davitadze, M **AEP655**, PEP14.8
Dazzi, D YI2, AEP651
De Angelis, C AEP412, YI1
De Angelis, M PEP13.1
De Block, C AEP157, AEP203, AEP11
De Donno, G AEP835
De Filippo, S AEP572
De Filpo, G PEP11.3, PEP14.7, PEP11.1
De Geyter, C OC4.1
De Graaff, L AEP681, AEP493
de Groot, C AEP280
de Herder, WW AEP839
de Herdt, C **AEP203**
de la Mata, M OC9.4, EP129
de Latouliere, L PEP14.3
De Leo, A PEP11.4
de León Durango, R EP14, **AEP174,** EP223, PEP15.8, PEP7.2, AEP800, AEP431
De Leyn, P PEP9.3
De Marinis, L AEP840
De Martino, D OC15.3
De Martino, MC PEP1.7
De Meijer, D AEP586
De Miguel Novoa, MP EP5
De Rijke, Y AEP235, OC7.3
De Taddeo, S EP64
De Toma, G AEP19
De Vincentis, G AEP19
De Vis, M **AEP510**
De Vitis, C PEP14.3
de Vries, F OC6.3
debbabi, W AEP374, EP36
Debeljak, Ž AEP445
Debowska, A AEP4
Decaluwé, H PEP9.3
Decoudier, B OC11.5
Dedov, I AEP126
Deering, KL AEP644, EP226
Defreyne, J AEP586
Degmečić, D AEP445
Degtyareva, Y **EP194**, **AEP530**, **EP222**, **EP39**
Deischinger, C **AEP184**
Dekkers, OM. AEP463
Del Bono, V AEP637
Del Olmo Sedano, J AEP736
Del Rio-Moreno, M OC7.2, OC9.4, EP129
Del Sindaco, G **AEP81**
Del Val Zaballos, F AEP760, EP202, AEP454
Delale, T OC12.2
Delgado, E EP78, AEP685
Delgado, L PEP10.6
Delgado, T AEP252, OC7.4
Delgado-Zayas, E AEP451
Delialis, D AEP570
Delivanis, DA PEP11.6
Della Casa, S PEP1.7
Della Morte - Canosci, D EP64
Dellacasa, C OC10.6
Dellal, FD AEP693, AEP870
Delli Veneri, A AEP412
Demidova, T AEP345, AEP317, AEP610
Demir, AS EP73, EP4, AEP675, EP221, AEP291, EP53, AEP473, AEP50, AEP343, EP110, AEP326, AEP724
Demir, Ö AEP44
Demirsoy, U AEP105
den Heijer, M AEP586, AEP592
Denham, S OC15.1
Deniz, MS AEP852
Deniz, S EP233, AEP894, AEP885
Deniziaut, G AEP695
Dennedy, MC PEP11.6, AEP77, OC11.6
Denton, M AEP750
Denver, N OC15.1
De-Rafael-Gonzalez, E AEP677
Derkaoui, N **EP44**, AEP344, AEP369, **AEP53**
Dervic, E AEP184
Detomas, M PEP1.7, **AEP838**, **AEP826**
Deus, J AEP466
Deutschbein, T OC3.3, OC13.1, AEP838
Devingenteuil, C OC9.5
Dhas, Y EP55
Dhoha, BS AEP25, EP89, EP10
Dhouha, BS AEP307
Di Costanzo, D AEP835
Di Dalmazi, G PEP14.7, **PEP11.4**
Di Filippo, L **AEP114**
Di Gangi, S PEP7.5
di Guisto, V OC14.5
Di Leo, S PEP4.3
Di Muro, G **PEP3.1**, OC8.4
Di Paola, N YI1
Di Stasi, V **AEP857,** AEP835, AEP803, AEP861
Diaconu, D AEP52
Diana, A AEP134
Diane, E AEP648
Dias, D **EP13**, **AEP578**
Días-Pérez, JA PEP9.6
Díaz-López, EJ **EP31**
Dickinson, R **OC14.2**, **AEP405**
Didushko, O **AEP289**
Diego, E OC9.1
Dieguez, C AEP267, OC3.2, AEP252, OC7.5, OC7.4
Diez, S AEP470
Diez Irizar, S AEP186, AEP160
Dikaiakou, E PEP3.6
Dilek, I AEP884
Dimai, H AEP159
Dimakopoulos, G AEP188, AEP804, AEP274
DiMarco, A AEP120
Dimitriadi, A AEP10
Dimitrova, D **AEP501**
Dimitrova, I **AEP666**
Dimofte, G AEP401
Dimov, R AEP719
Dinatolo, E AEP723
Dincer, N AEP865
Dinis, I AEP577
Dinis Sousa, M EP210
Dionisi-Vici, M OC10.6
Dios, E AEP837
D'Ippolito, I EP64
Dirikoc, A AEP882, AEP693, PEP15.7, AEP814, AEP852, AEP877, AEP811
Dirinck, E AEP203, AEP11, AEP157
Dischinger, U AEP826
Dito, G AEP131
Divanlioglu, D AEP850
Diyaolu, F **AEP716**
Djerroumi, I **AEP458**
Djukic-Cosic, D AEP404
Dobreva, E AEP139, AEP380
Dobrovolskytė, R **AEP518**
Dodova, R AEP666
Dogadin, SA PEP8.3
Dogan Cakir, S AEP524
Dojcinovic, T AEP318
Dökmetaş, M EP97
Doknic, M OC15.4, AEP522
Dolhnikoff, M OC14.3
Domagała, B **AEP7**
Domagalska, M PEP13.7
Domínguez Rabadán, R AEP349
Donath, MY OC4.1, **S12.3**
Donlon, P AEP77
Dores, J AEP398, AEP88, EP111
D'Oria, R OC2.6
Dorotenko, A **AEP448**
Dörr, HG PEP4.8
Dorra, G AEP339
Dorraelguiche, D **AEP579**, AEP863, **AEP864**
Dotan, Z AEP20
Dotres Fallat, KM **AEP272**
Dousset, B PEP11.5
Doval-Rosa, C YI8
Dovrish, Z AEP185
Dragomir, AS AEP603
Dragomirecka, E AEP76
Dragula, M AEP556
Drai, R AEP448, AEP233
Drakakis, P YI7
Drake, W AEP842, OC1.5
Drake, WM AEP495
Drakou, A EP34
Drakou, M AEP893
Draoui, N **AEP303**, AEP421
Dreval, AV OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6
Dridi, M EP104, EP106, **EP105**, AEP365, EP58, EP43, AEP209, AEP275
Driessens, N OC3.3, AEP31
Drozenova, J OC10.2
Druce, M OC14.5
Druzhkova, N **AEP155**
Duarte, H AEP395
Duarte, V EP86, EP76, **PEP7.7,** AEP112, EP42
Duarte-Neto, AN OC14.3
Dubin, I AEP372
Dubinski, I AEP6

Dubrov, S AEP722, AEP759
Duşceac, R AEP145
Dudinskaya, E AEP196
Dudka, J AEP689, EP184
Dudzik, N AEP891
Dueñas, A AEP83
Dueñas Disotuar, S AEP665, PEP9.8
Dufour, H AEP844
Duger, H AEP816, AEP873
Dukanovic, S PEP13.3
Dullaart, RPF OC7.1
Dumitraşcu, A AEP536, AEP482, EP149, PEP1.4, PEP13.4
Dumitriu, R **AEP568**
Dumitru, AM AEP603
Dumitru, N **AEP52**
Dumitru, T AEP622, AEP150
Dundua, K AEP170
Dunne, D EP54
Dupuy, N OC12.6
Dural, C AEP422
Durante, C AEP642, OC5.5
Durcan, E **AEP585**
Durduran, T PEP5.4
Durmaz, H AEP885, **AEP795,** PEP15.1, AEP846
Durmu, B EP233
Durmus, B AEP811, AEP788
Dusceac, R AEP568, EP127, AEP479
Dusek, T OC11.5
Duskova, J EP201
Duskova, M **AEP620**
Dydyshka, Y **AEP667**, **AEP668**, **AEP669**, **AEP733**, **AEP734**, AEP229
Dydyshko, Y **AEP821**
Dzeranova, L PEP8.7, AEP416, AEP126, AEP483, AEP468
Dzherieva, I EP194, AEP530, EP222, EP39
Ebeling, T PEP9.1
Echchad, L AEP676
Echchad, l **EP189**, **EP235**, **EP236**
Edgunlu, T OC8.5
Efremov, S AEP144
Eftimovska Otovikj, N AEP143
Egaña Zunzunegui, N AEP703, **EP152**
Egido Arroyo, JF AEP186, AEP160
Eid, Y AEP720, AEP259
Ekerstad, E AEP39
Ekman, B AEP789
EL Abbassi, I EP93
El Ach, K EP230
EL Ansari, N AEP765, EP161, AEP604, EP46, EP118, EP95, AEP308
El Arbi, K EP62, **AEP73**, **EP199**, **EP200**
El Aziz, S AEP626, AEP66, AEP347, AEP359, AEP417, AEP418, AEP752, EP25, AEP670, AEP732, AEP776, AEP514, AEP515, EP168
El Bekay, R EP52, AEP165
El Bouzegaoui, N **PEP13.2**
El Euch, K EP171
El Hadadi, F **AEP698**
El Halawany, S AEP720, **AEP173**
El-Hajj Fuleihan, G **S25.2**
El Mghari, G AEP765, EP161, AEP604, EP46, EP118, EP95, AEP308
El Miski, F **AEP615**, **AEP269**, **EP93**, EP94, AEP231, AEP350
El Yamani, N **AEP452**, **AEP455**
Elarem, S **EP63**, **AEP340**
Elbuken, G AEP557
Eldepp, M AEP720
Eleftheriadis, M AEP570
Elen, Ö AEP506
Elena, M-S AEP490
Elena Teodora, G **AEP487**
Elezi, E AEP375, AEP740
Elezovic Kovacevic, V AEP402, EP126
Elftouh, N AEP206
Elgharroudi, F AEP604
Elhalawany, S AEP259
Elhassan, Y OC11.1, PEP1.7
Elhem, BJ AEP358, AEP278, AEP328, EP119, EP137, EP140
Elias Ortega, C EP152, **AEP703**
Elisei, R AEP875
Elkhomri, A **EP25**
Eller Vainicher, C OC6.4
Elleuch, H. AEP238
Elleuch, M AEP197, EP133, EP91, EP50, EP192, **EP61**, AEP440, AEP762, **EP211**, **AEP764**, AEP731, AEP70, EP75, AEP210, EP62, **EP71**, AEP362, EP175, **AEP306**, EP165, EP159, AEP366, AEP548, AEP253, AEP584, EP56, AEP363, EP87, EP66
Ellingham, H AEP111
Ellis, M AEP185
Elmacı, İ AEP851
Elmehraoui, O EP44, AEP535, EP170
Elsaify, W AEP785
Elshowaya, S AEP836
Eltayeb, R **AEP783**
Eltumi, H **PEP13.8**
Elvas, AR AEP273, AEP247, **AEP742**, **AEP743**, **AEP56**
Emile, JF AEP695
Emmer, L AEP613, **AEP599**
Emur Gunay, Y EP110, AEP326, AEP724, AEP473, AEP50, AEP343, EP73, EP4, AEP675, EP221, EP53
Endo, Y AEP167
Enikeeva, S AEP829
Ercolino, T PEP11.3, PEP11.1
Erel, O AEP879, AEP869
Erem Basmaz, S AEP524
Eremkina, A AEP139, EP30, AEP128, AEP106, AEP380, **EP22**, **AEP124**, **AEP101**
Erez, D AEP185
Erichsen, T AEP507
Eriksen, E OC6.6
Eroglu, E AEP705
Erol, S **AEP524**, AEP464, **AEP109**
Ersen Danyeli, A AEP851
Ersen Kural, E PEP5.1, AEP43
Ersoy, O AEP869, AEP856
Ersoy, R AEP885, PEP15.1, EP238, EP233, AEP788, AEP877, AEP693, PEP15.7, AEP879, AEP814, AEP870, AEP795, EP239, AEP856, AEP846, AEP811, AEP865, AEP882, AEP886, AEP852, AEP872, AEP825, AEP782, AEP799, AEP884, AEP794, AEP796, AEP847, AEP894, AEP850
Ersoz, HO AEP291, AEP640
Ersoz Gulcelik, N OC10.1
Ersozlu, I AEP705
Ertl, D-A AEP116
Eryomushkin, M AEP239
Escalada San Martín, J AEP834, AEP837
Escobar-Morreale, HF OC1.1
Escudero, A AEP252
Escudero Gomis, AI AEP685
Esen Pazır, A AEP489
Eskes, S AEP281
Espada Saenz-Torre, M AEP736
Espartero, JL AEP397
Espersen, R **AEP36**
Espinosa De Los Monteros, P AEP434, **AEP774**, AEP639
Esposito, G AEP572
Esposito, MG AEP633, OC5.4, AEP641
Esposito, V PEP13.1
Essa, N **AEP596**
Essayeh, S **AEP625**, **EP3**, EP185, **AEP609**, EP69, **AEP709**
Esteban, C-A AEP490
Esteban Rodríguez, I AEP478
Esteves Ferreira, S AEP96
Estrella Santos, A AEP809
Eszter, B **AEP634**
Etchie, L **AEP215**
Evaggelos, S AEP87
Evangelou, E AEP617
Evans, N PEP14.8
Evanson, J AEP495
Eveslage, M AEP500, AEP477, AEP528
Evranos Ogmen, B AEP814

Ezzin, A AEP883
F Fondevila, M **AEP267**
F. Leite-Moreira, A AEP212
Fabio, F OC1.3
Fadda, G OC5.5
Fadhel, G EP74, EP206
Fadiga, L AEP96, AEP392, AEP456, EP26, PEP4.7
Faggiano, A AEP575, AEP22
Fainstein-Day, P **AEP827**
Fakas, N AEP95
Fakhfakh, F AEP361
Faki, S AEP693, **AEP894**, AEP879, **AEP885**, **EP233**
Falanga, DL AEP412
Falch, CM **AEP463**
Falcone, S AEP104
Faliush, O **AEP595**
Fambrini, M AEP803, AEP857, AEP861
Familiar Casado, MC AEP774, AEP639
Fanciulli, A OC3.2
Faouzi, K EP206, EP74
Faraci, D OC10.6
Faria, M **YI11**
Farina, L AEP77
Fasano, N AEP457
Fassnacht, M OC11.1, OC11.3, PEP1.7, AEP838, AEP826, OC11.5, PEP11.6
Faten, HK EP188, **AEP654**, EP192, **AEP628**, EP61, AEP762, EP211, AEP764, **AEP731**, AEP70, EP75, AEP210, EP62, EP71, **EP121**, AEP362, EP175, AEP306, **EP165**, AEP73, **EP173**, **EP159**, EP199, AEP548, **AEP216**, EP200, EP133, **AEP307**, **AEP287**, **EP163**
Faten, HK AEP339, EP10, AEP25, EP89
Faten, T AEP339
Fatiha, M EP18, **EP177**
Fatima, S AEP881
Fatma, H EP206, EP74
Fatma, M EP121, EP173, AEP216, AEP307, AEP287, AEP339, EP61, AEP25, EP10, EP89, EP163
Fattoruso, M AEP412
Faustine, T **AEP612**
Favero, V **YI2**
Fawzi, W AEP469
Fawzy Abouelezz, N AEP156
Fazzino, G AEP748
Federici, S **OC4.3**
Feelders, R OC3.1, AEP839
Fei, L PEP11.1, **PEP11.3**
Feigerlova, E **AEP580**
Feki, M AEP220
Feldt-Rasmussen, B AEP507
Feldt-Rasmussen, U AEP481, AEP383, AEP507
Felicetti, F OC10.6
Fellinger, P AEP62
Fennell, D AEP728, **AEP552**
Fenske, WK PEP4.8
Feola, T **AEP475**, **AEP19**, PEP13.1
Ferjan, S AEP163
Fernandes, V AEP224
Fernandez, N AEP83
Fernandez, R **AEP451**
Fernández, U **OC7.4,** AEP267
Fernandez Argüeso, M AEP14, AEP499
Fernández Fondevila, M OC7.5, OC7.4, AEP252
Fernández Paz, U OC7.5, AEP252
Fernández Peña, JI PEP9.8, AEP408
Fernández Pombo, A AEP521
Fernandez Ramos, D OC7.5
Fernández Soto, ML AEP333
Fernandez Valero, A AEP213, AEP346, **AEP293**
Fernández Vázquez, G AEP504
Fernández-Cuesta, L OC9.3
Fernandez-Felix, BM AEP332
Fernández-García, JC AEP165
Fernandez-Trujillo-Comenge, PM PEP7.2, EP223, AEP800
Fernando, D AEP638, AEP215
Ferone, DI AEP680
Ferraro, A AEP630
Ferraù, F PEP14.7
Ferraz, R AEP650
Ferreira, J AEP876
Ferreira, L AEP398
Ferreira, MJ **EP178**, **AEP69**, **AEP176**
Ferreira, P AEP600
Ferreira, S EP178, AEP69
Ferreira Barros, I **AEP543**
Ferrero, A PEP12.6
Ferrigno, R **AEP412**, YI1
Feten, F AEP24, AEP99, AEP485
Feyka, BM EP45
Fex, M **S4.1**
Fichtali, K AEP269, EP93, EP94, AEP231, AEP350
Fidalgo, M AEP252, AEP267
Fideline, B PEP11.5, **OC9.5**
Fiers, T OC4.6
Filetti, S AEP642
Filigheddu, N PEP7.8
Filipowicz, D **PEP13.7**, **AEP866**
Filippi, S AEP861
Filippo, LD **JS3.2**
Finnes, T AEP4
Finucane, F EP54, AEP674
Fischbach, A OC5.1, PEP10.1
Fishman, B AEP20
Fleseriu, M **PEP8.5**, OC13.6, PEP3.2, PEP8.1, **PEP8.3**, PEP13.6, **OC8.2**, PEP8.6, AEP546, **OC13.6**
Flitsch, J OC3.6, AEP500, OC13.1, OC8.1
Flores-Guerrero, JL **OC7.1**
Florou, P AEP574
Fojas, EG AEP164
Fokina, N AEP51
Foll, M OC9.3
Fonseca, F AEP582
Fonseca, I AEP833
Fonseca, L EP111
Fontaine, J PEP12.1
Fontes, M AEP409
Foo, R AEP787
for the study of MEN and PPGL, Spanish group OC9.1
Formenti, AM AEP114
Forno, I OC6.1
Fortis, A AEP121, AEP130, AEP68
Foscarini, A OC15.3
Fostira, F AEP13
Fotiadou, A EP35
Foudil, D AEP458
Fourati, C AEP731
Fourneaux, R **AEP844**
Foy, S EP54
Frädrich, C **OC5.1**, PEP10.1
Franceschetti, P AEP723
Franchini, M AEP835
Franco, M PEP14.7
Franco, S **AEP311**, **EP210**
Francque, S AEP157, AEP203, AEP11
Franzini, M AEP802
Franks, S **S13.2**
Frara, S AEP114
Freda, PU **PEP3.2**
Fredj, H **AEP602**
Freitas, C AEP629, PEP5.3, AEP398, AEP551, AEP756, OC10.3, AEP673, AEP137
Friedrich, C AEP500
Frigerio, S **AEP9**, AEP21
Frikha, F EP188
Frikha, H AEP764, EP71, EP165, AEP584
Froelich, J OC5.2
Fruhbeck, G OC7.5
Fuentes-Bullejos, P AEP677, PEP14.4
Fuentes-Fayos, AC OC3.2, OC3.4, **PEP9.6**, **YI8**, OC9.6, EP129
Fuertes Rioja, L EP88
Fugazzola, L AEP642, OC14.5
Fugleholm Buch, K AEP383
Fuhr, U PEP1.3
Fureraj, T AEP740
Furtado, J **AEP177**
Furukawa, S EP51
Fylaktou, E PEP8.4, OC2.5
G I Suliman, S AEP164
Gabalec, F EP17, AEP129, EP203
Gabulavichene, Z AEP377
Gacs, Z **AEP3**
Gad, H **AEP491**
Gadelha, M **OC3.1**, OC13.1, OC15.4
Gadipudi, LL PEP7.8

