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European Journal of Endocrinology Prize Winner

The European Journal of Endocrinology Prize is awarded to a candidate who has contributed significantly to the advancement of the knowledge in the field of endocrinology through publication. Further information on the prize can be found at http://www.ese-hormones.org/prizes/. This year's recipient is Professor Jason Carroll. The prize will be presented as part of the ECE 2016 opening ceremony where Professor Carroll will deliver his lecture.

Jason is an Australian who completed a PhD in 2002 at the Garvan Institute of Medical Research and University of New South Wales, Sydney, with Prof. Rob Sutherland and Prof. Liz Musgrove. He conducted postdoctoral work with Prof. Myles Brown at Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA from 2002–2006. He has been running his own group at Cancer Research UK, Cambridge Research Institute and University of Cambridge since 2006. Jason has been a senior group leader since 2010 and a member of the EMBO Young Investigator programme since 2010. He is a fellow at Clare College, University of Cambridge.

The European Journal of Endocrinology Prize Lecture

EJE1

Understanding estrogen receptor gene regulation in breast cancer

Jason Carroll
UK

Estrogen receptor (ER) is the defining feature of luminal breast cancers, where it functions as a transcription factor. ER requires associated proteins to interact with the DNA, including the pioneer factors FoxA1 and GATA3, both of which mediate where in the genome ER resides. In the absence of FoxA1, ER binding and transcriptional activity is diminished, even in endocrine resistant contexts. We have utilized ChIP-seq in primary tumor material, coupled with functional analysis, to identify mechanisms that govern FoxA1-ER DNA interactions and the variables that alter binding capacity. Based on these findings, we have screened chemical libraries to identify specific inhibitors of FoxA1, with the goal of blocking ER function via inhibition of its associated pioneer factor. In addition, we have sought to discover novel ER associated proteins that are involved in endocrine resistance and to achieve this, we have established a method for rapid unbiased discovery of protein interacting complexes, which we have applied to discover ER and FoxA1 associated proteins. We find an unexpected interaction between ER and progesterone receptor (PR) in ER+ breast cancer. We show that PR is a negative regulator of the ER complex, where it is important for modulating cellular growth. Our findings suggest that there is substantial cross-talk between parallel hormonal pathways and that we can use this information to repurpose existing steroid receptor ligands for therapeutic use.

DOI: 10.1530/endoabs.41.EJE1

Geoffrey Harris Prize Winner

The European Society of Endocrinology is pleased to present the annual Geoffrey Harris Prize. This prestigious prize is designed for established researchers in the field of neuroendocrinology and is the first of its kind in Europe. The prize will be presented at the annual European Congress of Endocrinology, where the winner will be asked to give one of the main lectures, in addition to two other lectures at future ESE scientific meetings.

Dr Albert Beckers MD, PhD, is Chief of the Department of Endocrinology at the University Hospital Centre, Liège and Full Professor at the University of Liège, Belgium. After completing his medical degree at the University of Louvain, Belgium, Prof. Beckers undertook specialty training in Endocrinology, Internal Medicine and Nuclear Medicine. He oversees a Department with multiple clinical and research areas of interest, including pituitary tumors, thyroid disease, genetic causes of endocrine cancers and rare inherited syndromes. Prof. Beckers has taken a particular interest in endocrine education, authoring a highly regarded series of digital projects on aspects of pituitary disease. He has published more than 250 original articles in journals such as the *New England Journal of Medicine*, *Endocrine Reviews*, and the *Journal of Clinical Endocrinology & Metabolism*. Research highlights include the original characterization and description of the syndrome, Familial Isolated Pituitary Adenomas (FIPA) and a newly described pediatric syndrome X-Linked Acrogigantism (X-LAG).

Prof. Beckers has served two mandates as President of the Belgian Endocrine Society, has been the Secretary of the European NeuroEndocrine Association (ENEA), and has organised many national and international Congresses. Current research interests include the genetics of pituitary diseases, molecular and genetic investigation of rare disorders of endocrine development, gigantism and acromegaly and the study of new treatment options for aggressive endocrine tumors.

The Geoffrey Harris Prize Lecture

GH1

Beyond the Adenoma Valley: from FIPA to gigantism and back

Albert Beckers
Belgium

'Je résolus de m'informer du pourquoi, et de transformer ma volupté en connaissance' Baudelaire.

One of the great blessings in life is to be able to work at something that inspires and interests you. For me, exploration of the diseases caused by abnormal neuroendocrine function has been my passion. Its complexity and interlinked nature can be both startlingly confusing and, when better understood, remarkably logical. But above all, the clinical impact of disordered neuroendocrine function on the patient is often dramatic, and demands our attention and care.