Gado, M **OC12.1**
Gaelle, B EP220
Gaetan, G OC1.3
Gaetan, P EP220
Gagliardi, I **PEP15.3**, **AEP723**, **PEP5.2**
Gahete, MD OC9.3, AEP382, EP129, AEP397, YI6, OC13.5, **S16.2**
Gahete Ortiz, M AEP384, OC3.4, OC9.4, YI8, OC9.6, OC9.2
Gajate Borau, P AEP871
Gala-Bladzinska, A AEP744
Galagudza, M OC12.3
Galakhova, R AEP862
Galitzky, J PEP12.1
Gallo, A AEP627
Gallo, D AEP748
Galofré Ferrater, JC AEP871
Galvez Moreno, MA AEP132, PEP9.6, AEP241, AEP349, AEP382, OC3.4, AEP621
Gamalero, E AEP166
Ganenko, L EP194, AEP530, EP222, EP39
Ganji, Z EP183
Gao, X OC7.6
Garberoglio, S OC5.4
Garça, M AEP756
Garcia, E OC7.1
García, ML **PEP15.5**
García, RD PEP12.8
Garcia Arnes, JA OC3.4
García Centeno, R OC1.1
Garcia Delgado, C AEP703, EP152
Garcia Fontana, B AEP136
García-Fernández, J NSA4
Garcia Garcia, M YI8, **OC9.6**
García Lavandeira, M OC8.3
García Monzon, C AEP252
García Moreno, R AEP504, AEP478
García Moreno, RM **AEP542**, AEP531
García Urruzola, F EP78
García Vence, M AEP252
García-Barcina, M J AEP828
García-Blasco, L **AEP834**
García-Monzón, C OC7.4
García-Pascual, L AEP282
García-Ramírez, M AEP227
García-Unzueta, MT AEP221
García-Vioque, V OC9.3
Gardovskis, J AEP51
Gargouri, I AEP237
Garifalos, F AEP412
Garnysz, K AEP178
Garuti, M AEP835
Gateva, A AEP92, AEP200
Gathercole, L YI3
Gatti, F **OC10.6**
Gauffin, E **AEP789**
Gaurav, K AEP822
Gavotti, C PEP8.2
Gavric, E AEP39
Gavrila, C AEP142
Gavrish, T AEP503
Gavryliuk, N EP85, **EP59**
Gaztambide, S OC9.1
Gaztambide Saenz, S AEP736
Geigenberger, V AEP532
Genc, B PEP15.7, AEP814
Genchi, VA PEP4.3, **OC2.6**
Genovesi, E PEP15.5
Gentile, AM EP52
Gentile, M **AEP572**
Gentile, T AEP572
Genzel, D AEP500
Georgescu, CE OC3.3, AEP484
Georgiopoulos, G AEP570
Georgiou, E AEP127, AEP379, AEP494, AEP635
Georgopoulos, N YI10
Geraldes, F AEP577
Geraul, C OC6.5
Gerbracht, C AEP183
Gerek, ME AEP878
Geru, DL **AEP603**
Gesmundo, I OC13.4, OC12.5, **OC3.2**
Gezer, E AEP506, EP145
Ghada, S AEP368, AEP770
Ghammem, M EP230, EP68, AEP371, AEP781, EP117
Ghamrawi, S YI5
Gharbi, MEH EP236, EP235, EP189
Gharbi, R AEP460, AEP579, EP150, AEP864, AEP863, AEP709
Gharsallah, I AEP277
Ghatan, S **PEP2.2**
Ghemigian, A AEP52
Ghenoiu, S **AEP536**
Gheorghe, DM AEP536
Gheorghiu, M AEP735
Gheorghiu, ML EP197, EP158
Gherissi, W **AEP777**, AEP362, **EP133**, **AEP197**
Gherlan, I PEP1.4
Ghervan, C **AEP576**
Ghervan, L AEP576
Ghigo, E OC13.4, OC12.5, OC3.2, PEP4.8
Ghizlane, EM AEP746, EP212, EP109, AEP348, AEP564
Ghodke, S AEP309
Ghosh, S AEP208, AEP248
Ghyar, P AEP565
Giaccone, L OC10.6
Giacobini, P **S7.3**
Giamello, J AEP457
Giampietro, A AEP840
Giangaspero, F PEP13.1, AEP19
Gianfrilli, D **S9.2**
Gianno, F AEP19, PEP13.1
Giannopoulos, G AEP121
Gianotti, L **AEP457**, **AEP637**
Gibson, I EP54
Gietka-Czernel, M AEP686
Gil, Â AEP409
Gilgun-Sherki, Y OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6
Gilis-Januszewska, A OC3.1, AEP538, AEP399, AEP472
Gillet, P AEP580
Gillett, CDT AEP175
Gillett, D YI4
Giménez-Palop, O **AEP476,** AEP466
Giona, F AEP475
Giordano, F PEP4.3
Giordano, R OC3.3, PEP14.7
Giorgino, F PEP4.3, OC2.6
Giovannopoulos, I EP195, PEP10.5
Girgis, D AEP720
Giri Ravindran, S **EP20,** EP40
Gironi, V AEP803
Githanga, J AEP817
Gittoes, N AEP93
Giuca, DC **AEP479**
Giurato, L EP64
Giusti, M AEP680
Giustina, A AEP114
Giwercman, A **MTE10**
Gizatulina, G EP194
Gkaniatsa, E **AEP39**
Gladkova, I **AEP144**
Glavey, S AEP65
Glavnova, O **AEP862**
Glazieva, V AEP126
Gleeson, H AEP175
Glibka, A EP217
Glikofridi, S OC1.4, AEP323
Glingani, C AEP835
Glinicki, P AEP686
Globa, E AEP182
Główka, F AEP866
Gluchowska, M AEP178
Gluvic, Z AEP294, AEP474
Go, SM AEP554, AEP588
Godlewska, M AEP472, **AEP538**, AEP399
Godsland, I PEP11.7, OC1.6
Goemaere, S OC4.6
Goena Iglesias, MM AEP703, EP152
Goena Vives, C AEP160, AEP186
Gogas Yavuz, D AEP534, AEP471, AEP540, **AEP447**, AEP27, AEP331
Goggi, G OC4.3
Gogiashvili, L AEP711
Gohar, M AEP646
Gohil, S AEP842
Gökçay Canpolat, A AEP342, **OC5.6**
Gołąbek-Dropiewska, K AEP151
Golchert, J PEP15.2
Golfieri, R PEP11.4
Golounina, O **AEP416**
Golovatuk, K AEP425
Golovchenko, G PEP10.7
Golu, I AEP702, AEP889
Gomes, L PEP4.7, AEP18, AEP587
Gomes, P EP13, AEP252
Gomes Porras, M AEP531, **AEP478**, **AEP504,** AEP542
Gómez Alfonso, FJ EP202, AEP454
Gómez Balaguer, M AEP871
Gómez García, I AEP381, EP202, AEP454

Gómez Gerique, N AEP476
Gomez Hoyos, E EP5
Gómez Huelgas, R EP70
Gómez Montes, MDLP AEP809
Gómez Pérez, AM AEP293
Gomez Tijero, N AEP160
Gómez-Gómez, E YI6, AEP397, AEP384, OC9.2, OC13.5
Gomova, I AEP407
Gonçalves Ferreira, A AEP311, EP210
González Blanco, C AEP871
González Boillos, M EP154
Gonzalez Diaz-Faes, A AEP221
González Lázaro, P **AEP381**, AEP760, EP202, AEP454
Gonzalez Lopez, E AEP221
González Martínez, S **AEP685**
González Pernas, M PEP15.5
González Rellán, MJ OC7.4, AEP252
González Rodríguez, A AEP252, OC7.4
Gonzalez Vidal, T EP78
Gonzalez-Diaz, P EP223, PEP15.8, AEP174, **AEP431**, AEP800
González-Rellán, MJ AEP267
González-Serrano, MC AEP828
Gonzalo Marin, M AEP250
Gonzalo Redondo, MDLA AEP809
Goodchild, E OC1.5
Gorbacheva, A **AEP426**, AEP128
Gorchène, A EP16
Gordon, MB OC13.6, PEP3.2, PEP8.1, PEP8.3, **PEP13.6**, **OC15.4**
Gorgi, K EP235
Gori, A AEP651
Gosmanova, E PEP6.8, PEP6.6, PEP6.7
Goulis, D AEP652, AEP574, AEP225
Gountios, I AEP127, AEP494, AEP635, AEP379
Goutas, N AEP893
Graça Fonseca, JA OC8.3
Gracia Gimeno, P OC1.1
Graillon, T AEP844
Granata, R OC12.5, OC13.4, OC3.2
Grani, G AEP642, OC5.5
Granic, M AEP404
Grasemann, C AEP116
Grassa, A AEP863
Grassi, G **OC6.4**
Graveling, AJ YI4, AEP533
Gravholt, CH PEP4.8
Gravvanis, C **OC1.4**
Grbic, A AEP270, AEP517
Grebennikova, T PEP8.7
Greco, GF AEP835
Greenman, Y AEP730
Grigorie, D AEP134
Grigoriev, A AEP501, AEP468, AEP566
Grigoriu, C AEP757
Grigorovich, A AEP891
Grimbizis, G AEP574
Grimmichova, T **AEP739**
Grimnes, G AEP4
Grineva, E OC13.6, AEP425, AEP545, AEP108
Grira, W EP174, EP180, AEP64, AEP58, AEP71, AEP57, EP166, AEP727
Grønning, K AEP4
Groti Antonic, K **PEP7.1**
Grottoli, S OC3.2
Groussin, L PEP11.5, OC9.5
Grozinsky-Glasberg, S OC14.5
Grubczak, K AEP892
Grujicic, D AEP522
Gruppetta, M AEP385, PEP9.7
Guabello, G AEP131
Guadalix Iglesias, S AEP871
Guarnieri, G AEP861
Guarnieri, V PEP6.2
Guarnotta, V PEP14.7
Guastella, C YI2
Gudelj, L AEP706
Guermazi, F AEP777
Guerneri, S PEP6.2
Guerra, S AEP23, AEP411, AEP749, AEP406
Guerra Ruiz, A AEP221
Guglielmotto, M OC13.4
Guibourdenche, J OC9.5
Guidi, F PEP8.2
Guignat, L PEP11.5
Guillamon, A AEP451
Guimarães, MJ AEP251
Guimarães, S OC14.3
Guimarães, T AEP176
Guizani, R AEP779, AEP694, AEP149, AEP304, AEP745, AEP119
Gulde, S **OC15.3**
Guler, I OC9.2
Gulin, P AEP102
Gulli, F PEP4.2
Gumber, L **PEP9.4**
Gumeniuk, O **PEP10.7**
Gunaldı, O AEP422
Gunarathne, K AEP320
Gunay, YE AEP291
Güner, H AEP192
Gurevica, M AEP849
Gurnell, M YI4, AEP533, OC1.5
Gutierrez Hurtado, A EP78
Gutu, O **AEP246**, **AEP180**
Guvercin, B AEP473
Gvianishvili, T **AEP711**
Haak, HR OC11.3, AEP1, OC11.5
Haanpää, M OC15.2
Haberal, K Murat AEP688
Hacioglu, A AEP843
Haddada, I EP63, AEP340
Hadj Ali, Z AEP275, AEP365, AEP321, AEP283, PEP2.8, EP106, AEP714, AEP46, EP104, EP43, EP65
Hadj Kacem, F EP56, AEP72, AEP361, AEP584, AEP707, EP7
Hadj Sliman, C AEP625
Hadjkacem, F AEP197
Hadzovic-Dzuvo, A PEP14.2
Haeusler, G AEP116
Hahner, S AEP35
Haider, A AEP162, OC2.3, AEP232
Haider, KS AEP162, OC2.3, AEP232
Haifa, A PEP2.5
Haj Ali, Z EP105, AEP290, AEP301
Haj Elamin, M AEP78
Haj Kacem, F EP87, EP50, EP66, AEP363, EP91
Haj Salah, A EP63, AEP340
Hajer, B AEP754
Hajizada, A **AEP758**
Hajji, E AEP657, **AEP887**, **AEP883**
Hakiri, G EP106, **AEP275**, **AEP209**, AEP365, **EP43**
Haklar, G AEP534
Halawa, M AEP259
Halawa, MR AEP156
Hali, F EP25
Halloul, I **EP141**, **AEP645**
Halmi, S **AEP410**, AEP634
Halperin, I PEP5.4
Haluzík, M AEP334
Hamaguchi, R AEP167
Hamdi, F EP173
Hamdi, S AEP612
Hammami, A AEP771
Hammami, B AEP220
Hamza, F AEP777
Han, A **PEP8.6**
Han, M AEP266
Hanafi, A AEP615
Hanane, L AEP455, AEP452
Hanania, T PEP14.8
Handelsman, DJ OC4.2
Handgriff, L AEP791
Handkiewicz-Junak, D PEP8.8
Hanif, W AEP248
Hannula, P PEP9.1
Hantel, C OC11.2
Hany Abdelaziz, N AEP156
Hanyaloglu, A S13.2
Hanzu, F OC3.3, PEP5.4, AEP834, AEP837
Haraj, NE AEP359, AEP417, AEP418, AEP752, AEP670, AEP732, AEP776, AEP514, AEP515, EP168, AEP626, AEP66, AEP347, EP25
Harangi, M AEP634
Hardy, K S13.2
Harno, E **S11.3**
Haroche, J AEP695
Haroun, O EP185, EP69, AEP284, EP9, EP11, AEP437
Harris, S YI3
Harsunen, M **OC2.1**
Hasan, T AEP143, **AEP319**
Hasenmajer, V PEP14.7
Hasnain, S **AEP122**, AEP647, AEP111, EP24, AEP141

Hasnaoui, M AEP302, AEP119, AEP745, EP204, AEP304, AEP338, AEP245, AEP753, AEP694, EP27, EP208, AEP708, AEP149, AEP779
Hasni, Y EP16, AEP368, AEP12, AEP771, EP141, EP230, EP171, AEP645
Hassan, A AEP78
Hassan, M **AEP702**
Hassani Azad, M AEP424
Hasse-Lazar, K AEP399
Hatfield, E AEP486
Hatipoglu, ES AEP705
Hatunic, M AEP553
Haudum, C PEP6.3, AEP159
Hava Rosenblum, R AEP135
Haverinen, A **PEP4.1**
Haviv, A OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6
Havlinova, B **EP17**, AEP129
Havrylyuk, M EP59
Hawley, J AEP6
Hawley, JM PEP1.1, PEP1.5
Hawrylowicz, CM AEP414
Haxhiraj, A AEP740
Hayon Ponce, M **AEP136**, EP207
Hazra, P AEP264
He, Q AEP266
Heaney, A OC3.1
Heard, F AEP699
Hebbar, M AEP175
Heck, A AEP463
Heerkens, YF AEP537
Heffez-Ayzenfeld, R AEP242
Hegab, A AEP259
Hegedüs, L AEP734, OC5.2, AEP733
Heide, LD **JS7.4**
Heijboer, AC AEP592
Heikinheimo, O PEP4.1
Heinrich, A OC12.1
Hela, C AEP754
Helal, R **AEP161**
Hélène, L OC11.5
Helleputte, S YI9
Helvaci, B **AEP872**, **AEP788**
Henanger, P AEP789
Henda, J AEP240, AEP314
Hendawy, l **AEP259**
Henneicke, H OC12.1
Hepsen, S **AEP873,** AEP816
Heredia, CMH AEP632
Hermán-Sánchez, N OC9.4, **EP129**
Herms, J OC8.1
Hermus, ARMM OC13.1
Hernandez, C EP88
Hernandez, G AEP83
Hernandez Garcia, C AEP213
Hernández Lázaro, A EP14, **PEP7.2**, AEP174, AEP800
Hernández Olmeda, F AEP434, AEP774, **AEP639**
Hernandez-Felipe, E PEP7.2, AEP431, EP223
Hernández-Hernández, I AEP490
Hernandez-Lazaro, A AEP431, **AEP800,** EP223, PEP15.8
Hernandez-Losa, J PEP5.7
Herrera-Martínez, AD OC3.4, PEP9.6, AEP241, AEP382, OC9.3
Herrero-Aguayo, V AEP397, OC9.2, OC13.5, YI6
Herron, B AEP488
Herzig, S OC7.5
Heshmati, H **AEP432**, **AEP819**
Heuer, H PEP15.2
Heurtier, V OC1.3
Heyfa, BHM AEP766
Hiasa, Y EP51
Higgins, L OC14.2, AEP405
Hilal, Z EP6, AEP42
Hill, M AEP739
Hilliquin, S OC6.2
Hillman, S AEP175
Hiltunen, L PEP4.1
Hinault, C OC14.1
Hind, A AEP564
Hind, D AEP590
Hintnausova, B EP201
Hirani, D **AEP42**, EP6
Hirsch, D EP12
Hočevar, M AEP91
Hoeks, S AEP235
Hofbauer, LC OC12.1
Hoffman, WB AEP177
Hofland, H AEP839
Hofstetter, G OC3.1
Hogea, M EP131
Holland, JA AEP552
Hollenberg, AN OC5.3
Holmes, C AEP248
Holováčová, D AEP556
Holst, JJ AEP507
Holte, S AEP4
Homaei, A AEP867
Homuth, G PEP15.2
Honegger, J OC8.1, OC13.1, OC3.6
Hooshyar, D AEP453, AEP424
Horacek, J EP17
Horackova, l AEP620
Hornemann, S AEP183
Hortobagyi, T EP160
Horzelski, W AEP125, AEP178
Hospodarskyy, I EP85, EP59
Hossainpour, S AEP335
Hotz, L PEP7.5
Hou, X AEP266, AEP60
Houde, G OC8.2
Houssein, M AEP846, AEP847, AEP794
Hoxha, V AEP740
Höybye, C **OC13.3,** AEP4
Hrabal, P OC10.2
Htira, Y AEP301, EP104, EP65, AEP321, EP107, AEP275, AEP365, EP58, EP106, AEP290, PEP2.8, AEP46, EP43, EP105, EP124, AEP283, AEP714
Huang, M PEP1.2
Huang, W PEP3.2
Hubalewska - Dydejczyk, A AEP649, OC3.3, PEP9.2, AEP7, AEP509, AEP538, AEP399, PEP8.8, AEP472
Hübner, A PEP4.8
Hudzik, B EP116
Huguet, I AEP773, AEP316
Huhtala, H PEP9.1
Huisinga, W PEP1.3
Huisman, SD AEP537
Hunter, S AEP488
Husebye, E AEP26
Husebye, ES PEP4.8, AEP4
Hussain, A AEP122, AEP647, AEP111, AEP512, EP24, **AEP141**
Hussein, Z EP2
Hutkai, D AEP410
Hyka, B AEP511
Hynes, M EP54
Iacono, M YI1
Iacovidou, N PEP8.4
Iakovou, I AEP574
Iancu, M **AEP520**
Iasevoli, F PEP14.7, AEP412
Ibañez Costa, A AEP384, **OC3.4,** OC9.3
Ibarra, J NSA4
Ibarra, M AEP282
Ibragimov, Z AEP330, AEP207, AEP263
Ibragimova, E AEP330, AEP207, **AEP263**
Ibrahim, A AEP460
Ibrahim, H AEP122, AEP647, **AEP111**, AEP512, **EP24**, AEP141, **AEP793**
Iconaru, L EP187, EP15
Idorn, T AEP507
Idrees, S EP196
Idris, MA **AEP190**
Ifigenia, KA AEP310, **AEP79**
Igaz, P OC11.2
Iglesias, C PEP5.7, OC7.5
Ijdda, S **EP46**, **EP118**, **EP95**, **AEP308**
Ilchenko, I AEP653
Ilias, I **EP49**
Ilic, D EP126, AEP402
Ilie, I **AEP695**
Illouz, F YI5
Ilovayskaya, I AEP508
Imane, R EP44, AEP344, AEP53
Imen, C EP188, EP89
Imen, S PEP2.5
Imene, G EP163
Imene, H **AEP240**, **AEP314**
İmga, NN AEP782
Imran, A AEP832
Inácio, I **AEP577**
Inamdar, A **EP108**, PEP7.6
Inan, MA AEP856
Inashvili, E AEP169
Ince, N **AEP811**, **AEP852**, **AEP846**
Ince, N **AEP877,** AEP782
Indi, S **PEP10.3**
Infante-Amorós, A EP31
Inglese, F AEP835
Inoue, T PEP2.6, PEP2.7, EP112
Insaf, O EP58
Ioan, B EP131, AEP401
Ioana, G AEP868
Ioana Chisalita, S AEP789
Ioannidis, D AEP893

Ionova, T AEP144
Iordan, IA AEP855
Iqbal, A AEP833
Iqbal, K AEP93
Iqbal, S **AEP256**
Iraqi, H EP236, EP235, AEP676, EP189
Iraten, Y AEP458
Irgasheva, S **AEP330**, AEP207
Irina Andreea, B **EP158**
Isachkina, V **AEP433**
Isaeva, E OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6
Isaeva, J **AEP233**
Isailovic, T AEP402
Isal Arslan, A AEP461
Isenovic, ER AEP294, AEP474
Ishanhodjaev, T AEP330, AEP207, AEP263
Ishtiaq, O OC4.2
Ishtiaq, O EP182
Isidori, AM PEP14.7
Ising, M AEP532
Islam, N EP156, AEP881
Islamiana, D AEP860
Islomov, J EP198
Ismaeel, GL AEP624
Ismail, M OC4.2
Ismailov, S EP205, EP198, EP231
Iso-Mustajärvi, I AEP560
Issam, J EP206, EP74
Istemihan, Z AEP480
Iulia-Florentina, B EP127
Iulia-Ștefania, P AEP550
Ivannikova, T **AEP692**
Ivanova, G AEP82
Ivanova, R AEP666
Ivanova, S AEP51
Ivashenko, O AEP468
Ivo, C EP86, EP76, **EP42**, **AEP112**, PEP7.7
Ivovic, M AEP16, PEP11.6
Iyer, A AEP235
Iyer, R **AEP841**
Iyidir, O EP213, **AEP688**
Izatt, L AEP388
Izmailova, M AEP610
Izquierdo, M PEP8.5, OC8.2
Izquierdo Coca, J AEP775
J. Bonnema, S OC5.2
Jaatinen, P PEP9.1, AEP560
Jabczyk, M AEP351, EP116
Jácome de Castro, J AEP112, EP42
Jadoon, N **AEP336**
Jaffrain-Rea, M-Lise PEP13.1, AEP475, AEP19
Jaggi, S AEP824
Jahan, S AEP594, OC4.5
Jajah, MB **AEP671**, **AEP78**, **AEP729**
Jakubíková, I **AEP334**
Jamal, A AEP315, EP113, EP57, AEP421, **AEP370**
Jambrović, M **EP228**
James, A AEP218, AEP491, AEP523
James, J AEP488
Jane, M AEP786
Janez, A AEP91, AEP37, PEP4.5, AEP163
Japón, M OC8.3
Jardak, I AEP777
Jarque, S **NSA4**
Järvelä, I OC2.2
Jarzab, B OC3.3, AEP399
Jashi, L **AEP170**
Jasser, M **EP9**, **EP11**
Jastrzębska, H AEP686
Jauze, L OC6.2
Javier Martinez-Martin, F EP14, EP223, PEP7.2, AEP174, AEP431, AEP800, PEP15.8
Javorac, D AEP404
Jayaprakash, S AEP175
Jazbinsek, S AEP91
Jaziri, H AEP771
Jdid, J EP87, AEP366, AEP253, EP56
Jemaa, M **EP166, EP181, AEP58**
Jemel, M AEP460, EP150, AEP563, AEP579, AEP324, AEP709, **AEP863**, AEP864
Jemni, A EP63
Jemuovic, Z AEP522
Jena, R AEP593
Jensterle, M **AEP37**, **PEP4.5**, **AEP163,** AEP91
Jeon, MJ PEP5.8
Jeong, S **AEP588**, **AEP618**, EP98, AEP554
Jespersen, ML OC10.5
Jesús González Rellán, M **OC7.5**
Jeung, EB AEP554, **EP142**, AEP588, AEP618, EP98, PEP4.6
Jia, Q OC10.4
Jihen, C AEP373, AEP772
Jiménez, I AEP639
Jimenez Licera, E EP123
Jiménez Portilla, A **EP125**
Jiménez Vacas, JM OC9.2, AEP397, OC13.5, YI6
Jin, M **PEP5.8**
Jitka, P AEP76
Jódar, E **AEP83**
Joel Rudy, E EP46, EP118
Joergensen, M AEP507
Johannsson, G AEP39, OC14.5
Johnson, A AEP208, AEP248
Johnston, D OC1.6, PEP11.7
Jokelainen, J OC2.2
Joksimovic, B **AEP474**
Jolapara, N AEP793
Jones, JH AEP105
Jones, L **AEP662**
Jones, M AEP352
Jones, SG AEP638
Jørgensen, A AEP4
Jørgensen, N **AEP507**
Joseph, V AEP559
Joshi, A AEP264
Joshi, M AEP388
Joshi, S AEP624
Josifovska, S AEP319
Jovanovic, M EP126
Jovanovska Mishevska, S AEP143
Jukone, U AEP51
Jumani, A AEP624
Jumani, D **AEP624**
Jung, Y-S AEP741
Jung-Sievers, C AEP532
Jurecka-Lubieniecka, B AEP538, AEP399
Juri Mandić, J AEP706
Juskiene, R AEP459
Juszczak, A AEP248
Juul, A PEP4.8
Kaabar, M EP150
Kabir, SPMH AEP836
Kacavenda, E AEP404
Kacem, M EP16, EP141, EP171, AEP771, AEP645, AEP12
Kadioglu, P AEP585
Kadıyoran, C AEP784
Kafetzi, M PEP3.6
Kafri, E AEP372
Kahramanca, FD EP238
Kais, C AEP202
Kalantzis, I AEP823
Kalashnikov, V AEP407
Kaleta, M AEP184
Kalinin, A AEP692
Kallel, F AEP777
Kalogeris, N AEP823
Kalogirou, T AEP68, AEP121, AEP130
Kalra, S **AEP822,** AEP264
Kaltsas, G AEP5, PEP1.7, AEP63, AEP555
Kalugina, V **PEP11.8**
Kamaruddin, MS AEP394
Kamaruddin, NA AEP895, AEP820, PEP7.4
Kamel, M YI4
Kamenov, Z AEP92, AEP200
Kamilia, O PEP2.5
Kaminski, G PEP8.8
Kammoun, H AEP616
Kammoun, I AEP460, AEP579, AEP324, EP150, AEP563, AEP863, AEP864, AEP709
Kammoun, T AEP616
Kamoun, E EP155, AEP75, AEP437, AEP438, AEP419, AEP567, AEP420, EP138, AEP569, AEP80, AEP747
Kamoun, M. AEP238
Kamoun, T AEP887
Kämpe, O AEP4
Kamyshna, I **AEP658**
Kamyshnyi, A AEP658
Kanaka Gantenbein, C AEP323, OC2.5, PEP8.4
Kanakis, G AEP617
Kandara, H AEP460, AEP579, AEP709, EP150, AEP563, AEP863, AEP864
Kaneva, R AEP666
Kangasniemi, M PEP4.1
Kaniuka-Jakubowska, S **AEP842,** AEP151
Kankaanranta, H AEP414
Kantárová, D AEP556
Kanti, G **AEP323**
Kanyari, Z AEP410
Kanzaki, S EP51
Kaoukis, A OC1.4
Kaouthar, C AEP754

Kaparos, G AEP236, AEP97, AEP90, AEP570
Kapoor, A AEP469
Kapoor, N AEP264
Kapuścińska, R AEP686
Karaahmetli, G AEP865, AEP872
Karaarslan, O AEP505, AEP489
Karaberi, C AEP188
Karaca, Z **AEP843**
Karachentsev, I AEP503, AEP611
Karagiannis, A **PEP5.6**
Karagkouni, I AEP236
Karahmetli, G **AEP847**, **EP238**
Karakas Celik, S OC8.5
Karakose, M AEP798, AEP784, AEP878
Karakullukcu, S AEP291, AEP640
Karakurt, F AEP798, AEP784, AEP878
Karakus, D AEP679
Karalazou, P AEP274, AEP804
Karalilova, R AEP413
Karamaoun, C OC14.1
Karamat, M AEP248
Karamfilova, V AEP92, AEP200
Karampela, A EP195, PEP10.5, EP34
Karapanagioti, A AEP5, **AEP555**, YI7
Karatas, İ EP60
Karavitaki, N OC14.5, PEP14.8
Karaśniewicz-Łada, M AEP866
Kardel-Reszkiewicz, E AEP151
Kardi, A AEP220, EP215, AEP715, EP80, EP216
Kardonaite, D PEP15.6
Karelina, Y AEP144
Kareva, M AEP692, AEP829
Karhu, A **MTE15**
Karim, C AEP612
Karima, K AEP718
Karlovich, N AEP158
Karonova, T AEP425, PEP6.1, AEP108, OC12.3
Karppinen, N PEP9.5
Karppinen, S OC15.2
Karras, S **AEP274**, **AEP804**
Karrou, M EP99, AEP117, AEP601, AEP344
Kars, TU AEP878
Karvar, M AEP167
Kasalicky, P AEP100
Kasparov, E EP83
Kassi, E AEP63, AEP555, YI7, AEP5
Kassis, M EP56
Kastelan, D PEP11.6, OC11.5
Katalinic, D **PEP3.3**
Katamadze, N AEP483
Katkó, M AEP634
Katra, R OC10.2
Katsafyloudi, M AEP823
Kattner, E PEP3.3
Katz, D **AEP546**
Kaufman, J-M OC4.6
Kaul, S PEP6.6
Kausar, N **AEP594, OC4.5**
Kautzky-Willer, A AEP184, AEP62
Kavousi, M PEP2.2
Kawthar, EA EP61, AEP216
Kayıgil, O EP238
Kayikci, O AEP705
Kaynar, K AEP473
Kazemijahromi, M **AEP453**, **AEP424**
Kazmi, SK AEP312
Kazokaite, M PEP15.6, AEP387
Kazukauskiene, N AEP222
Kdissa, A **EP229**
Keevil, B AEP6, PEP1.1
Keevil, BG PEP1.5
Kehinde, R EP20
Kek, PC AEP787
Kelepouris, N OC13.3
Kelestimur, F AEP843
Kellam, S AEP783
Keller, P AEP55
Kemény, V AEP3
Kemp, E PEP13.8
Kempegowda, P AEP655, AEP208, AEP248, AEP175, PEP14.8
Kendereski, A AEP16
Kennerson, M OC4.2
Kerkar, P AEP264
Kerkeni, H AEP340
Kermaj, M **AEP740**, **AEP375**, **AEP511**, **EP81**
Kermani, W EP68, EP230, AEP781, EP117, AEP371
Kero, J OC15.2
Kerstens, M AEP790
Keskin, C AEP825, AEP795, AEP894
Keskin, M AEP852, **AEP782**
Kessomtini, W EP63, AEP340
Ketata, N **EP56**, AEP253
Kettunen, J OC2.1
Khadidja, B **EP186**, **EP148**, **AEP623**, EP114
Khalaf, R **AEP283**, **PEP2.8**, **AEP714**, **AEP321**, **EP65**, **AEP46**
Khaldi, S EP141, AEP12
Khalid, M AEP751
Khalifa, M AEP149, AEP304, AEP745, AEP338, AEP779, AEP119, EP208, EP204, AEP694, AEP753, AEP245, AEP708, AEP302, EP27
Khalil, C EP206, EP74
Khalil, H AEP175
Khalzova, A PEP6.1, OC12.3
Khamal Doghri, S EP235, EP236, **AEP676,** EP189
Khan, A OC6.6
Khan, H **AEP94**
Khan, MAI AEP265, **AEP638**
Khan, SA **EP156**
Khan, SM AEP701, AEP265, AEP638, AEP632
Khan, SMS PEP9.4
Khan, S AEP662, AEP86, AEP42, AEP312
Khandaeva, P AEP416
Khanna, U AEP264
Khaoula, BA **AEP277**
Khaoula, Z EP100
Kharkevich, G EP217
Kharrat, I AEP374, EP36
Khelifi, D **AEP374**, **EP1**, **AEP352**, **EP36**, **EP146**
Khellaf, A AEP619
Khessairi, N EP180, AEP64, AEP57, AEP727, EP166, EP181, EP174, AEP58, AEP71
Khiari, K AEP41, AEP561, EP224, AEP75, EP146, AEP589, AEP437, AEP438, AEP419, AEP567, AEP420, EP138, AEP569, AEP393, AEP80, AEP747, EP29, EP176, EP130, EP225, AEP519, EP37, EP134
Khochteli, I AEP831, AEP657, EP190, AEP32
Khoo, CM AEP787
Khouchaf, H **AEP670**, **AEP732**, **AEP776**
Khouloud, B AEP339
Khuntia, M AEP234, PEP7.3
Khyzhnyak, O **AEP611,** AEP503
Kiefer, FW PEP4.8
Kilci, F **AEP105**
Kilcoyne, C **AEP553**
Kılıçlı, F EP97
Kılıcyazgan, A AEP877
Kilinç, İ AEP879
Kim, B OC11.2
Kim, I AEP194
Kim, KM **AEP554**, EP142, PEP4.6
Kim, K AEP194
Kim, TY PEP5.8
Kim, WB PEP5.8
Kim, WG PEP5.8
Kimpel, O **OC11.3**, PEP1.7
Kineman, R OC7.2
Kirilov, G AEP663
Kirschner, LS PEP13.6
Kirstein, J PEP15.2
Kiseleva, T AEP59
Kishor, K AEP264
Kishore Doulatram Gamgaram, V **EP103**, AEP250, AEP700, EP70
Kisioglu, SV **AEP291**, **AEP640**
Kistorp, T AEP383
Kiyar, M AEP586, AEP451
Kizilgul, M AEP873, AEP816
Klein, M AEP580
Kleinendorst, L AEP280
Klessens, F AEP281
Klimaite, R **AEP61,** AEP387
Klimek, P AEP184
Kloft, C PEP1.3

Klose, M AEP383, AEP507, AEP481
Knight, PG **S13.1**
Knip, M OC2.1
Knispelis, R AEP518, PEP8.1
Kobaidze, A AEP655
Kobrynska, O AEP289
Kocabas, M **AEP798**, **AEP784**, **AEP878**
Kocak, M EP110, AEP326, AEP724, AEP473, AEP50, AEP343, EP73, EP4, AEP675, EP221, AEP291, EP53
Kocjan, T AEP91, AEP37
Kocsis, J AEP400
Kodetova, D OC10.2
Köhrle, J OC5.1, PEP10.1
Kokko, E **AEP792**
Köksalan, D EP145
Kolasińska-Świkła, A PEP8.8
Kolatorova, L AEP620
Kolesnik, E PEP6.3
Kolibianakis, E AEP574
Komninos, J AEP617
Kondratovich, V AEP667, AEP668, AEP669
Kondrotienė, A **AEP387**
Kononykhina, A AEP483
Konrade, I PEP3.7
Konstantinou, A AEP79, AEP310
Kontolaimaki, K AEP13, PEP10.2
Kontou, L AEP236
Kopaleishvili, A AEP169
Koramannil Radha, S **AEP164**
Korbonits, M AEP488, AEP842
Korkmaz, FN **AEP44**, AEP27
Korolenko, G AEP891
Korpershoek, E AEP839
Kos, S AEP710
Kos Kudla, B PEP8.8
Koshkin, N EP194
Kosmopoulou, OA EP187
Kostadinov, N OC15.6
Kostakis, ID AEP63
Kostiainen, I **PEP9.5**
Kostitska, I **AEP678**
Kostoglou-Athanassiou, I AEP130, **AEP68, AEP121**
Kotsa, K AEP804, AEP274
Kotton, DN OC5.3
Kouerinis, E AEP570
Koufakis, T AEP804, AEP274
Koukoulioti, E EP195, PEP10.5, EP34
Kounadi, T AEP10, AEP323
Kourti, E **PEP11.5**
Koussay, A AEP368, AEP770
Koussay, EE AEP355, EP229
Koutsikos, J AEP95
Koutsilieris, M PEP5.6
Koutsogeorgopoulou, L EP34
Kouvelioti, S EP195
Koval, G PEP10.4, AEP327, AEP313, AEP656
Koval, H **AEP614**
Koval, S **AEP279**, **PEP12.2**
Kovaleva, E AEP128, EP22, AEP124, AEP101
Kovaliov, O AEP377
Kovatcheva, R AEP82, AEP663
Kovatcheva, R AEP666
Kovše Krajnc, M AEP449
Kowalska, A PEP8.8
Kozak, A AEP827
Krajnc, M **AEP449**
Kraoua, L AEP609, AEP602
Krasner, A OC15.4
Krause, K AEP35
Kravchuk, O AEP697
Kravos Tramsak, NA PEP4.5
Krawczyk, A AEP7
Krebs, M AEP62
Krejčí, H PEP2.3
Krętowski, A AEP390
Krifa, H EP1
Krishnan, S AEP312
Kristensen, SG S13.2
Kristof, van D AEP203
Krogh, J **PEP3.5**, **PEP3.4**, **PEP13.3,** AEP481
Kroiss, M OC1.3, AEP838, OC11.5
Krssak, M AEP62
Krupinova, J **YI12**, **AEP380**
Kruteleva, S EP217
Krygier, A PEP13.7
Krytskyy, T **EP219**
Ksira, I EP1
Ku, EJ AEP741
Kuchynska, I EP120
Kuckuck, S **OC12.4**
Küçük, Ö AEP44
Kuehne, J **AEP465**
Kuklina, M AEP407
Kulaksizoglu, M AEP798, AEP784, AEP878
Kulchinska, V **AEP571**
Kumar, J AEP751
Kumar, R AEP841, AEP824
Kunori, T **AEP874**
Kupari, J OC8.3
Kuprionis, G EP218
Kural, RF PEP5.1, AEP43
Kural Rahatlı, F AEP688
Kurashvili, R AEP169
Kuria, J AEP817
Kursina, N AEP377
Kurzyńska, A AEP509
Kusačić Kuna, S AEP706
Kushlinskii, N PEP11.8
Küster, J AEP527
Kuzior, A EP14, AEP174, PEP7.2, EP223, AEP431, AEP800, PEP15.8
Kuzmenkova, E AEP891
Kvanchakhadze, R AEP170, AEP305
Kyaw Tun, T EP67, AEP750
Kyithar, MP **AEP191**
Kyriakakis, N AEP842
Kyriakopoulos, G AEP5, AEP63, AEP555
Laaksonen, DE PEP9.1
Laamouri, R **AEP561**, **EP224**, AEP75, **AEP589**, **AEP567**, AEP569, AEP80, EP225, EP134
Laamouri, R AEP761
Lackovic, M AEP474
Lacroix, A OC11.5
Ladha, T **EP6**, **AEP86,** AEP42
Laforest, S **OC15.1**
Lafrance, J-P AEP206
Lages, A AEP392, AEP107
Laguillier-Morizot, C OC9.5
Lahmar, R EP27, AEP745, AEP779, AEP371, AEP403, EP68, AEP302, AEP338, AEP119
Lai, A AEP748
Lai, J AEP786
Lajic, S PEP4.8
Lajili, O AEP314
Lakhoua, Y AEP41, AEP561, EP224, AEP75, EP146, AEP589, AEP437, AEP438, AEP419, AEP567, AEP420, EP138, AEP569, AEP393, AEP80, AEP747, EP29, EP130, EP225, AEP519, EP37, EP134
Laktionov, K EP217
Lamas, C OC9.1
Lambert, P AEP40
Lambrinoc, D AEP539, **AEP145**
Lambrinoudaki, I AEP97, AEP90, AEP236, AEP570
Lamounier Filho, A EP151
Lampropoulou, P AEP10
Lamrissi, A AEP269, EP93, EP94, AEP231, AEP350
Landoni, V AEP166
Landwehr, L-S OC11.1
Lanes Iglesias, S EP78
Lang, K PEP11.6
Lanza, P PEP8.2
Lanzo, N AEP748
Lapauw, B YI9, OC4.6
Lapshina, A AEP501
Larcan, R AEP630
Lardo, P AEP22, AEP28
Larina, I AEP106
Larissa, Z **AEP260**, **AEP299**, **AEP300**, **AEP226**, **AEP262**, **EP122**
Larrañaga, I **AEP186**, **AEP160**
Larrañaga Gomez, I AEP186, AEP160
Larsen, N AEP701, AEP632
Lässer, C AEP414
Lassila, R PEP4.1
Lassoued, N **AEP441**, **AEP373**, **AEP772**, **AEP341**, **AEP364**, **AEP378**
Lastuvka, P OC10.2
Latrech, H AEP315, EP113, EP99, AEP117, EP44, AEP285, AEP601, AEP344, AEP535, EP139, AEP369, EP82, EP170, AEP53, EP57, AEP421, AEP370, AEP303