Pituitary hormonal secretion grabbed my interest as a young researcher, particularly the abnormalities associated with pituitary adenomas, like my first publications on FSH secreting and mammosomatotrope pituitary adenomas about 30 years ago. This interest has led me on a very interesting journey that has been punctuated by research projects that have hopefully contributed positively to the neuroendocrinology field. Usually these observations have very ordinary beginnings, usually in a normal endocrine clinic setting, while talking to my patients and puzzling over a result that seems not to have an easy explanation. From patients with unexplained familial occurrence of pituitary adenomas arose the first studies that eventually gave rise to my description of familial isolated pituitary adenomas (FIPA). From those FIPA cases, it was a logical step to explore the role of the AIP gene in various settings, including its contribution to a younger, more severe phenotype in acromegaly. This, in turn, led our work into the area of gigantism, one that I have found fascinating since I was a young researcher. This recently came full circle with the discovery of X-LAG syndrome, a disorder of extreme pituitary gigantism due to a Xq26.3 microduplication, which itself can present as FIPA. The act of counting off where my patients lived on my drive home from work in the so-called Adenoma Valley provided the seed for studies demonstrating the important prevalence of pituitary adenomas in the general population.

While the initial observations might come from a mundane setting, the proof of a clinically important finding is the work of many people. In the setting of rare neuroendocrine disorder research where genetics plays a central role, the journey to discovery must pass through many stations and airports. It involves the collaboration and shared work of colleagues around the world, each contributing their own vital piece of the jigsaw puzzle.

DOI: 10.1530/endoabs.41.GH1

Clinical Endocrinology Trust Award & Lecture

The Clinical Endocrinology Trust (CET) Award is given for clinical research that addresses aspects of endocrinology at the forefront of clinical practice. The award is sponsored by the Clinical Endocrinology Trust, and consists of an honorarium and a prize medal. The winner is invited to give a lecture at the annual European Congress of Endocrinology.

Wiebke Arlt is the William Withering Chair of Medicine and Director of the Institute of Metabolism and Systems Research at the University of Birmingham. As a clinical endocrinologist she works at the Queen Elizabeth Hospital Birmingham, where she leads the adrenal and reproductive endocrine specialist services.

Wiebke has studied Medicine at the University of Cologne before moving to the University of Würzburg for specialist training in Endocrinology and Internal Medicine, under the auspices of Bruno Allolio. This was followed by postdoctoral training at the University of California at San Francisco with Walter Miller. In 2002, she moved to Birmingham to work with Paul Stewart and has stayed there ever since, initially as a Heisenberg Senior Fellow, then as a Medical Research Council UK Senior Fellow and from 2006 as a Professor of Medicine.

Wiebke leads a large, multi-disciplinary research group working on steroid biology and biochemistry and its translational applications, with a special focus on androgens, both in the context of rare adrenal and gonadal disorders and common disease associated with adverse metabolic risk, such as polycystic ovary syndrome and adrenal incidentaloma.

Clinical Endocrinology Trust Award & Lecture

CETL1

Adrenal

Wiebke Arlt
UK

Steroids are central regulators of human physiology and disease. Steroid synthesis does not only taking place in adrenal and gonads but in all cells of the body that are equipped with steroidogenic enzymes, which allows targeted tissue-specific steroid activation and inactivation. We have developed steroid metabolomics as an innovative approach to the understanding of steroid biology by combining mass spectrometry-based steroid measurement with large scale data analysis with machine learning based computational methods. Over recent years, steroid metabolomics has emerged as a powerful tool for the dissection of disease mechanisms and the development of personalized diagnostic and therapeutic strategies in patients with adrenal and gonadal disorders. The lecture will introduce the principles of steroid metabolomics and provide two recent examples of its utility, both in the context of adrenal disease: firstly, as a biomarker tool for identification and monitoring of malignancy in adrenal incidentalomas, and secondly, for the elucidation of novel disease mechanisms in primary aldosteronism.

DOI: 10.1530/endoabs.41.CETL1

Plenary Lectures

PRRT, NETTER-1, and the new Era

PL1

Abstract unavailable.

Endocrine disruptors and the thyroid (*Endorsed by Endocrine Connections*)

PL2

Environmental chemicals, thyroid signalling and early brain development

Barbara Demeneix
France.