Latrofa, F AEP875, AEP880
Lau, E **EP2**
Laukiene, R **PEP5.5,** AEP459
Laukkarinen, J PEP9.1
Laukytė, I **AEP459**
Laura, I **PEP6.4**
Lauretti, L AEP840
Lauria, G AEP637
Lauro, D EP64
Lavín Gómez, BA AEP221
Laviola, L PEP4.3, OC2.6, **D2.2**
Lavrador, M AEP273, AEP247, **EP8**, **AEP107**, **AEP430**
Lax, A PEP6.7
Laycock, K OC1.5
Lazar, D-G **EP149**
Lazari, J AEP793
Lazid, S AEP302
Lazova, M AEP230
Lazzaroni, E YI2
Leal, A EP28
Leal-Witt, MJ PEP12.4
Lebedev, D **AEP219**
Łebek-Szatańska, A **AEP30**
Lebl, J **PL7**
Leborgne, C OC6.2
Lecumberri, B AEP542, AEP531
Lecumberri Santamaría, B AEP504, AEP478
Lee, B PEP4.6
Lee, D AEP787, AEP405
Lee, E **AEP741**
Lee, J AEP194, AEP588, AEP618, EP98, AEP554
Lee, M PEP4.6, AEP618, **EP98**
Lee, MJ AEP194
Lee, SH AEP414
Lee, Y-M PEP5.8
Leen, E AEP65
Leese, G AEP842
Léger, J PEP4.8
Leichsenring, C EP13
Leitão, F PEP4.7
Leitão Martins, V AEP577
Leite, AR AEP212
Leiva, M AEP252
Leka-Emiri, S **PEP3.6**
Lekić, I AEP445
Lekva, T OC8.6
Lengton, R OC7.3
Lengyel, I AEP410
Lengyel, IM AEP634
León, S **AEP241, OC12.6**
León Utrero, S EP79, AEP211, **AEP333**, EP207
Leone, I PEP12.6
León-González, AJ **AEP397,** OC13.5
León-Idougourram, S AEP382
Leonova, N OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6
Leonova, T AEP667, AEP668, AEP669
Lepanto, S AEP748
Lerchbaum, E AEP159
Lerin, C PEP12.4
Lerner, A S13.2
Lessan, N AEP164, AEP161
Leszczynska, D AEP30
Letizia, C AEP19
Leustean, L EP131, AEP622, AEP150, AEP401
Levy, MJ AEP842
Levy, S AEP185, EP12
Lewandowski, K **AEP178**
Lewinski, A AEP125, AEP178, PEP10.8
Lewis, M **AEP40**
Lewis, R AEP495
Ležaić, L AEP91
Lhamyani, S **EP52**
Li, J AEP266, **AEP60**
Li, N OC10.4
Li, Q **AEP322**
Li, R **EP96,** PEP2.2
Liao, Z OC3.1
Libe, R PEP11.5, OC1.3, OC11.5
Libran, M AEP282
Lider Burciulescu, SM **AEP2**, **EP197**, EP158
Liew, D AEP17, AEP33
Lilis, D AEP893
Lim, YJ OC11.6
Lima, C EP28
Lima, J EP13
Lima, N AEP267
Linda, S PEP6.4
Lines, K **S21.1**
Lindén, R PEP9.5
Lindner, V AEP55
Linglart, A AEP81, AEP116, OC6.2
Linhas, R AEP650
Linkeviciute, A AEP661
Liotta, M AEP630
Lippert, J OC11.1
Lisdero, AP PEP15.5
Litaiem, N AEP352
Liu, H OC7.6
Liu, Q AEP167
Liu, Y AEP60, AEP266
Livadas, S AEP225
Lizarraga Zufiaurre, A AEP775
Llahana, S AEP583
Llanos Muñoz, M AEP871
Lobashova, V AEP733, AEP821
Lobatto, DJ AEP537
Lobna, C AEP754
Lobo, A AEP56
Lobo, I **AEP103**
Locatelli, M OC8.4, PEP3.1, AEP114
Loffing, D AEP8
Loffing, J AEP8
Logvinova, O AEP426
Loh, LM AEP787
Loktionova, A **AEP508**
Loli, P OC11.5, OC3.3
Lomas Meneses, A EP202, AEP454
Lombardi, CP AEP642
Lombardi, G OC6.1, AEP21
Longari, V AEP651
Longhi, M AEP131
Loo, MR AEP394
Lopes, L EP86, EP76, PEP7.7, AEP112, EP42
Lopez, M AEP267, OC7.5, OC7.4, AEP252
López- Ibarra Lozano, PJ EP79
López López, C AEP871
López Merseguer, M EP125
Lopez Nevado, C AEP434, AEP774, AEP639
López-Cánovas, JL EP129, **OC9.4**
López-Ibarra Lozano, PJ AEP211
Lopez-Martos, A PEP14.5, AEP677
López-Mezquita Torres, E EP79
López-Miranda, J YI6
Lopitz Otsoa, F OC7.5
Lordan, J AEP394
Lorenzo Hernández, E **EP70**
Lorenzo-Lozano, M-C PEP14.5, AEP677, PEP14.4
Lottspeich, C AEP6
Loughrey, PB **AEP488**
Louis, M AEP206
Louis, P AEP648
Loukili, MA AEP315, EP113, **EP57**, **AEP421**, AEP370
Loustau, P AEP644, EP226
Loyola Correa, T **PEP12.3**
Luboshitz, B AEP242
Luca, BL AEP809
Lucas, M EP13
Lucidi, V AEP31
Luconi, M PEP11.1, PEP11.3
Łuczkiewicz, P AEP151
Ludgate, S **AEP728,** AEP552
Ludlam, WH OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6
Luger, A AEP62, OC14.5
Luiro, K PEP4.1, **OC2.2**
Luiza, V EP143
Lukas, J **EP201**
Lumsden, MA AEP414
Lundbäck, B AEP414
Luo, R OC15.4
Luo, Y AEP414
Lupi, I AEP875
Lupo, S AEP723
Luppa, P AEP613, AEP599
Luque, RM PEP9.6, OC9.4, OC9.2, OC9.3, AEP384, OC3.4, YI8, OC9.6, AEP382, OC13.5, AEP397, EP129, OC3.2, AEP499
Lushchyk, M **PEP15.4**, **AEP891**
Lutsenko, A **PEP8.7**
Lymareva, A AEP595
Lymperopoylos, K AEP10
M Jiménez-Vacas, J AEP384, YI8
M. Luque, R YI6
Ma, C AEP167
Maaloul, M AEP777
Maamri, H AEP366, EP56, **AEP253**
Maaroufi, A EP171, EP141, AEP645, EP16, AEP12, AEP771
Maazoul, F AEP602

Macauley, M AEP785
Macech, M PEP11.6
Macedo, S **OC14.3**
Macias-Gonzalez, M AEP165
Macioniene, E AEP661
Macleod, K AEP405
Macut, D EP126, AEP402
Macut, DP OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6, AEP225
Madan, A OC15.4
Madhbouh, M AEP324
Madhi, W AEP709, AEP324, **EP174,** AEP64
Madrona, A AEP397
Madu, I-J PEP1.2
Maganeva, I **AEP128**, **AEP106**
Magdalena, S AEP150
Maggi, M AEP857, AEP803, AEP861, PEP11.1, PEP11.3, AEP835
Maggio, R AEP22, AEP28
Maggiore, R PEP6.2, OC6.1
Maghakyan, S **EP162**
Maghnie, M **JS2.1**
Magruk, M AEP233
Maguire, B EP54
Maha, BF AEP754
Maha, K AEP368
Maha, K AEP770
Mahapatra, H **AEP234**, **PEP7.3**
Mahapatra, L AEP234, PEP7.3
Mahdaoui, S AEP615
Mahjoub, F AEP240, AEP314
Mahjoub Rkik, N EP133
Mahmood, A AEP367
Mahmood, I EP144
Mahmood, M OC7.2
Mahmoud, R AEP720
Mahrez, A AEP209
Mahroug, I AEP117, AEP601
Mai, K AEP183
Main, AM **AEP383**
Maiorino, A EP64
Maiter, D OC3.3
Maíz Alcorta, B AEP186, AEP160
Majdoub, M AEP41, AEP718, AEP75, AEP589, AEP80, EP29, EP176, EP130
Majeed, A PEP11.7, OC1.6
Majeed, M AEP161
Majic, A AEP102
Makarenko, I AEP233, AEP448
Makedou, K AEP274, AEP804
Makhlina, E **AEP436**, EP132
Makker, T AEP512
Makkonen, K **OC15.2**
Makni Ayadi, F AEP73
Makras, P **MTE9**
Maksutova, N AEP330
Malesevic, G AEP270, AEP271, AEP318, AEP517
Malevanania, E AEP862
Malevanaya, E PEP11.8
Malha, A EP18, EP114, AEP154, EP100, AEP147, EP38, AEP549
Malik, I **AEP195**, **EP77**
Malik, MF **AEP751**
Malíková, M AEP620
Malki, A **AEP315**, **EP113**, **AEP285**, EP57, AEP370, AEP691
Mallea-Gil, S **AEP470**
Mallek, A EP234
Mamadjanov, A AEP357
Mamedova, E **AEP566,** PEP8.7
Mamoojee, Y AEP394, AEP523, AEP491
Manani, C **AEP87**
Mañas Alonso, L AEP186, AEP160
Mancini, A PEP4.2, PEP8.2
Mancini, R PEP14.3
Mancioppi, V AEP201, PEP12.6, AEP166
Mandic Rajcevic, S AEP404
Mane, A AEP822
Manel, N AEP754
Manfrini, S AEP627, AEP104
Mangili, F PEP3.1, OC8.4
Manique, I **AEP582**, **AEP199**, AEP246
Manita, I AEP311
Mankovsky, B AEP171
Mankovsky, G AEP171
Manne, M AEP140
Mannelli, M PEP11.3, PEP1.7, PEP11.1
Mannstadt, M AEP644, EP226, OC6.5
Manojlovic Gacic, E AEP522
Manolopoulos, K AEP175
Manolopoulos, KN PEP11.6
Mansoor, Q OC4.2
Mansour, S AEP74, AEP55
Mantega, M AEP120
Manthou, E AEP274
Mantovani, G PEP14.7, AEP81, PEP3.1, OC8.4, AEP651, **S14.1**
Marañon, P AEP252
Maravall, J EP154
Marazuela, M OC14.5, OC1.1
Marcelino, M EP86, EP76, PEP7.7, AEP112, EP42
Marchan Pinedo, M AEP499
Marchenkova, L **AEP113**, **AEP152**, AEP239
Marchiani, S AEP857
Marchuk, Y AEP614, AEP656, PEP10.4, AEP327, AEP313
Marcocci, C AEP875, OC6.6
Marcos, M AEP267, OC7.4
Marcuello Foncillas, C AEP774
Marelli, C AEP93
Maresch, Â PEP4.7
Margarit, E AEP659
Mari, G PEP6.2, OC6.1
Maria Fernandez-Trujillo-Comenge, P **EP14**, AEP174, AEP431, **PEP15.8**
Marić, A EP228
Marie, V AEP844
Marie-Christine, V OC1.3
Marin, A AEP54
Marina, L **AEP16**
Marinaki, S OC14.4
Marinakis, T AEP10
Marinelli, L OC10.6
Marinova, G **AEP767**
Marin-Peñalver, JJ AEP773
Marion, S PEP13.2
Marius, R AEP848
Markantes, G **YI10**
Markatos, F YI10
Marker, A OC1.5
Markou, A OC1.4, AEP10
Markova, D OC6.6
Marline Yvonne Dinghat, O **AEP359**
Marmon, T OC15.4
Marmouch, H AEP831, AEP657, EP190, AEP32
Maroni, P PEP6.2
Marova, E AEP126, AEP416, AEP468, AEP483, PEP8.7
Marques, B AEP742, AEP743
Marques, H AEP148
Marques, O AEP543
Marques, S AEP148
Marques-Sá, J **AEP562**, AEP189
Marquina, C AEP17
Marra, G PEP3.1, OC8.4
Martelli, M PEP15.3
Martín Nieto, A **AEP736**
Martin Rojas, P AEP103, AEP504
Martin Timon, I AEP316, **AEP773**
Martin-Colom, J YI8
Martinez, A AEP502
Martinez, D EP88, **PEP12.4**
Martinez Chantar, ML OC7.5
Martínez Chantar, M AEP252
Martínez Martínez, AL AEP775
Martinez Montoro, JI AEP213, **AEP346**, AEP293
Martinez Tames, G EP78
Martinez-Chantar, ML AEP267, OC7.4
Martínez-Fuentes, AJ OC13.5, PEP9.6
Martínez-Martínez, AL AEP828
Martínez-Vilavella, G AEP466
Martinho, M AEP597, AEP497
Martini, G AEP457
Martinkevich, O AEP631
Martino, M PEP14.7
Martin-Perez, M PEP7.2
Martins, AC AEP199, PEP2.1, AEP246
Martins, LS AEP88
Martins, MD AEP650
Martins, RG AEP742, AEP56, AEP743
Martins, T AEP742, AEP743
Martins da Silva, A AEP673

Martin-Torres, E PEP14.5
Marusic, S AEP102
Marwa, BN AEP753
Marwa, R AEP708
Marwah, T AEP264
Marwood, O AEP783
Maryem, B AEP269, EP94, AEP231, **AEP350**
Marzullo, P AEP201
Mascarenhas, MR AEP876
Mascarós Martínez, JM EP125
Mascha, O AEP130, AEP310, AEP79
Maseroli, E AEP861, AEP835, AEP857, **AEP803**
Masjkur, JR PEP11.6
Masmiquel Comas, L AEP272
Masmoudi, M **AEP302**, **AEP119**, **AEP745**, **EP204**, **AEP304**, **AEP338**, **AEP245**, **AEP753**, **AEP694**, **EP27**, **EP208**, **AEP708**, **AEP149**, **AEP779**
Massa, N AEP166
Massarella, A AEP429
Mastnikova, K OC10.2
Mastorakos, G AEP617
Mastorodemos, V PEP10.2
Matchekhina, L **AEP196**
Mateen, A AEP120
Matei, A **AEP98**
Matezius, I AEP862
Mathilde, G AEP859
Mathur, MB AEP414
Matikainen, N PEP9.5, AEP792
Matinho, M AEP409
Mato, J OC7.4
Mato, JM OC7.5
Matos, AC EP13
Matos, A **AEP409**
Matos, P YI11
Matson, M OC1.5
Matsuura, B **EP51**
Matthias, K OC11.3, PEP1.7
Mattogno, PP AEP840
Matveeva, M **AEP286**
Matyjaszek-Matuszek, B AEP249
Maurier, A AEP580
Mauricio, D **S18.1**
Mauroy, B OC14.1
Mavrogianni, D YI7
Maxime, H PEP6.4
Mayilvaganan, S AEP726, **EP196**
Maznichenko, V AEP759
Mazur, L **AEP684**
Mazurina, N **EP217**
Mazzilli, R **AEP575**, AEP22
McArt, D AEP488
McBride, M **AEP423**, **AEP415**
McBrinn, R AEP405
Mccarthy, CG AEP177
McConnachie, A OC1.5
McDermott, J EP21, AEP750, AEP65, EP67
McGinnis, C OC14.2, AEP405
McGowan, B AEP388
Mchirgui, N AEP41, AEP561, AEP718, EP224, AEP75, EP146, AEP589, AEP437, AEP438, AEP419, AEP567, AEP420, EP138, AEP569, AEP393, AEP80, AEP747, EP29, EP176, EP130, EP225, AEP519, EP37, EP134
McIntosh, A OC1.5
Mckiddie, F YI4
McQuaid, S AEP728, AEP552
Md, R AEP389, AEP726
Med Elmokhtar, S AEP363, EP91
Medina, C PEP2.2
Medina, JL PEP10.6
Mednieks, J AEP243
Meeran, K AEP486
Megerle, F OC11.3, PEP1.7
Megnis, K PEP3.7
Mehdi, R EP9, EP11
Meherzi, A EP230
Mehmet, B **AEP583**
Mehrez, A EP105
Mehrzi, A **EP45**, **EP124**, **EP107**, **EP47**, **AEP324**
Mehtälä, J AEP560
Meier, C AEP89
Meizoso-Pita, O AEP773
Mejdoub, N AEP762, EP211, AEP731, AEP70, EP75, AEP210, EP199, EP200
Mejdoub, R EP61
Mejdoub, Y EP87, EP56, AEP253, **AEP366**
Mekni, S AEP437, AEP438, AEP419, AEP420, EP138
Melania, B AEP868
Melguizo-Melguizo, D AEP763, PEP14.4
Melkozerov, K AEP407
Mella, A AEP723, PEP5.2
Melmed, SK OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6
Melnichenko, G AEP501, AEP483
Melo, G AEP168, AEP48
Melo, M AEP198, EP26, AEP247
Melson, E AEP655, AEP208, **AEP248**, AEP332, AEP175, PEP14.8
Menafra, D AEP412
Mendes Costa, M **AEP876**
Mendoza, N AEP486
Menendez Torre, EL EP78, AEP685
Meneses González, D AEP809
Meng, L **AEP85**
Meng, Z OC10.4
Mera Carreiro, S AEP38
Merchante Alfaro, AÁ EP154
Mereghni, S AEP563
Merenkova, M EP39
Merino, S AEP828
Merke, D PEP1.2
Merlo, I AEP828, **AEP502**
Merlo Pascual, I AEP775
Merrow, M PEP13.5
Mert, M AEP505, AEP422, AEP489
Mertens, J **AEP157**, **AEP11**
Meskine, D AEP154, EP100, EP177, AEP147, EP38
Meskinyte, I AEP61
Messina, C AEP104
Mestiri, S EP230
Metello, JL AEP600
Methlie, P AEP4, AEP26
Metin, D AEP422
Metindogan, O AEP856
Metso, S PEP9.1
Metz, M AEP62
Meyer, G PEP4.8
Meyer, LS **AEP791**
Mezosi, E OC3.3, OC15.4
Mezoued, M **EP18**, **AEP549**, **EP114**
Mhamdi, Z AEP698
Micev, M EP126
Michalakos, S PEP3.6
Michalis, E AEP10
MIchalopoulos, A PEP6.5
Michaylova, E AEP296
Michelet, R PEP1.3
Mickuviene, N **AEP222**
Miclea, D AEP576
Miettinen, PJ OC2.1
Miglinas, M AEP661
Mignone, F AEP166
Mihaela, V AEP868
Mihai, D AEP54
Mihaj, I EP81
Mihneva, V AEP810
Mihon, C AEP199
Mikadze, K AEP305
Mikael, K OC2.2
Mikhail, S AEP260, AEP299, AEP300, AEP262, EP122
Mikhaylova, D **AEP468**
Mikolaj Kirić, M EP228
Mikovic, N AEP575
Mikulska, AA AEP866
Milano, S OC12.2
Mili, N **AEP236,** AEP570
Milicevic, M AEP522
Milin Lazovic, J AEP16
Miliou, M EP34
Miljic, D AEP522
Millet, O OC7.5
Milojevic, T AEP522
Mimouni, S AEP458
Minasi, A EP64
Minasian, S OC12.3
Mingozzi, F OC6.2
Minguez-Alarcon, L **S5.3**
Minni, F PEP11.4
Minorini, V YI2
Miranda, AR EP210
Miranda, G **AEP801**
Mirante, A AEP577
Mirica, A EP32, AEP429, **EP143**
Mirică, A EP179
Mirjam, C-C AEP467
Mirmiran, P AEP335
Mishra, DN **EP55**
Mishra, S AEP593
Missaoui, A AEP731, AEP70, EP71
Misso, C OC5.4, AEP641, AEP633

Mitchell, A AEP836
Mitchell, DM AEP644, EP226
Mitka, K **AEP649**
Mitrofanova, O AEP386
Mitrovic, B **AEP294**, AEP474
Mitru, N EP32
Mitru, NR **EP179,** AEP429
Mittag, J OC15.5, **S11.2**
Miyake, T EP51
Miyazaki, M EP51
Mizouni, H AEP123
Mizouri, R AEP240, AEP314
Mkrtumyan, A AEP300
Mlawa, G **AEP836**, **AEP832**, EP167
Mlekus Kozamernik, K **AEP91**
Młodożeniec, A **AEP744**
Mnif, F AEP762, EP211, AEP764, AEP731, AEP70, AEP202, EP75, EP71, AEP237, AEP362, EP175, AEP306, EP165, AEP73, EP159, AEP548, AEP363, EP91, EP133, AEP197, EP50, AEP72, EP192, AEP584, EP66, EP7, EP133, AEP197, AEP764, EP75, AEP210, EP71, AEP762, EP211, AEP731, AEP70, EP62, AEP362, EP175, AEP306, EP165, EP159, EP199, AEP548, EP200, EP91, EP192, EP66, EP50, AEP363, AEP72, EP7
Mnif Feki, M AEP238, AEP361, AEP616, AEP584, AEP707
Moalla, N AEP306
Modamio, J AEP316
Modroño Mostoles, N AEP809
Mofokeng , TRP **AEP360**
Mogos-Cioncu, R AEP98
Mohamed, A AEP355, AEP754, AEP691, AEP780, AEP766, AEP403, EP229, AEP654, AEP628, EP61, AEP440, AEP764, AEP731, AEP70, AEP202, EP75, AEP210, EP62, EP71, AEP237, AEP362, EP175, AEP306, EP165, AEP73, EP159, EP199, AEP366, AEP548, EP200, AEP253, EP10, EP163, AEP287, EP121, EP173, AEP216, AEP307, AEP339, EP89, AEP25
Mohamed, M EP74, EP206
Mohamed, R EP89
Mohamed Ahmed, MA EP7, AEP72, **EP62**, **AEP238**, EP199, AEP548, EP200
Mohamed el Hassan, G AEP676
Mohamed Elmoctar, S **EP50**, AEP72, EP7, EP159, EP199, EP200
Mohamed Habib, S AEP441, AEP373, AEP772, AEP341, AEP364, AEP378
Mohamed Hendawy, L **AEP156**
Mohammed, A AEP394
Mohammed, T AEP140
Mohandas, C AEP367
Mohd Nor, S AEP895
Mohr, H OC15.3
Mohseni, M **OC7.3**, AEP235
Moilanen, L PEP9.1
Moita, R EP178, AEP69
Mokhort, TV AEP631
Mokhort, T AEP158
Mokni, M EP230
Mokrysheva, N AEP128, YI12, AEP106, AEP380, EP22, AEP124, AEP101, AEP483, AEP426, EP30, AEP139
Mola, L **AEP632**
Mola Reyes, L AEP632
Moldoveanu, G AEP672
Molina, MJ AEP241
Molina-Puertas, MJ AEP382
Molinaro, E AEP875
Molitch, ME OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6
Molka, C AEP770, AEP368
Mollejo, M AEP110, AEP768
Momoh, R **EP33**
Monahan, M OC15.4
Monastirioti, N OC1.4
Mondher, K AEP253
Monia, G EP229, AEP355, AEP780, AEP766, AEP403
Moniuszko, M AEP892
Montalbán Carrasco, C AEP221
Montalban Mendez, C AEP760, EP202, AEP454, AEP381
Montanelli, L AEP875
Montano, L AEP572
Montebello, A **AEP385**, **PEP9.7**
Monteiro, AM AEP148
Monteiro, MP PEP4.4
Monteiro, M AEP836, AEP832
Monteiro, N AEP115
Montero Benítez, MZ AEP760, EP202, **AEP454,** AEP381
Montero-Hidalgo, AJ **OC9.2,** AEP397
Montò, T YI1
Montoya Alvarez, T AEP809
Monzani, F AEP802
Monzon, A AEP502, AEP828
Monzón Mendiolea, A **AEP775**
Moodley, P AEP376
Moonim, M AEP120
Mora, M PEP5.4
Morace, R PEP13.1
Morais, S EP13
Morange, I AEP844
Moravcova, J OC10.2, AEP739, AEP129
Morawiec-Sławek, K AEP509
Morea, A **AEP539,** AEP145
Morelli, A AEP861
Morelli, V AEP9, **AEP21,** PEP14.7
Moreno, C AEP392, AEP456, EP26, EP8
Moreno Domínguez, O AEP103
Moreno Rodrigo, A AEP186, AEP160
Moreno Tirado, A AEP381, **AEP760**, EP202, AEP454
Moreno-Montilla, MT OC9.4
Moreno-Montilla, T YI6
Moreno-Moreno, P OC3.4, **AEP621,** AEP227
Moreno-Ruiz, I AEP773, AEP316
Morgan, G PEP14.8
Moriarty, D PEP1.2
Moriarty, M EP6, AEP86
Morotti, A PEP6.2
Mosconi, C PEP11.4
Moskalenko, O **EP83**, **EP84**
Mosnerova, E EP17
Mosnier-Pudar, H OC9.5
Mosse, I PEP15.4
Motoiu, S AEP142
Mouelhi, Y EP174, EP166, **AEP64**
Mouna, B EP229
Mouna, E EP10, AEP339, AEP307, AEP25, EP173
Mouna, G AEP24, **AEP99**, AEP485
Mouna, M EP121, EP173, AEP216, AEP307, AEP25, AEP287, EP61, EP163, EP10
Mouna, MF AEP339, EP89
Mouna, S AEP24, AEP99, AEP485
Moura, J AEP217
Mourinho Bala, N **AEP23**, **AEP406**, **AEP411**, **AEP749**
Mourya, S OC6.6
Moustaki, M **AEP823**
Moustogiannis, A AEP5
Mparmpa, E AEP127, AEP379
Mrad, R AEP609, AEP602
Mu, F PEP6.8, PEP6.6
Mueller, SC AEP451
Mulla, K EP20, **EP40**
Mullen, N **AEP77**
Muller, I YI2, **AEP651**
Müller, H **AEP500**, **AEP462**, **AEP477**, **OC3.5**, AEP528
Müller, TD OC7.5
Mumbach, AG PEP15.5

Munier, M YI5
Munir, A AEP833
Muñoz, C AEP241
Muñoz Torres, M AEP136
Muntean, V AEP576
Muraleedharan, V AEP215
Muratova, S EP214
Muresan Oltean, BT EP125
Murray, C OC14.2
Murray, RD AEP842
Musa, A **AEP255**
Musat, M AEP695
Mustafa, N AEP895
Mustafakulov, M AEP330, **AEP207**
Mustonen, J AEP792
Mutanen, A AEP792
Mykytyuk, M AEP503
Myriam, D AEP648
Myśliwiec, J AEP390
Mytareli, C AEP49
Mytilinaiou, M PEP10.2, AEP13
Nabila, R AEP339, EP10, EP61, EP121, EP173, AEP216, AEP287, EP89, EP163, AEP307, AEP25
Naciu, AM AEP104
Nadia, C AEP25, EP89, AEP287, AEP339, EP163, EP121, EP173, AEP216, AEP307, EP10, EP61
Nadiani, B AEP651
Nadjmutdinova, D EP231
Nagy, E OC5.2, AEP733, AEP734
Nagy, EV AEP634
Nagy, R **EP160**
Nagy, RÁ AEP400
Nagy, VE AEP410
Naifar, M AEP73
Naik, S AEP593
Nair, N AEP218
Nair, S OC4.4
Najla, B EP185, EP69, AEP284
Najoua, M EP99, AEP117, EP44, AEP285, AEP601, **AEP344**, AEP369
Nakaguchi, H EP51
Nakhle, S PEP1.2
Nakouti, T PEP5.6
Naliato, E EP151
Nam, K-H AEP741
Nam Tran, D EP142, AEP588
Naouar, R AEP32
Napodano, C PEP4.2
Napoli, A AEP575
Napoli, N AEP104
Nardini, P PEP11.3
Narendran, A AEP175
Narendran, P AEP208, AEP248, PEP14.8
Nascimento, J EP151
Naseem, AA EP182, OC4.2, OC4.5, AEP594
Naser, I **AEP720**
Nasir, S **AEP312**
Nasiri-Ansari, N AEP5, AEP63, AEP555, **YI7**
Nasiroglu Imga, N AEP796, AEP850, AEP788
Nasri, I EP71
Nastina, O AEP377
Nastos, K AEP13
Natalicchio, A PEP4.3, OC2.6
Navardauskaite, R AEP598
Navarro, E OC9.1, **AEP665**, **PEP9.8**
Navarro González, E AEP871
Navarro Martín, M AEP871
Navis, G OC7.1
Navmenova, Y AEP436, **EP132**
Nawal, EA EP212, AEP746, AEP564, EP109, AEP348
Nawaz, G AEP439
Nazir, HI AEP529
Nazzal, M AEP177
Nedeska, N AEP319
Nedeva, I **AEP200**
Nedjatian, N OC13.3
Nedra, B PEP2.5
Nedrebø, BG AEP4
Neele, M AEP710
Neggers, S AEP839
Negri, M YI1
Negro, R AEP733, OC5.2, AEP734
Nemtzova, V AEP653
Neou, M OC1.3
Nermoen, I AEP4
Neselioglu, S AEP869
Nesi, G PEP11.1, PEP11.3
Nesim, M AEP720
Neuenschwander, M OC5.1, PEP10.1
Neumann, U PEP4.8, PEP1.3
Nevalainen, P AEP792
Neves, C AEP578, OC14.3, **PEP10.6**
Neves, JS AEP212, PEP10.6
Neves, J AEP246
Neves, M AEP228
Newell-Price, J OC8.2, PEP13.8
Newfield, R PEP1.2
Ng, CY PEP14.8
Ng, KF PEP7.4, AEP820
Ngandu, DL AEP836
Ngaosuwan, K **PEP11.7**, **OC1.6**
Nguyen, V AEP786
Ng-Won, K AEP490
Ni Chinneide, A EP67
Niazi, R EP182
Niciporuka, R AEP51
Nicolau, J AEP272
Nicoli, F AEP131
Niculescu, DA AEP659, AEP479
Nicusor, P AEP146
Niedra, H PEP3.7
Nielsen, SB **S17.1**
Nielsen, V OC10.5
Nieman, L **OC3.3**
Niemelä, O AEP792
Nijhoff, M OC6.3
Nikaina, E PEP8.4
Nikitina, T AEP144
Nikolaiev, R **AEP503,** AEP611
Nikolakopoulou, S AEP79
Nikolaou, N YI3
Nikolic Djurovic, M AEP522
Nikolov, R AEP810
Nirantharakumar, K PEP11.6
Nissim, E AEP372
Nitu, I AEP539, AEP672
Nivelo Rivadeneira, ME AEP800, PEP15.8, PEP7.2, EP14, AEP174
Niven, M **AEP372**
Nizharadze, N AEP170
Njagi, E **AEP817**
Nobels, S AEP586
Nocentini, A PEP11.3
Nogueira, F AEP578
Nogueiras, R **AP2.** AEP267, OC7.4
Nogueiras Pozo, R AEP252, OC7.5
Noiszewska, K AEP818
Noll, M OC12.1
Nölting, S OC15.3
Nomikos, A AEP121
Nonchev, B AEP719, AEP413, AEP636
Nor, MA AEP191
Nora, I AEP590
Nora, L AEP149
Nouira, M AEP887, AEP883
Nour El Houda, K **AEP717**
Novak, Z AEP739
Novoa, E OC7.4, **AEP252,** AEP267
Nowak, A OC14.6, AEP472
Nowak, J **AEP351**, **EP116**
Nowak, K AEP30, **AEP325**
Nowé, V PEP9.3
Nowotny, H PEP1.1
Nowotny, HF **AEP6,** AEP45, **PEP4.8**
Nsengimana, J AEP785
Ntikoudi, A **AEP617**
Nuhoglu, I EP221, AEP291, EP110, AEP326, AEP724, AEP473, AEP50, AEP343, EP73, EP4, AEP675, EP53
Núñez Abad, M EP125
Nuralieva, N AEP193, **EP19**, AEP830
Nurmatov, U AEP414
Nuutila, P PEP9.1
Nwaru, BI AEP414
Nyari, G EP160
Nyiraty, S AEP400
O'Reilly, MW PEP11.6
Obermayer, A AEP159
Obermayer-Pietsch, B PEP6.3, AEP159
Obradovic, M AEP294, AEP474
O'Connell, P PEP8.5
O'Donovan, O OC4.4
Oei, L PEP2.2
Oelkrug, R OC15.5
Offi, C **AEP633**, **OC5.4**, **AEP641**
Ogmen, B PEP15.1, AEP799, AEP847
Ognjanovic, S EP126, AEP402
Oguz, S AEP640
O'Halloran, M AEP77
Ohana, N AEP135
Ohwovoriole, AE AEP190
Ojewuyi, T PEP1.8
Okamura, H AEP200
Okoye, C AEP802
Øksnes, M AEP4
Oláh, A AEP400

Olana, S AEP575, AEP22
Olarescu, C AEP463
Olarescu, NC OC8.6
Olariu, C AEP672
Oleaga Alday, A AEP775
Olfa, B AEP240, AEP314
Oliva, A PEP4.2
Oliva, JC AEP476
Oliveira, AC AEP212
Oliveira, MJ AEP168, PEP14.1, EP209, AEP48
Oliveira, PF PEP4.4
Oliveira, S AEP742
Oliveira de Oliveira, I PEP12.3
Oliver, N OC1.6, PEP11.7
Olivier, L EP114
Ölmez, ÖF EP97
Olsen, LG OC8.6
Olson, S YI4
Olsson, DS AEP39
Olteanu, A-M AEP52
Olveira, G EP52
Olveira Fuster, G EP103, AEP700
Omer, T **AEP329**, EP144
Onak Kandemir, N AEP825
Onalan Etem, E OC8.5
Ons, T EP61
Oo, A OC11.2
Ooi, CP **AEP895**
Ooi, E AEP655, **AEP208,** PEP14.8
Opalic, M EP126, AEP402
Opalinska, M **AEP509**
Oprea, L AEP695
Oprisan, B AEP608, AEP607
Orcajo, L AEP871
Oreski, I AEP102
Orgill, D AEP167
Oriola, J OC9.1
Orłowska-Florek, R AEP744
Orme, SM AEP842
Ornella, R PEP13.2
Orois, A AEP282
Oros, SE EP149
Ortega Juaristi, M AEP809
Ortez Toro, JJ AEP725, EP193, AEP778
Oruk, G AEP758, **PEP5.1**, **AEP43**
Oruk, GG AEP679
O'Shea, P AEP77
Osmani, M AEP680
Osorio-Conles, O PEP12.4
Ostberg, J EP40
Otero, J PEP15.5
Otieno, F AEP817
O'Toole, S OC1.5
Otte, A AEP500
Ouafidi, B AEP269, EP93, EP94, **AEP231**, AEP350
Ouertani, H AEP625, EP3, AEP609
Oueslati, I AEP71, **AEP123**, **AEP47**, **EP155**, **AEP34**, **AEP761**, AEP727, **AEP558**, **EP215**, **EP23**, **EP216**, **AEP220**, **AEP715**, **EP80**, **EP157,** EP181
Ounaissa, K AEP209, EP47
Outas, MC EP197
Outtaleb, FZ **AEP590**
Ovize, M OC12.2, OC6.5
Øystese, KAB OC8.6
Owens, L S13.2
Ozanne, S **S5.1**
Ozcelik, O AEP811, AEP794, AEP788
Ozdemir, D PEP15.1, AEP825, AEP846, EP239, AEP877, **PEP15.7**, AEP879, **AEP814**, AEP870
Ozdemir, E AEP886
Ozkan, C **EP232**, **EP240**, **EP164**, AEP854
Ozkan, E AEP44
Ozkaya, HM AEP585
Ozturk, AM EP232
P. Castaño, J OC13.5
Paccapelo, A PEP11.4
Pace, D OC5.4
Pačesová, P AEP739
Pach, D AEP649, AEP7
Padhye, D **AEP218**
Padilla Segura, MR EP154
Paduraru, D AEP142
Pagliaro, P OC12.5
Pagotto, U AEP153, PEP11.4, OC6.6
Pahirko, L PEP15.6, AEP243
Paiva, I AEP198, AEP392, AEP456, EP26, EP8, AEP107, AEP430, AEP273, AEP247, AEP96, PEP4.7, AEP18, AEP56, AEP587
Paiva, S AEP56, AEP198, AEP273, AEP247, AEP96
Paja, M AEP502
Paja Fano, M OC9.1, **AEP828,** AEP775
Pak, K **AEP194**
Pakhomov, Y EP231
Pal, A AEP495, AEP842
Palaiologou, A AEP90
Palamarchuk, V AEP759
Palazzo, F AEP662, AEP42
Paldánius, PM PEP2.4
Paleń-Tytko, J AEP509
Palermo, A **AEP627**, AEP104, OC6.6
Palha, A PEP2.1
Pallarés, R AEP434, AEP639
Palma, I AEP276, AEP398
Palma, P AEP276
Palmieri, S OC6.4
Palumbo, G AEP475
Palumbo, V PEP13.1
Pamedytytė, D AEP387
Pamuk, N AEP505, AEP422, AEP489
Pamukçuoğlu, M AEP885
Panagiotou, G **AEP523**
Panarra, A AEP199
Panayi, A **AEP167**
Pancevacki, S AEP474
Panchangam, RB EP196, **AEP389**, **AEP726**
Panchulidze, M AEP305
Pandit, K AEP264
Pandzic Jaksic, V **AEP102**
Pang, EJ **AEP701**
Pangui, HL **AEP626**, **AEP66**, **AEP347**
Panidis, S PEP6.5
Pankiv, I **PEP10.4**, AEP327, AEP614, AEP313, **EP101**, AEP656
Pankiv, V **EP48**
Pankratova, M **AEP829**
Panoskaltsis, T AEP236
Panoulis, K AEP90, AEP97
Pantelidis, P PEP6.5
Pantelinac, P AEP606
Paolicchi, A AEP802
Papadimitriou, E AEP10
Papadopoulou, IB EP187
Papaioannou, M PEP6.5
Papanastasiou, L OC1.4, **AEP10**, AEP323
Papanikola, N AEP823
Paparodis, R AEP225
Papatheodorou, A AEP95
Papatheodorou, G AEP95
Papavassiliou, AG AEP63, YI7
Papavramidis, T PEP6.5
Papavramidis, TS AEP87, EP35, AEP652
Papierska, L AEP30, AEP325
Papini, E AEP734, OC5.2, AEP733
Pappa, D AEP494, AEP379, AEP127, AEP635
Paragh, G AEP634
Paragliola, RM PEP14.7
Pareja, R AEP476
Parianos, C **AEP63**
Park, SM AEP588, AEP618
Parkes, E AEP488
Parra Ramírez, P AEP504, OC1.1, AEP103
Parvanta, L OC1.5
Pásaro, E AEP451
Paschke, R **MTEBS2**
Paschou, S AEP97, **AEP90**, AEP236, AEP570, OC14.5
Pascual-Corrales, E AEP14, **AEP499**
Pashkovska, N PEP10.4, AEP327, AEP614, **AEP313**, AEP204, AEP656
Pashkunova, S **OC15.6**
Pasqualini, V AEP627
Passeri, E AEP9
Passone, C AEP493
Passos, D EP42, PEP7.7, EP76, AEP112, EP86
Patalano, R YI1
Patera, B **AEP748**
Pathmakanthan, S PEP14.8
Patou, G OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6
Patrunov, Y EP227
Patyra, K OC15.2
Paul, C AEP388
Paul, D EP220
Paul, S OC11.3
Pauline, B AEP648
Pauliukienė, R AEP518
Paun, DL EP143
Pavai, D AEP556
Pavel-Tanasa, M AEP98
Payer, J AEP556
Pazos, M **AEP434**, EP5, AEP38, AEP774
Pecce, V **OC5.5**
Pecori Giraldi, F **AEP15**, **AEP806**
Pecoriello, A AEP835