During vertebrate evolution thyroid hormone acquired multiple roles in development, especially brain development. Examples include promotion of myelination thereby increasing speed of neuronal transmission, as well as modulation of neuronal differentiation, as exemplified by the exquisite sensitivity of the Purkinje neuron to thyroid hormone deficiency. Research in the last 15 years has demonstrated that early development, the first trimester of pregnancy in humans, is an unexpectedly thyroid- hormone dependent period. In the same time span we have witnessed an unprecedented increase in autism spectrum disorders (ASD) incidence, correlated in many data sets with loss of IQ. Although, changes in diagnosis and awareness can contribute the ASD increase, many authors consider that environmental factors, possibly exacerbating genetic susceptibilities, are implicated. Four main arguments support this hypothesis. First, increasing numbers of chemicals are found routinely in human amniotic fluid. These include, pesticides, plasticizers (such as phthalates, BPA), nitrates, perchlorate, antimicrobials (such as Triclosan), flame-retardants, surfactants and mercury (produced by fossil fuel burning). Second, many of these chemical categories can interfere with thyroid hormone signalling, a pathway essential for orchestrating brain development. Third, prenatal exposure to many chemicals is significantly associated with both IQ loss and increased ASD risk. Fourth, production of many of these chemicals has risen exponentially in the last few decades, continually increasing exposure. The cost of exposure in socio-economic terms has been estimated for just two or three chemicals to be in the order of 150 billion Euros per annum for Europe. I will present and discuss data showing that cocktails of these chemicals found in amniotic fluid can interfere with thyroid hormone signalling and brain development, affecting genes and developmental pathways (neuronal proliferation, migration) that are regularly associated with brain development and with ASD.

DOI: 10.1530/endoabs.41.PL2

Testosterone trials

PL3

Abstract unavailable.

Gut microbiota, inflammation and metabolism (*Endorsed by Endocrine Connections*)

PL4

Modulation of the gut microbiome by nutrients is implicated in the control of inflammation and metabolic disorders

Natalie Delzenne
Belgium.

Experimental data in animals, but also observational studies in patients, suggest that dysbiosis, meaning changes in the composition and/or of the metabolic activity of the gut microbiota, occurs upon the development of obesity and related metabolic diseases In this presentation, we will evaluate the rationale to propose prebiotic approach (consisting in the administration of dietary fermentable carbohydrates able to change the gut microbiota composition or function) in the management of metabolic disorders such as steatosis, insulin resistance, and vascular dysfunction. We will show, in view of experimental data in animals, that dietary glucans, arabinoxylans, or fructans can modulate host gene expression and metabolism, by changing gut microbiota composition and function. Even if the increase in Bifidobacteria remains the major and common signature of the prebiotic approach, a complex modulation of the gut microbial ecology occurs upon prebiotic treatment in obese individuals, which extent the panel of interesting microbial targets in the management of obesity-related diseases. The promotion of gut hormones release, changes in the gut barrier integrity, and/or the production of bacterial-derived metabolites could all participate in the improvement of host health by prebiotics. Appropriate human intervention studies are programmed in order to evaluate the interaction between the gut microbiota and 'non digestible' food components, which might contribute to adequate nutritional advices in the management of metabolic disorders.
I declare no conflict of interest concerning this presentation.

DOI: 10.1530/endoabs.41.PL4

Insulin signalling and action

PL5

Abstract unavailable.

Bionic pancreas

PL6

Abstract unavailable.

Symposia

Thyroid and Pregnancy

S1.1

At which TSH cut-off should we start LT4 therapy during pregnancy

Erik Alexander
USA.

Hypothyroidism in pregnancy is generally considered harmful. However, the definition of hypothyroid during pregnancy remains controversial. Measurements of maternal serum TSH have traditionally been used to define hypothyroidism, with values >2.5 mIU/l generally warranting treatment. However, recent data have suggested that the 'normal' reference range for serum TSH in healthy pregnant women varies by region as well as by ethnicity. Importantly, changing the upper reference range for maternal serum TSH during pregnancy from 2.5 mIU/l to 4.5 mIU/l can impact treatment decisions for millions of women worldwide. This symposium will explore the most recent data pertaining to this complex topic, and also explore the subgroup of pregnant women with normal serum TSH values but low free thyroxine concentrations. What is a normal TSH concentration during pregnancy? What values of serum TSH are harmful to the pregnancy or the developing fetus?

DOI: 10.1530/endoabs.41.S1.1

S1.2

Abstract unavailable.

S1.3

Abstract unavailable.

Mixtures, medicines and diet, where now for endocrine disrupting compounds? (*Endorsed by Endocrine Connections*)

S2.1

Abstract unavailable.