Peculis, R PEP3.7
Pedaran, M **OC15.5**
Pedersen, M PEP3.5
Pedone, C AEP627
Pedraza Arévalo, S PEP9.6, OC9.3, OC13.5
Pedro, J AEP176
Pedroncelli, A OC3.1, PEP8.5, OC8.2
Peeters, R AEP664
Peitzsch, M PEP11.2
Pejicic, N AEP271, AEP318
Pekic Djurdjevic, S AEP474, **AEP522**
Pekova, B **OC10.2**, AEP739
Pellegata, NS OC15.3
Pellenz, F PEP12.7
Pellikaan, K **AEP681**, AEP493
Pelosini, C PEP12.6
Peltola, E **PEP9.1**
Peng, J AEP477
Penkova, M PEP12.2
Penna, C OC12.5
Perdomo-Herrera, E EP223
Perea, V AEP282
Perego, S AEP21
Pereira, AM OC14.5, OC6.3
Pereira, C AEP88
Pereira, F AEP176
Pereira, MT AEP629, OC10.3, EP111, AEP398, PEP5.3
Pereira, T AEP251
Pereira da Silva, A AEP876
Peretianu, D **AEP607**, **AEP608**, **AEP142**
Pérez Álvarez, M AEP531
Pérez Candel, X AEP434, EP5, **AEP38**, AEP774, AEP639
Perez de Ciriza Cordeu, M EP152
Perez Fernandez, R OC7.5
Pérez Galende, E AEP725, EP193, AEP778
Perez Gomez, J **OC13.5**
Pérez López, C AEP478, AEP531
Pérez Naranjo, S EP154
Pérez Yéboles, J AEP186
Perez-Castrillon, JL AEP83
Perez-Garcia, MDP **EP223**, AEP431
Perez-Rivas, L OC3.6
Perez-Rivas, LG OC8.1, **OC13.1**
Pérez-Romero, S OC8.3
Perge, P OC11.2
Perini, A AEP29
Perlemoine, K PEP1.6
Perotti, P OC11.4, OC11.5
Perpinia, A AEP10
Perrini, S PEP4.3, OC2.6
Perros, P AEP733, OC5.2, AEP734
Persani, L OC14.5, OC4.3
Perticone, F AEP114
Perumal, S AEP367
Peskavaya, N **AEP573**
Pestana, A OC14.3
Petakov, M AEP474, AEP522
Peteiro Miranda, CM AEP778
Peterkova, V AEP829
Petkovic, A EP126
Petkovic, D-S AEP16
Petraglia, F AEP857, AEP861, AEP803
Petrangeli, E AEP28
Petria, AR EP149
Petronyte, D AEP661
Petrou, V PEP3.6
Petrova, M AEP217
Petrucca, A PEP14.3
Pettiti, G AEP637
Petychaki, F AEP49
Peverelli, E PEP3.1, OC8.4
Pfeiffer, A AEP183
Pfister, H AEP532
Phatale, H AEP624
Pheiffer, C EP88
Philip, S YI4, AEP533
Philippou, A AEP5, PEP5.6
Phylactou, LA PEP4.8
Phyo, NE **AEP376**
Pia, A AEP29, OC11.4
Piaditis, G OC1.4
Piaggi, P AEP875
Piaggio, G PEP14.3
Piantanida, E AEP748
Piatti, P PEP2.4
Picazo-Perea, M-P PEP14.5, AEP763, PEP14.4
Pickovsky, J AEP20
Piddubna, A PEP10.4, AEP327, AEP614, AEP313, **AEP656,** AEP678
Pieber, T PEP6.3, AEP159
Piemonti, L **NSA2**
Pierre, B PEP6.4
Pierre Jean, G EP220
Pigarova, E **AEP126**, AEP468, AEP483, YI12, PEP8.7
Pihl, S OC6.6
Pikunov, M AEP416
Pilar Betran, A AEP332
Piltonen, T PEP4.1
Pineda Cantero, A EP103, AEP700
Pinés Corrales, P AEP834, AEP837
Pinheiro, G AEP756
Pinheiro, N EP13
Pinto, CS AEP822
Pinto, JP AEP148
Pinzón Martín, JL AEP346
Pirags, V PEP3.7, AEP51
Pirga, IA **AEP696**
Piskinpasa, H AEP505, AEP422, **AEP489**
Pisoschi, M AEP608, AEP607
Pittaway, J OC11.3
Pivonello, C **YI1**
Pivonello, R **AP4,** PEP8.5, OC8.2, AEP412, PEP14.7, YI1
Pla Peris, B **EP154**
Plate, A PEP7.5
Plegermane, A AEP133, EP41
Pletsch-Borba, L **AEP183**
Pliakos, I AEP87, PEP6.5
Płoszaj-Neć, M AEP151
Plotnikova, A AEP229
Plotuna, I AEP889
Plowman, N AEP495
Pocino, K PEP4.2
Podbregar, A AEP37
Podlipskyte, A AEP222
Poduval, A AEP215
Pogosian, K **AEP108**
Pohrt, A AEP183
Poiana, C AEP568, AEP659, AEP536, AEP479, AEP541, AEP482, AEP539, PEP1.4, AEP855, AEP145
Pokramovich, Y OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6
Polak, M AEP493
Polat, B AEP894
Polat, SB AEP886, AEP799, AEP884, **AEP693**, **AEP870**
Polavarapu, NK AEP822
Polidoro, MA **PEP13.1**
Polymeris, A AEP893
Pompeo Romano, A AEP272
Pontecorvi, A AEP642
Pontecorvi, A AEP840
Pontes Cavalcante, I OC1.3, **PEP1.6**
Pontrelli, M PEP5.2
Popa, L PEP1.4
Popa, ML AEP659, **AEP855**
Popa Ilie, IR AEP484
Popescu, ML AEP696
Popławska-Kita, A AEP390
Popovic, B EP126, **AEP402**
Popovic, M **OC4.1**
Popovic, P AEP37
Popovic Pejicic, S AEP270, **AEP271**, **AEP318**, AEP517
Popovic-Brkic, V **AP1.2**
Pörsti, I AEP792
Porteiro, B AEP267
Portelli, D AEP385
Porter, J PEP1.1, PEP1.5
Portugal, J AEP311
Portyanko, A AEP667, AEP668, AEP669, **OC5.3**
Poshi, K AEP740
Poswa, N AEP360
Potasso, L **AEP89**
Poteshkin, YE OC13.6
Potlukova, E PEP7.5
Poulsgaard, L AEP481, AEP383
Pourasghar, M EP183
Povaliaeva, A AEP126
Pozzilli, P AEP627
Pradilla Dieste, A **OC8.3**
Prakash, P AEP77
Pramaningtyas, MD AEP860
Preda, C AEP98, AEP622, AEP150, EP131, AEP401
Preda, D EP179, EP32, AEP429
Preda, DM EP143
Preiksa, RT AEP598
Prete, A OC11.1, **PEP11.6**, **PEP1.5**
Priede, Z AEP51
Priego Zurita, AL **AEP116**
Priya, G AEP822
Prodam, F PEP7.8, AEP201, PEP12.6, **AEP166**
Prokop, J AEP246
Prokopchuk, O **EP85**, EP59
Provera, A PEP7.8
Prylutskaya, V **AEP179**

Przhiyalkovskaya, E AEP501, PEP8.7, AEP407
Przybylik-Mazurek, E PEP9.2, AEP7, AEP538
Psachna, S AEP893
Psifis, M EP34
Puar, HK **AEP786**, **AEP787**
Pubul Núñez, V AEP871
Puchowicz, M OC7.2
Puga, F **AEP551**, **AEP629**
Pugliese, F AEP9, AEP21
Pugliese, G AEP575, AEP22, AEP28
Puglisi, S AEP29, OC11.4, OC11.5
Puig Domingo, M AEP871, OC14.5
Pujol, J AEP466
Puri, D OC4.4
Purice, M AEP735
Puxeddu, E AEP642
Qamar Masood, M AEP881
Qayum, M **AEP439**
Qayyum, M OC4.2, OC4.5, EP182, AEP594
Quarta, C OC12.6
Queirós, JA AEP276
Quesada Gómez, JM AEP132
Quinkler, M AEP4, OC11.3, PEP1.1, PEP1.7, OC11.5, PEP11.6
Quinn, M **AEP388**
Quint, J OC1.6, PEP11.7
Quintana-Arroyo, S AEP800
Quintas Ovejero, L AEP186, AEP160
Quintero Platt, G AEP376
Quirós, C AEP282
R. Dahl, S AEP26
Racca, G AEP457
Rachel, D PEP13.2
Rachinger, W OC8.1, OC13.1, OC3.6
Racolta, N AEP74, AEP55
Radian, S AEP659, AEP479
Radić, M AEP706
Radovic, M AEP474
Radzeviciene, L PEP15.6
Raffa, S AEP28
Rafi, M OC4.5
Rafi, S AEP765, EP161, AEP604, EP46, EP118, EP95, AEP308
Rafik, K PEP6.4
Ragazzon, B OC1.3, PEP1.6
Ragnarsson, O AEP39
Rahman, M **AEP120**
Raida, H AEP358, AEP278, AEP328, EP119, EP137, EP140
Raimondo, S AEP572
Raimundo, L AEP311
Raineri, D PEP7.8
Raja, S AEP754
Rajan, R **AEP533**, **YI4**
Rajas, F OC6.2
Rakhimova, G EP231
Rakhmetova, M **AEP292**
Rakusa, M AEP37
Ram, N EP156
Ramalho, D **AEP168**, PEP14.1, EP209, AEP48
Ramavath, NN PEP7.8
Ramirez, K AEP451
Ramírez-Izcoa, A EP31
Ramona, A EP158
Ramon-Krauel, M PEP12.4
Ramos, E AEP38
Ramos, R AEP543
Ramos Perez, L EP88
Ramzi, K EP9, EP11
Ranathunga, I **EP90**
Randeva, H OC15.4, YI7
Ranetti, A AEP142
Rao, P AEP55
Rapola, J PEP9.5
Raposo, J F. AEP228
Raposo, N AEP411, AEP749, AEP23, AEP406
Rasa, I **AEP849**
Rashid Abdalla, RA AEP596
Rasmussen, K AEP383
Rastrelli, G **AEP835,** AEP857, AEP861, AEP803
Rathore, A PEP1.8
Rauf, S OC4.2
Rauner, M OC12.1
Raverot, G OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6
Re, T AEP651
Real Mendes, L AEP578
Reano, S PEP7.8
Rebai, H. AEP238
Rebollo-Román, Á **AEP227**, **AEP132**, AEP621
Rebrova, OY AEP483, AEP101
Reddy-Kolanu, V PEP14.8
Redondo, E EP79, **EP207**
Redondo Torres, E AEP333
Reeve, MP OC15.2
Refardt, J AEP465, AEP89, AEP467
Regaieg, S. AEP238
Rego, T AEP582, AEP199
Rehders, M PEP15.2
Rehmani, H AEP836
Rehorkova, P AEP129
Reilhac, A AEP787
Reimondo, G **AEP29**, OC11.4
Reincke, M OC3.3, OC8.1, OC13.1, AEP791, PEP13.5, AEP45, OC3.6
Reis, M AEP148
Reis Guiomar, J **AEP392**, **AEP456**, **EP26**, AEP247, PEP4.7
Reisch, N PEP1.1, **PEP1.3,** AEP45, PEP4.8, AEP6, OC14.5
Rejnmark, L AEP116, AEP36, PEP6.8, PEP6.6, PEP6.7, OC6.6
Rekik, N AEP616, AEP197, EP91, EP50, AEP584, AEP72, EP7, AEP363, EP66, EP192
Rekik Majdoub, N AEP764, EP62, AEP362, EP175, AEP306, EP165, EP159, AEP548
Rekik Mejdoub, N AEP238
Remec, K AEP91
Remedios, D AEP120
Ren, Y EP96, AEP322
Rengarajan, L AEP208
Renko, K OC5.1, PEP10.1
Repaci, A AEP153
Reshetnikov, I EP194, AEP530, EP222, EP39
Revuelta, R AEP110, AEP768
Reza, M AEP122
Reznikov, A AEP595
Ribeiro, S AEP756
Ribeiro dos Santos, L OC14.3
Ribes, C PEP1.6
Ricca, V AEP803
Ricci, A PEP14.3
Rico Dadebat, N AEP160, AEP186
Ricotti, R AEP166
Rieznik, L PEP12.2
Rifai, K AEP676, EP235, EP189, EP236
Rigana, M AEP823
Rigla, M AEP476
Rihab, A **EP171**, AEP441, AEP373, AEP772, AEP378, **AEP770**, **AEP368**
Rim, H EP204
Rinaudo, L AEP104
Ringvoll Normann, K **OC8.6**
Risovic, I **AEP270**, AEP271
Ristea, RP **AEP845**
Rivadeneira, F PEP2.2
Rizk-Rabin, M PEP1.6
Rizos, D AEP97, AEP236
Rizvi, SSR EP182, AEP594, OC4.5, OC4.2
Rizzo, M AEP163
Röber, S OC8.1
Robert, SA AEP820, PEP7.4
Robins, E AEP787
Robinson, L AEP175
Robinson, S PEP11.7, OC1.6, AEP662, AEP86
Robles Lázaro, C OC1.1
Rocha, S AEP148
Rocha, T **AEP332**
Rodien, P YI5
Rodrigues, D AEP18, AEP587
Rodrigues, F AEP742, AEP743, AEP56
Rodrigues, T AEP96
Rodriguez, J AEP502
Rodríguez, A OC7.5
Rodríguez Carnero, MG AEP521
Rodriguez Escobedo, R **EP78**
Rodríguez Rodríguez, I AEP272
Rodríguez Soto, MJ AEP775
Rodriguez-Perálvarez, M OC9.4, EP129
Rodríguez-Soto, J AEP828
Rodríguez-Villanueva García, J AEP871
Roemmler-Zehrer, J AEP532
Rohatgi, R **AEP309**
Rohayem, J PEP4.8
Roitman, E AEP185

Rojbi, I AEP41, AEP718, EP224, AEP75, EP146, AEP589, AEP437, AEP438, AEP419, AEP567, AEP420, EP138, AEP569, AEP80, AEP747, EP29, EP176, EP130, EP225, AEP519, EP134, AEP561, AEP393, EP37
Rojo Alvaro, J EP152, AEP703, AEP160
Roland, C AEP838
Roman Gimeno, S **AEP725**, **EP193**, AEP778
Romano, M EP64, AEP450, OC13.2
Romano, RM AEP633
Romero LLuch, AR AEP665, PEP9.8
Romero Porcel, JA AEP396, EP123
Ronan, R AEP648
Ronchi, C **OC11.1**, PEP1.7
Ronchi, CL OC11.2
Ronzitti, G OC6.2
Rosenberg, A AEP681, **AEP493**
Rosengård-Bärlund, M PEP9.5
Roshdy Mohamed, N AEP156
Rosic, N AEP16
Rosinha, P **AEP254**
Ross, IL PEP14.6
Ross, R PEP1.1
Ross, RJ PEP1.5
Rossi, M PEP5.2
Rossi, R PEP5.2
Rossing, CM AEP383
Rosso, D OC10.6
Rosu, M **EP15,** EP187
Rotermund, R OC8.1, OC13.1
Rotman-Pikielny, P AEP135
Rouf, S AEP315, EP113, EP99, AEP117, EP44, AEP285, AEP601, AEP344, AEP535, EP139, AEP369, EP82, EP170, AEP53, EP57, AEP421, AEP370, AEP303
Roughton, M OC3.1, OC8.2
Rovite, V **PEP3.7**
Roxana Novac, E **AEP516**
Rozhinskaya, L AEP416, AEP126, AEP468, PEP8.7
Rrupulli, A **AEP712**
Ruas, L AEP587, AEP18
Ruas, R AEP650
Rubin, M OC6.6
Rubio-Brotons, M NSA4
Rubio Herrera, MA AEP837
Ruchala, M PEP8.8, PEP13.7, AEP866
Rudenko, V AEP722
Ruggeri, R **AEP630**
Rui, Z OC10.4
Ruiz, A **PEP12.8**
Ruiz, S PEP5.4
Ruiz Berjaga, J EP125
Ruíz García, I AEP700
Ruiz Sánchez, JG AEP434, **EP5**, AEP38
Ruiz-Gines, J-A PEP14.5, PEP14.4
Ruiz-Gines, M-A **PEP14.5**, **AEP763**, **AEP677**, **PEP14.4**
Ruksha, K AEP667, AEP668, AEP669
Runkle, I AEP434, EP5, AEP38
Ruotolo, V EP64
Rusakov, V AEP144
Russo, D OC5.5
Russo, G PEP4.8
Ruth, D PEP6.4
Rutigliano, G AEP880
Rutjens, M AEP1
Ruza, I **AEP133**, **EP41**
Ryom Riis, K **OC5.2**
Ryzhkova, D AEP108
Rzepka, E PEP9.2
S. Pereira, R AEP148
Saad, F **AEP162**, **OC2.3**, **AEP232**
Saad, G AEP771, EP141, EP16, AEP12, EP171, AEP645
Saafi, W **AEP771**
Saatov, T AEP357, AEP330, AEP207, AEP263, AEP172
Saba, A AEP802
Sabah, M AEP269, EP93, **EP94**, AEP231, AEP350
Sabbadin, C PEP14.7
Sabino, T AEP199
Sabio, G AEP267, AEP252
Sabir, AA AEP190
Saboo, B AEP264, **AEP268**, **AEP297**, **EP72**, **PEP7.6**
Saboo, S AEP297, PEP7.6
Sabrine, Z AEP365
Sacconi, A PEP14.3
Sachynska, O AEP595
Sacikara, M **AEP865,** EP239, AEP796, AEP872
Sadoine, J OC6.2
Sadowski, C AEP206
Saez de Parayuelo, V EP5
Sáez-Martínez, P OC13.5, AEP397, **YI6**
Saffari, F **AEP867**
Safi, E EP47, **AEP365**, **EP58**
Safi, W EP199, EP200, AEP210, AEP584, AEP616, AEP707, AEP361, EP7, AEP72, EP87, EP175, AEP238
Ságová, I **AEP556**
Sahay, M AEP264
Sahay, R AEP264
Sahbaz, NA AEP422
Sahdev, A OC1.5
Sahin, M AEP342, OC5.6
Sahin, S AEP851
Şahin, B AEP643
Sahoo, A AEP264
Sahoo, AK PEP7.3, AEP234
Said, A AEP738
Said, W AEP563, AEP340, EP63
Saida, F EP177
Sailer, C AEP465, **AEP527**, AEP467
Sainio, S PEP4.1
Sakali, A-Konstantina AEP635, AEP494, AEP379, AEP127
Sakarwadia, R AEP647
Saksis, R PEP3.7
Salah, A AEP197, **EP91, EP87, AEP363, EP66**
Salaheldein Elzaki, SE AEP596
Saldiva, P OC14.3
Saleem, M AEP836
Salem, A **AEP301,** AEP290
Salerno, G PEP14.3
Salimova, M **EP205,** EP198
Sallai, Á AEP3
Salma, C EP74, EP206, EP121, EP89
Salma, G EP163
Salsbury, J OC1.5
Saltiki, K AEP95
Salto-Tellez, M AEP488
Salvati, V PEP14.3
Salvatori, M OC5.5
Salvi, M YI2, AEP651, **MTE1**
Samaras, C AEP79, AEP310
Samardzic, V AEP294, AEP474
Samarkhodjaeva, N AEP207
Sambo, M **AEP871**
Sameh, M AEP24, AEP99, AEP485
Samet, S AEP374, EP36
Samimagham, H AEP453, AEP424
Samir, G EP9, EP11
Samir, K EP89, AEP339, EP121
Samoilova, J AEP286
Samouh, N AEP615
Sampedro-Núñez, M **S18.3**
Samson, L AEP151
Samuiloviene, E EP218
Sana, R AEP746, AEP348
Sanaa, B EP212
Sanaa, R EP212, EP109, AEP564
Sancak, M AEP825
Sanchez Gomez, NM AEP809
Sánchez Juan, C EP125
Sánchez Lechuga, B AEP809
Sanchez Marin, L EP52
Sanchez-Escribano-Del-Palacio, F AEP677
Sánchez-Frias, ME OC9.4, EP129
Sánchez-Frías, M AEP384
Sánchez-Hidalgo, JM AEP384
Sánchez-Sánchez, R OC9.3
Sanchís Cortés, P AEP272
Sand, J PEP9.1
Sandrine, G AEP648
Sandoval, D **S3.2**
Sanina, Y AEP611
Sanson, G AEP627
Santamaría Nieto, A AEP521
Santamaría Sandi, J AEP871
Santambrogio, A OC1.2
Santana-Suarez, AD EP14, AEP174, PEP15.8
Santini, D PEP11.4
Santini, F AEP880, PEP12.6, AEP875

Santisteban, P **PL6**
Santopietro, M AEP475
Santos, AC AEP409, AEP228, AEP876
Santos, F AEP56
Santos, J AEP742, AEP743
Santos, MJ AEP562, AEP189
Santos, R AEP871
Santos, T **AEP137**
Santos Monteiro, S **AEP88**
Santos Silva, R EP178, AEP69
Sanz Martín, B AEP725, EP193, **AEP778**
Saparova, V AEP448
Sapinho, I EP13, AEP578
Saponaro, F **AEP802**
Sara, C AEP654, AEP628, **AEP564**, **EP212**, **EP109,** AEP746
Sara, l AEP779, AEP245, AEP338
Sarafoglou, K PEP1.2
Saraiva, F AEP212
Saraiva, J AEP138
Saraiva, M **AEP756**, **AEP138**, **AEP276,** AEP398
Sarantseva, K EP217
Šarauskas, V AEP387
Saravinovska, K AEP16
Sarbu, A AEP142
Sarchielli, E AEP861
Sardaeva, D AEP483
Sardella, C AEP875
Šarić, J AEP445
Sarmento-Cabral, A OC9.2, OC7.2, YI6
Sarra, R PEP2.5
Sarria-Estrada, S AEP490
Sartorius, G OC4.1
Sastre, J AEP110, AEP768, PEP14.5, AEP763
Satam, S OC15.3
Sattar, S AEP881
Sausa, S **AEP51**
Savas, M OC7.3
Savasteeva, I **EP115**
Savelli, A AEP49
Sawicka, B **AEP797**
Sayadi, H AEP831, AEP657, EP190, AEP32
Saygili, ES EP97, AEP524
Sazonava, A **AEP158**
Sbiera, S AEP838
Scapin, A AEP8
Scarabnii, T AEP755
Scaroni, C PEP14.7, PEP4.8
Scavello, I AEP857, AEP835, AEP803, AEP861
Schalin-Jantti, C AEP560, OC14.5, PEP9.5, PEP9.1
Schally, AV OC3.2, OC13.4
Schaper, S **AEP592**
Scheich, B EP160
Scheuermann, C AEP35
Scheurink, AJW OC12.4
Schiffer, L OC4.1, PEP1.5
Schilbach, K AEP532
Schilling, M AEP789
Schipor, S AEP479, AEP541
Schlaffer, S-M AEP838
Schmidt, A PEP6.3
Schmidt, H AEP6
Schneider, M AEP74
Schoeb, M **OC6.3**
Schoonen, L **AEP710**
Schopohl, J AEP532
Schwarz, P **OC6.6**
Schweighofer, N **PEP6.3**, AEP159
Schweizer, U PEP15.2
Sciacchitano, S **PEP14.3**
Scillitani, A AEP21, PEP6.2, AEP9
Scripcariu, V EP131
Sebai, I EP47, AEP209
Sebile Dökmetaş, H **EP97**
Seçme, M AEP192
Seechurn, S AEP120
Seegers, V YI5
Seery, S EP54
Segarra, A PEP15.5
Segkouli, S AEP188
Seguna, D **AEP495**
Segura, P OC9.1
Segura Huerta, Á AEP871
Seifert-Klauss, V AEP613, AEP599
Sekkat, K **AEP417**, **AEP418**, **AEP752**
Selek, A AEP506, **EP145**
Selivanova, L AEP566
Selva, S PEP11.4
Selvan, C PEP10.3, AEP391
Semeniene, K **AEP598**
Semiane, N EP234
Senanayake, R PEP3.8
Senanayake, R OC1.5
Senba, H EP51
Sencar, ME AEP873
Senda, R AEP441, AEP373, AEP772, AEP341, AEP364
Sendur, MA AEP788, AEP856
Sener, MK AEP878
Şenol, H AEP192
Senouci, K AEP698
Seo, S AEP194
Seoane, S OC7.5
Sepp, K AEP400
Septier, A OC1.3
Sequeira, M EP210
Sequeira, P EP210
Šerić, V AEP445
Serifoglu, İ AEP872
Serra, FI AEP578
Serra, MP AEP827
Serra-Caetano, J AEP577
Serrano, A EP52
Serrano Laguna, MDC **AEP211**, **AEP349**, EP79, AEP136, EP207, AEP333
Serrano-Blanch, R OC9.3
Sertedaki, A AEP323, **PEP8.4, OC2.5**
Sesé, M PEP5.7
Sesta, A AEP15
Severina, A AEP106
Sevillano-Collantes, C AEP773, AEP316
Seyffarth, C OC5.1, PEP10.1
Seyrek, FNC EP238
Sfakiotaki, M AEP13, PEP10.2
Sfar, R AEP883, AEP887
Sghir, M EP63, AEP340
Sgrò, D AEP875, AEP880
Sha, W OC3.2
Shaefler, C AEP185
Shafigullina, Z PEP11.8
Shafique, S AEP832
Shagazatova, B EP231
Shahid, G OC4.5, AEP594
Shaikh, A AEP815
Shaikh, S **AEP815,** AEP815
Shamansurova, Z EP205, **AEP172**, AEP330, AEP263, EP198
Shamkhalova, M AEP106
Shapiro, I PEP11.2, OC11.2
Shapses, SA AEP85
Sharifi, M AEP453
Sharma, A OC11.2
Sharma, B AEP120
Sharma, D AEP644, EP226, AEP118
Sharma, H AEP297, PEP7.6
Sharma, K AEP264
Shatylo, S EP120
Shawgi, M AEP785
Shehu, T AEP511
Sheikh, A AEP414
Sheikh, J **AEP175**
Sheikh, R AEP632
Sheinkova, G AEP92
Shekhda, KM **PEP1.8**
Shelestova, E AEP169
Shepelkevich, A AEP667, AEP668, AEP669, AEP733, AEP734, AEP229, AEP821
Sherry, N PEP6.8, PEP6.6, PEP6.7
Shimshilashvili, A PEP6.1, OC12.3
Shinkov, A AEP666, AEP82, AEP663
Shloma, A AEP667, AEP668, AEP669
Shlomai, G AEP20
Shong, YK PEP5.8
Shpilevaya, O PEP6.1, OC12.3
Shreder, E **AEP721**
Shu, A OC6.6
Shyshko, Y AEP179
Siahanidou, S PEP8.4
Sibony, M PEP11.5
Siddique, R **AEP67**
Siddiqui, S AEP815
Siderova, M AEP767
Sidi Mohammed, M AEP717
Sierra Poyatos, RM AEP809
Siewko, K AEP390
Siham, R AEP455, AEP452
Silipigni, R PEP6.2
Silva, AL YI11
Silva, DAF AEP392, AEP456, EP26, AEP247, **PEP4.7**
Silva, F AEP88
Silva, J EP86, EP76, PEP7.7, EP42, AEP112
Silva Rodriguez, MJ AEP809
Silva Santos, T AEP88
Silva-Fernández, J EP202, AEP454

Silva-Nunes, J PEP2.1, AEP246, AEP180, AEP199, AEP115, AEP582
Silvestrini, A PEP8.2
Silvestrova, S AEP299, AEP226
Sim, SY **AEP446**, **AEP853**
Simanavičienė, V AEP387
Simanenkova, A PEP6.1, **OC12.3**
Simeakis, G **AEP95**
Simeoli, C **PEP14.7**, YI1
Šimková, M AEP620
Simo Canonge, R AEP490, EP88
Simões, M AEP577
Simões Reis, I AEP600
Simon, J OC13.1, OC3.6, PEP13.5
Simon, V OC12.6
Simona Andreea, G **AEP659**, AEP855, AEP479, PEP1.4
Simonen, P PEP9.5
Simonini, C AEP28
Simó-Servat, A **AEP282**
Simpson, H AEP783
Simunkova, K AEP4
Singh, A **EP144**
Singh, R AEP175
Singla, A OC2.4
Singla, R **OC2.4**
Singla, S OC2.4
Sintenie, PJC OC6.3
Sirén, J PEP9.1
Sitch, AJ PEP11.6
Sitges-Serra, A **S24.1**
Sivappriyan, S AEP751
Sivasankaran, K PEP9.4
Skakkebaek, NE **AP3**
Skalniak, A **PEP9.2**, AEP7, AEP399
Skarakis, SN AEP10
Skov, J AEP4
Skowronska-Jozwiak, E **AEP125**
Skryplionak, T AEP179
Skuridina, D **AEP317**
Slashchuk, K AEP829
Slimani, L OC6.2
Slouma, M AEP277
Słowińska-Srzednicka, J AEP686
Smagala, A AEP55, AEP74
Smirnov, S AEP667, AEP668, AEP669
Smirnova, O EP84, EP83
Smith, G OC11.1
Snihurska, I AEP279
Snijders, F AEP681
Snyder, P OC3.1
Soares, P PEP10.6, OC14.3
Sobalska-Kwapis, M AEP325
Sobrinho-Simões, M OC14.3
Soby, S AEP332
Soelling, C AEP383
Sofia, N AEP310
Soinio, M PEP9.1
Sokolovska, J **PEP15.6,** AEP243
Sokołowski, G AEP649
Solak, C AEP878
Solari, D YI1
Soldat Stankovic, V AEP271, AEP318, **AEP517**
Soler Beunza, AG AEP272
Solito, A AEP166
Solitro, F AEP29
Solivera, J YI8, OC9.6
Sollid, ST AEP4
Solmaz, K EP238, AEP865
Solntsava, A PEP12.5, AEP573, AEP179
Solovov, V **AEP890**
Somasundaram, N EP90
Somasundaram, NP AEP320, EP147
Somoza, R PEP5.7
Sondos, A AEP441
Song, DE PEP5.8
Song, E PEP5.8
Sonia, N AEP460, EP150
Sophie, D AEP591, AEP859
Sorbi, F AEP803, AEP861, AEP857
Sørensen, MGR PEP3.4
Sorokina, Y EP194, AEP530, EP222, EP39
Sosedkova, A AEP667, AEP668, AEP669
Sota Ochoa, P AEP778
Soto-Moreno, A OC3.4
Soumaya, M **AEP358**, **AEP278**, **AEP328**, EP119, EP137, EP140
Soureti, A AEP97
Sourij, C AEP159
Sourij, H AEP159
Sourour, K AEP253
Sousa, A EP209
Sousa, R EP151
Sowa Staszczak, A AEP509, AEP399
Sowithayasakul, P AEP462, AEP477, OC3.5, AEP528
Soyhan, M AEP854
Soyluk Selcukbiricik, O AEP480
Sözen, M AEP506, EP145
Spada, A PEP3.1, OC8.4
Spanakis, K AEP13
Spanou, L AEP823
Sparavalo, R **AEP605**, AEP513
Speroni, R PEP15.5
Spiezia, S AEP633, OC5.4, AEP641
Spira, D AEP183
Sponziello, M OC5.5
Spranger, J AEP183
Spreafico, F AEP835
Springborg, JB AEP481
Springborg, J PEP3.4, PEP3.5
Spyrantis, A AEP310, AEP79
Spyropoulos, P AEP130, AEP68
Spyropoulou, O-M AEP79, AEP310
Squarcia, M PEP5.4
Šrámková, M AEP620
Sreenan, S EP21, AEP750, AEP65, EP67
Staby, I AEP481
Stachanow, V PEP1.3
Stalder, T AEP235
Stalla, G OC13.1, AEP532, OC3.6
Stamatelopoulos, K AEP570
Stamati, M EP35
Stanca, O PEP13.4
Stanciu, M AEP607, AEP845, AEP608, AEP142
Stancu, A-M **AEP735**
Stancu, C PEP13.4
Stankova, T AEP413
Stankovic, D AEP16
Starcea, M AEP622
Starchenko, T PEP12.2
Starka, L AEP620
Starosz, A AEP892
Starzyk, J AEP472
Stasiak, M PEP10.8
Stathias, K AEP13
Stawerska, R **PEP10.8**
Staynova, R **AEP288,** AEP413
Steenaard, R **AEP1**
Steenblock, C OC1.2, PEP11.2
Stefan Sojat, A AEP16
Stefanescu, C EP131
Stefanile, A PEP4.2
Stegenga, M AEP664
Steina, L PEP3.7
Steinhauer, S OC11.1
Stelmachowska-Banas, M AEP547, AEP496, AEP492
Stepura, O **AEP171**
Stevchevska, A AEP143
Stigliano, A AEP22, **AEP28**
Stirane, L **AEP243**
Stirans, K AEP243
Stoica, S EP149
Stojanovic, M AEP522
Stojanovic, N AEP832, EP167
Störmann, S **AEP532**
Stoynova, M **AEP663**
Stożek, K AEP892
Strasburger, CJ OC13.6, PEP3.2, PEP8.1, PEP8.3, PEP13.6
Strasser, M PEP6.3, **AEP159**
Strazhesko, I AEP196
Strebkova, N AEP692
Struthers, S OC15.4
Sturdy, E AEP488
Su, C AEP85
Subach, A AEP667, AEP668, AEP669
Subbiah, K **AEP367**
Subramanian, A PEP11.6
Sucaliuc, A **AEP134,** AEP757
Sucharita, S PEP7.3, AEP234
Sudar-Milovanovic, E AEP294
Sudarshan, V AEP439
Sudarto, HA AEP860
Suh, S AEP194
Sujani, BK AEP391
Sukor, N AEP895, AEP820, PEP7.4
Suleymanlar, E AEP851
Sumanatilleke, M EP90, EP147
Sung, T-Y PEP5.8
Supuran, CT PEP11.3
Suri, A AEP141

Sushinski, V AEP229
Suslov, G AEP722, AEP759
Sutcliffe, R OC11.1
Suteau, V **YI5**
Sutti, S PEP7.8
Svikle, Z PEP15.6
Svilias, I **EP203**
Svobodová, E **AEP129**
Swallow, E PEP6.8, PEP6.6, PEP6.7
Swan, K **OC10.5**
Świrska, J AEP249
Sworczak, K AEP151
Sydorenko, G AEP377
Sydorivska, O **AEP613**, AEP599
Syeda, A **AEP140**
Sykes, L AEP86
Sykorova, V OC10.2, AEP739
Sykorova, V EP201
Syndouka, E EP35
Syntzanaki, E-K AEP13, PEP10.2
Syrenicz, A PEP8.8
Syrucek, M EP201
Szanto, T PEP4.1
Szarmach, A AEP151
Szczepanek-Parulska, E PEP13.7, AEP866, **S1.2**
Szczepańska, E **AEP686**
Szini, E AEP757
Szostek, A **AEP547, AEP496**
Szucs, N EP160
Szumowski, P AEP390
Tabacco, G **AEP104**
Tabarin, A PEP11.6, OC1.3
Tabbebi, M AEP361
Taheri, S AEP843
Tahir, F OC4.5, AEP594
Tahrani, A AEP175
Tahri, A AEP303
Tahri, S AEP657, EP190, AEP887, AEP883
Taïeb, D **MTE4**
Taissir, BA EP208
Tait, K PEP14.8
Takeishi, S **PEP2.6**, **PEP2.7**, **EP112**
Talaat, A AEP720
Talaulikar, VS OC4.4
Talibov, M AEP414
Tallini, G AEP642
Talwar, G AEP704, AEP353, AEP205
Talwar, V **AEP205**, **AEP704**, **AEP353**
Tam, AA AEP693, AEP877, PEP15.7, AEP879, AEP870, AEP886, EP239
Tam, AA AEP825
Tamagno, E OC13.4
Tamara, N AEP260, AEP262, EP122
Tampouratzi, D PEP3.6
Tan, A AEP787
Tan, C AEP787
Tan, J OC10.4
Tan, MY AEP86
Tancic-Gajic, M AEP16
Tanda, ML AEP748
Tang, C **AEP8**
Tang, S **OC8.1**
Tang, X **OC7.6**
Tanna, S AEP218
Tapanainen, J PEP4.1, OC2.2
Tapella, L AEP15
Tarasenko, S **AEP722**, **AEP759**
Tarbaeva, N AEP407
Tardy, V PEP4.8
Tare, R **AEP690**
Tartaglione, T AEP840
Tashtemirov, A AEP263
Tassone, F AEP637
Tatjana, I EP126
Tatsi, E OC2.5, PEP8.4
Taudy, M OC10.2
Taujan, GC AEP603
Taujean, G EP15
Tauni, R EP20, EP40
Tavanti, GS PEP6.2, OC6.1
Tavares, P AEP115
Tayfur Yurekli, O AEP856
Taylor, AE OC4.1
Taze, SS AEP585
Tchernof, A OC15.1
Tebben, P AEP84
Tedoradze, N AEP655
Tee, S **AEP394**
Teheni, D **AEP754**, AEP780
Teixeira, S AEP254
Tejera, C AEP837
Telci Caklili, O **AEP480**
Teliti, M **AEP680**
Tell-Lebanon, O **AEP135**
Teodoriu, L **AEP401**, **EP131**
Terpos, E AEP95
Terriente, J NSA4
Terris, B OC9.5
Terzi, A EP215, EP216
Terzolo, M OC3.3, OC11.4, PEP11.6, AEP29, **OC11.5**
Tesic, D **AEP606**
Tessitore, A AEP19
Thangaratinam, S AEP332, AEP175
Thant, Y AEP265, AEP638
Thebault, E AEP81
Theel, W **AEP281**
Theodoropoulou, M OC8.1, OC13.1, OC3.6, PEP13.5
Thisiadou, K AEP804, AEP274
Thoda, P AEP127, AEP635, AEP379, AEP494
Thomas, J OC10.5
Thomas, L AEP208, AEP248, PEP14.8
Thorsby, PM AEP26
Thoulouzan, M PEP12.1
Thyagaraj, V PEP10.3
Tigas, S AEP127
Tiikkainen, M PEP9.1
Tikkakoski, A AEP792
Timkina, N **PEP6.1**, OC12.3
Timofeeva, V PEP6.1, OC12.3
Timon, V PEP9.3
Tinahones, FJ AEP346, AEP165, EP52
Tinahones Madueño, F AEP213
Tinahones Madueño, FJ AEP293
Tiranti, GM AEP29
Tiroille, V OC14.1
Tirosh, A AEP20
Tiscuka, A PEP15.6
Tiwaskar, M AEP264
Tkacheva, O AEP196
Tobisch, B AEP3
Tocino-Hernandez, AL EP223
Todisco, T AEP857, AEP803, AEP835, AEP861
Tojo, M OC7.4
Tőke, J OC3.3
Tolley, N AEP662
Tomasevic, R AEP294
Tomasik, A **AEP492**
Tomczuk-Bobik, P AEP390
Tome, M OC1.1
Tomic, M AEP606
Tomkowicz, A AEP4
Tomlinson, J YI3
Tong, A AEP787
Tonkih, O AEP286
Topaloglu, O AEP693, PEP15.7, AEP782, AEP879, AEP814, **AEP869**, AEP870, **AEP856**, EP233, **AEP882**, EP238, AEP825, AEP811, AEP850, AEP799, AEP846, AEP884, AEP872, AEP796, AEP886, AEP877, EP239, AEP788, AEP852, AEP847, AEP865, PEP15.1, AEP795, AEP794, **AEP187**, **AEP223**, **AEP643**, AEP885, AEP894
Topbaş, M AEP660
Topór-Kołkowska, J AEP7
Toppari, J OC15.2
Tordjman, K **AEP730**
Torlontano, M AEP642
Tortel, M-C AEP55
Toscano, V AEP28
Toth, J AEP410
Toth, M OC3.3, OC15.4
Totomirova, T **AEP230**
Touraine, P AEP591, AEP859
Touraine, P PEP4.8
Tous Romero, MC PEP9.8
Tovar, S AEP267
Trabelsi, M AEP602
Trajkovska, I AEP319
Trattnig, S AEP62
Trehan, S AEP824
Treppiedi, D PEP3.1, **OC8.4**
Trifanescu, R AEP659, AEP479, **AEP541**, **AEP482**
Trifonova, B **AEP296**, **AEP356**
Trimeche, O AEP70, **EP175**, EP165
Trimpou, P AEP39
Trivedi, A EP136
Trivedi, S **EP136**
Trofimiuk-Muldner, M AEP7
Troshina, E EP217, AEP193, EP19, AEP830
Trouillas, J **S10.2**
Trummer, C AEP159
Truran, P AEP394
Tsagarakis, S PEP11.6

Tsakalomatis, P-N AEP13
Tsakova, A AEP92
Tsareva, V EP231
Tsartsalis, AN AEP617
Tsaryk, I PEP10.4, AEP327, AEP614, AEP313, **AEP204,** AEP656
Tselebis, A EP49
Tseleni-Balafouta, S PEP5.6
Tseng, F-Y **EP135**
Tsiakas, S OC14.4
Tsiberkin, A **AEP697**
T'Sjoen, G AEP586, AEP451, AEP2, OC4.6
Tsonev, S OC15.6
Tsoy, A AEP172
Tsoy, U **AEP545**, AEP108
Tsvetov, G EP12
Tu, TM AEP786
Tubert, G AEP470
Tucci, L PEP11.4
Tudor, R EP67
Tudorache, A **AEP755**
Tudorean-Olteanu, A-G AEP622
Tufekci, D EP110, AEP326, AEP724, AEP473, AEP50, AEP343, EP73, EP4, AEP675, EP221, AEP291, EP53
Tuncel, A AEP796
Tuomi, T OC2.1
Tural Balsak, B AEP850, AEP885
Turan, K **AEP825**, **AEP850**, **AEP796**
Turan, S AEP585
Turan Erdogan, B **AEP794**, **PEP15.1**
Turgut, S **AEP505**, AEP422, AEP489
Türkölmez, Ş AEP894
Turnaoğlu, H AEP688
Tuszynska, A AEP30
Tuurinkoski, A AEP560
Tuzava, H PEP15.4
Twaheerah, AB EP121, AEP216, AEP307, AEP287
Twito, O **AEP242**, **AEP185**
Twito, O AEP135
Tyfoxylou, E OC1.4
Tzikos, G PEP6.5, AEP87
Tzioufas, A EP195, PEP10.5
Tzotzas, T AEP274
Tzovaras, D AEP188
Ubay, M EP240
Ucan, B AEP816
Uccioli, L EP64
Ucuncu, O **EP110**, **AEP326**, **AEP724**, **AEP473**, **AEP50**, **AEP343**, **EP73**, **EP4**, **AEP675**, **EP221**, AEP291, **EP53**
Ueland, GÅ PEP11.6, **AEP26**
Ugalde Abiega, B AEP773, **AEP316**
Ugur, K **EP60**
Uhlenhaut, H AEP45
Ulivieri, FM AEP104
Unal, E AEP343, EP53, PEP6.5
Undeutsch, HJ OC5.3
Unger, N OC3.3, PEP4.8
Ungureanu, C EP131, AEP401
Ungureanu, MC AEP622, AEP150
Unluhizarci, K AEP843
Urbanavicius, V PEP8.1
Urbonas, M AEP661
Urdaniz Borque, R AEP725, EP193, AEP778
Urinbaeva, D **EP198**
Urrutia Etxeberria, I AEP736
Urwyler, S AEP467
Ushanova, F **AEP345**, **AEP610**
Usman, A OC10.1
Üstay, Ö AEP27
Utkus, A AEP661
Uygur, MM **AEP471**, **AEP540**
Uzun, M AEP223
Uzun, YE **AEP705**
V. de Assunção, G **EP111**
Vaclavikova, E OC10.2, AEP739
Vaczlavik, A PEP11.5, OC9.5, OC1.3
Vadina, T AEP721
Vaduva, P **OC1.3**
Vágvölgyi, A **AEP400**, EP160
Vainikonyte Kristapone, J **EP218**
Vaira, V PEP6.2, OC6.1
Vaitsi, K **AEP652**
Vaitsi, V AEP617
Väkeväinen, M **AEP560**
Vakilgilani, T EP6, AEP86
Vakilgilani, T AEP42
Valadas, C AEP749, AEP406, AEP23, AEP411
Valderrábano Herrero, P OC1.1
Valderrabano, P **S1.1**
Valdés, N OC9.1
Valdés Hernández, S AEP250
Valdivia Bautista, J AEP871
Vale, C AEP212
Valente, A AEP228
Valera-Nuñez, E AEP677
Valickas, R AEP61
Valkusz, Z AEP400, EP160
Valland, S AEP4
Vallejo Casas, JA AEP871
Valverde, M AEP282
Vamvoukaki, R AEP13
van Beek, A AEP790
Van Cauter, E **PL2**
Van de Velde, F **YI9**
van de Wetering, J OC6.5
van den Akker, E AEP280, AEP235
van den Berg, S AEP710, AEP681
van den Berg, SAA OC12.4, OC7.3
van der Lelij, AJ OC12.2
Van der Lely, AJ AEP681, AEP493, AEP839
Van der Meulen, M **AEP537**
van der Valk, E AEP280, AEP235
Van der Valk, ES OC7.3, OC12.4
Van der Voorn, B OC7.3, AEP280, AEP235
Vanderschueren, D **JS8.2**
van Dijk, PR OC7.1
van Faassen, M AEP790
van Furth, WR AEP537
van Ginhoven, T AEP664
van Haalen, F OC6.3
van Haelst, M AEP280
Van Hul, W **PL5.2**
van Kemenade, F AEP664
van Kinschot, C AEP710
Van Mieghem, E **PEP9.3**
Van Nieuwenhove, Y YI9
van Noord, C AEP710
van Rossum, E AEP280, AEP235
van Rossum, EFC OC12.4
Van Rossum, LFC OC7.3
van Toor, H AEP710
Van Velsen, E **AEP664**
van Velthuysen, MF AEP839
van Wittenberghe, L OC6.2
Vandi, G **AEP153**
Vangelova, J OC15.6
Vankova, M PEP2.3, **AEP181**
Vannucchi, G YI2
Vaśiga, P AEP556
Vaquero-Barrios, J-M AEP227
Vara, G PEP11.4
Vara Luiz, H EP210, AEP311
Varallo, M AEP651
Varcus, F AEP889
Vardaka, M AEP10
Varela Rey, M OC7.4, OC7.5, AEP252
Varga, E AEP3
Varlamov, E PEP8.6
Varoneckas, G AEP222
Varro-Bodoczi, E AEP576
Varvanina, G AEP262, EP122
Vaschenko, E **AEP354**
Vashukova, M AEP425
Vasilescu, S EP32, EP179, **AEP429**
Vasileva, E **AEP413**, AEP288
Vasileva, V AEP113, **AEP239**
Vasilyev, E AEP830
Vasques, M AEP246, AEP115
Vasques-Nóvoa, F AEP212
Vassilakis, IA PEP8.4
Vassilev, D OC15.6
Vassiliadi, DA PEP11.6
Vasyhina, I AEP888
Vatalas, I-A AEP10
Vatansever, B **AEP854**
Vaychulis, I **AEP544**
Vazquez Martinez, C AEP809
Vázquez Salvi, LA **AEP221**
Vázquez-Borrego, MC OC3.4, **OC7.2**
Vcelak, J OC10.2, PEP2.3, AEP181, AEP129
Vcev, A PEP3.3
Vejrazkova, D **PEP2.3**, AEP181
Velasco de Cos, G AEP221
Velazquez, YE AEP431
Velecela Abambari, JV EP31

Velenciuc, N AEP401
Velez Romero, MDLA AEP809
Velija Asimi, Z **PEP14.2**
Velikanova, L PEP11.8, AEP862
Velikova, T AEP200
Velkeniers, B AEP510
Veltri, A AEP29
Velusamy, A AEP841, AEP388
Venegas Moreno, E OC3.4
Venegas Nebreda, I AEP703, EP152
Veneti, S AEP652
Venugopalan, V **PEP15.2**
Verbovoy, A PEP8.3
Verburg, F AEP664
Verdelli, C PEP6.2, OC6.1
Vere, CC AEP479
Veresani, A PEP14.7
Vergani, E PEP4.2, **PEP8.2**
Veríssimo, D **EP86**, **EP76**, PEP7.7, AEP112, EP42
Verkauskienė, R AEP387
Verrey, F PEP15.2
Verrienti, A OC5.5
Verroken, C OC4.6
Veyrat-Durebex, C OC7.5
Viale, ML AEP827
Viana, C AEP148
Vicennati, V PEP11.4
Vicente, A AEP110, AEP768
Vicentini, L PEP6.2, OC6.1
Vidal, C AEP713
Vieira, I **AEP587**, **AEP18**, **AEP217**
Vignozzi, L AEP861, AEP803, AEP857, AEP835
Viikari, L OC15.2
Vikulova, O PEP8.7
Vila, G OC8.2, AEP62
Vilaverde, J AEP398, EP111
Villanelli, F AEP861
Villanueva Silva, MJ AEP871
Villar Taibo, R **AEP521**
Vinderskaya, G AEP233
Vintderdag, H AEP93
Viola, N AEP880, AEP875
Violante, A **EP151**
Visser, E AEP710
Visser, WE AEP664
Vitanova, D OC15.6
Vitelli, R AEP412
Vítkş J AEP620
Viukari, M AEP792
Viveiros, F AEP650
Viyuela-García, C AEP384
Vlachopapadopoulou, E PEP3.6
Vlachou, E AEP555, AEP617
Vlad, M **AEP550**, AEP702, AEP889
Vladoiu, S AEP541
Vlasov, T PEP6.1, OC12.3
Vlatkovic, V AEP270
Vlcek, P OC10.2
Vliet Vlieland, TPM AEP537
Vogel, F PEP13.5
Vogiatzi, E **AEP893**
Vogt, D AEP467, OC4.1
Voitenko, V AEP759
Voitovica, L PEP15.6
Vojtková, J PEP4.8
Vokes, TJ OC6.6
Volkanovska Ilijevska, C **AEP143**, AEP319
Volkova, N **PEP12.5,** EP194, EP222, EP39, AEP530
Voltas Arribas, B EP125
von Hafe, M AEP212
von Kries, JP OC5.1, PEP10.1
Vonghia, L AEP157
Vorackova, A EP201
Vorokhobina, N PEP11.8, AEP862
Voronkova, I YI12, AEP380
Vorontsov, A AEP407
Vorontsova, M **MTE8**
Votis, K AEP188
Vouche, M AEP31
Voulgaris, N OC1.4
Vovk, A AEP163
Vrbica, S AEP513
Vrbikova, J AEP739, **AEP76**
Vryonidou, A AEP823
Vujosevic, S AEP442
Vujovic, S AEP16
Vukov, M AEP296
Vulto, A **AEP790**
Wadii, T AEP753, AEP245, EP27, AEP149, EP204, AEP694, EP208, AEP708, AEP304
Wafa, A AEP341, AEP364, AEP378
Wagner, C **AEP55**, **AEP74**
Wahlberg, J AEP4
Wajda, M AEP789
Wajdi, S EP61, AEP287, EP10, AEP25, **AEP339**, **EP89**
Walia, R OC8.2
Wallett, L AEP208, AEP248
Wang, L OC7.6
Wang, S OC10.4
Wang, X AEP85, OC10.4
Warde, K AEP77, **OC11.6**
Warmington, E **PEP14.8**
Wass, J **AP1.1,** AEP842
Wassim, K AEP355, AEP691, AEP780, AEP766, AEP403, EP229
Wasyluk, W **AEP249**
Watanabe, K EP51
Weber, J PEP15.2
Weber, S AEP613, AEP599
Weeks, J AEP833
Wei, Z OC7.6
Weir, P AEP488
Weiss, B AEP644, EP226
Welling, M **AEP280**
Wenceslau, CF AEP177
Were, J AEP93
Wernicke, C AEP183
Wernig, F EP128
Wester, V AEP235
Whalley, C OC11.1
Whatmore, J PEP13.8
Whelan, C AEP793
Wicart, P AEP81
Wicks, S AEP175
Wiebke, S AEP838
Wiebolt, J AEP281
Wiedersich, D OC12.1
Wiem, G EP206
Wiem, M **EP150**, **AEP563**
Wiepjes, C AEP592
Wiese, N OC5.1, **PEP10.1**
Wijewickrama, P **EP147**, **AEP320**
Wild, V AEP838
Wilhelms, D AEP789
Williams, TA AEP791
Wills, A AEP94
Winter, EM OC6.3
Winzeler, B AEP465, **AEP467**
Wirth, E PEP15.2
Wissam, A EP206, EP74
Witek, P OC3.1
Wojna, J OC3.1
Wolf, P **AEP62**
Woodhoo, A OC7.5
Wu, M AEP167
Wu, W-C EP135
Wu, X **OC1.5**
Wydra, J AEP496
Xagas, E OC14.4
Xanthakou, E AEP68, AEP130
Xega, V AEP712
Xekouki, P PEP10.2, AEP13
Xhemollari, I EP81
Xhindi, M AEP375, EP81
Xie, Y AEP8
Xin, W YI3
Yaacov, H **EP12**
Yaccobi, E AEP135
Yahiaoui, R AEP209
Yahyaoui, R EP47
Yaich, S EP87, EP56
Yaker, F **AEP648**
Yalalova, I AEP357
Yaman Kalender, DS **AEP679**
Yamanishi, K AEP200
Yanevskaya, L AEP108
Yang, D AEP266, AEP60
Yang, G AEP266, AEP60
Yang, J AEP60, AEP266, EP96, AEP322
Yankova, I **AEP82**
Yarman, S AEP480
Yaroma, A **AEP261**, **AEP812**, **AEP805**
Yasar, M AEP534
Yawa, A AEP648
Yaylali, G OC8.5, **AEP192**
Yaylamaz, S AEP585
Yazici, D AEP471
Yazicioglu, MO AEP870
Yazicioglu, O AEP882
Yazidi, M AEP761, AEP220, EP80, EP216, AEP558, EP155, AEP727, AEP47, EP166, AEP71, EP215, EP23, AEP123, EP157, AEP34, EP174, AEP715
Yazidi, Meriem AEP64, EP181
Yedinak, C **PEP14.6**
Yee, S AEP787
Yefimova, O AEP722
Yelehe, M AEP580
Yempabou, S AEP591, AEP859
Yener Ozturk, F AEP109, AEP524, **AEP464**
Yerlikaya Aydemir, FH AEP798, AEP784, AEP878
Yeste, D PEP4.8

Yevstratieva, Y **AEP687**
Yi, D EP142, **PEP4.6**, EP98
Yildiz, D AEP524
Yıldız Toksöz, D AEP187
Yis, OM AEP581
Ylisaukko-Oja, T AEP560
Ylli, A AEP375, AEP511, EP81, AEP740
Ylli, D AEP740
Yoldi Arrieta, A AEP703, EP152
Yönet, F AEP878
Yoo, WS AEP741
Yoshida, H AEP874
Yosra, H AEP770, EP45
Young, J OC14.5, PEP8.5
Young, V EP21
Young, WF PEP11.6
Younger, A **AEP785**
Youssef, L AEP718, EP176
Yu, C AEP86
Yukina, M **AEP193**, EP19, **AEP830**
Yüksel, N AEP894
Yüksel Güler, B AEP879
Yurenia, A AEP733, AEP734
Yushko, K AEP279
Yusof Khan, AHK AEP895
Z.M. Homer, N OC15.1
Zabuliene, L **AEP661,** EP49
Zafon, C PEP5.7
Zafón Llopis, C AEP871
Zaharieva, E AEP92
Zaidi, MS **EP102**, **EP92**, **EP237**
Zainutdinov, B AEP330, AEP207, AEP263
Zajickova, K **AEP100**
Zalewska, E **AEP151**
Zamarrón Pérez, Á AEP531, AEP478
Zamora, J AEP332
Zampetti, B OC3.3
Zamponi, V AEP575, **AEP22**
Zanchi, D AEP467
Zapanti, E AEP95
Zargni, A **AEP362**, AEP73, **AEP548**, EP133
Zarrilli, S AEP412
Zatelli, MC OC3.2, AEP642, PEP15.3, AEP723, PEP5.2
Zavatta, G AEP153, **AEP84**
Zavattaro, M OC10.6
Zayani, C AEP361
Zbucka-Krętowska, M AEP390
Zebolis, E PEP5.6
Zechmann, S **PEP7.5**
Zeglaoui, F AEP352
Zelinka, T **MTE6**
Zelinska, N **AEP182**
Zenkova, T PEP8.7
Zerva, D AEP379
Zetsche, A AEP35
Zeynalova, G AEP464
Zgliczynski, W AEP325, AEP30, AEP547, AEP496, AEP492, AEP686
Zgliczyński, S AEP686
Zhang, G-Q **AEP414**
Zhang, J **AEP266,** AEP60, AEP41
Zhang, L OC7.6
Zhang, M AEP786
Zhang, W **AEP45**
Zhang, Y AEP60, AEP266
Zheng, W **OC10.4**
Zherdova, N AEP171
Zhou, D AEP208, AEP248, PEP14.8
Zhu, S OC7.6
Zhu, Z OC7.6
Zhukouskaya, V **OC6.2**
Zhukov, AY AEP126
Zhurakivska, O AEP678
Zhurakivskiy, V AEP678
Zia, N AEP175
Zibarev, A EP194, AEP530, EP222, EP39
Zielinski, G AEP538
Zilaitiene, B AEP61, AEP518, AEP387
Zillikens, C PEP2.2
Zissimopoulos, A AEP769
Zivkovic, M AEP143
Zlatar, M AEP706
Zlatkina, V **AEP653**
Zmierczak, H-G OC4.6
Znaidi, N AEP715
Zografos, G AEP5, AEP63
Zohra, BHA EP45
Zopp, S AEP45, PEP13.5
Zouaoui, C AEP277, AEP625
Zouhir, B AEP654, AEP628, AEP24, AEP99, AEP485
Zouli, C EP35
Zoumpouli, C AEP893
Zouraq, IA AEP93
Zrilic, A AEP102
Zubelewicz-Szkodzińska, B AEP351, EP116
Zucchi, R AEP802
Zugasti, A **AEP837**
Zuhur, S **AEP461**, **AEP498**, **AEP557**, **AEP427**
Żukowski, Ł AEP390
Žvirblienė, A AEP387
Zwinczewska, H AEP509
Zwolak, A AEP249