S2.2

Mixture effects of endocrine disrupters in animal models

Ulla Hass
Denmark.

Risk assessment of chemicals based on no observed adverse effect level (NOAEL) from animal models is normally done for one chemical at a time, but several endocrine disrupting chemicals (EDCs) have been detected in mixtures in humans. For combinations of EDCs with similar mechanism, there is clear evidence that mixture effects can arise at doses around NOAELs. Also, the mixture effects can be predicted based on dose-addition.

There is also good evidence that combinations of EDCs with diverse modes of androgen action, but similar effects induce mixture effects when each component is present at doses equal to NOAELs. We have investigated mixtures of a widely used plasticizer, di(2-ethylhexyl) phthalate (DEHP); two fungicides, vinclozolin and prochloraz; and a pharmaceutical, finasteride for effects on male sexual development in the rat. When the four chemicals were combined at doses equal to their NOAEL, significantly reduced anogenital distance (AGD) was observed in male offspring. Surprisingly, the effect of combined exposure on malformations of external sex organs was synergistic. For effects on AGD, retained nipples, and sex organ weights, the combined effects were dose additive.

We have also studied effects of mixtures modelled based on high end human intakes. We selected 13 EDCs where data about human exposures was available, including phthalates, pesticides, UV-filters, bisphenol A, parabens and the drug paracetamol. The results suggest that highly exposed women of reproductive age may not be protected sufficiently against the combined effects of EDCs that affect the hormonal milieu required for normal sexual differentiation of male foetuses.

In conclusion, the chemical-by-chemical approach in risk assessment appears as insufficiently protective against the possibility of mixture effects. In most cases the mixture effects were dose additive. Thus, cumulative risk assessment for endocrine disrupters is both relevant and feasible and dose addition as an assessment method is recommended.

DOI: 10.1530/endoabs.41.S2.2

S2.3

EDCs: assessing the risks of exposure to environmental chemicals and pharmaceuticals

Rod Mitchell
UK.

Many industrial chemicals and pharmaceutical products have been proposed to result in endocrine disruption in humans. This includes potential effects on reproductive development in males and females. Chemicals that have been proposed to impact on male reproductive development include plasticizers, synthetic oestrogens and analgesics. Much of the data on the effect of exposure to these agents are based on studies conducted in rodent models; however, confirmation of such findings in human model systems at human-relevant exposure levels are lacking.

We have developed model systems to determine the effects of exposure to a variety of proposed 'EDCs' on human fetal testis development and function. Using a xenograft system designed to reproduce normal fetal testis development and in-utero hormonal environment, our results demonstrate important species differences in the effects of exposure to chemicals such as di-*n*-butyl phthalate (DBP) and diethylstilboestrol (DES) in terms of testosterone production. We have also demonstrated that exposure to analgesics, such as paracetamol, result in a significant reduction in testosterone production and also impact on germ cell development in the human fetal testis. Importantly, these effects are apparent at therapeutic levels of exposure using a standard therapeutic regimen.

Our work, in addition to that of several other groups, highlight the importance of choosing an appropriate model species, experimental system and relevant exposure regimen in order to determine the potential impact of EDC exposure in humans. Findings from rodent studies should, where possible, be confirmed using human tissue models in order to determine the relevance to human health.

DOI: 10.1530/endoabs.41.S2.3

Senescence and plasticity in the anterior pituitary

S3.1

Programmed cell senescence: IL-6 role in the pituitary

Eduardo Arzt

Cellular senescence is a state of permanent and stable proliferative arrest in G_1 phase of the cell cycle through activation of the p53/p21 and pRb/p16 signalling pathways. Oncogene-induced senescence (OIS) is a highly proliferative state, which mimics transformation, but this mitotic burst is gradually replaced by senescence. Several lines of evidence have implicated OIS as a vital cause of arrest of benign neoplasms. Pituitary tumors are mostly benign, non-metastatic and monoclonal neoplasms. The precise mechanisms underlying the unique indolent growth of these benign adenomas remain unknown.

Normal pituitary cells are under auto-/paracrine control of numerous growth factors. Altered expression of cytokines/growth factors and their receptors, has been observed in pituitary tumors. IL-6 plays an important role in pituitary tumor progression. IL-6 is produced by tumoral cells but is also delivered to the normal or adenoma cells through folliculo stellate (FS) cells, which mix up with the normal pituitary cells and further surround the pituitary tumors. It has been shown that IL-6 inhibits normal pituitary cell proliferation and has opposite effects in normal and tumoral pituitary cells.

IL-6 plays a key role in OIS induction indicating that IL-6 is a pleiotropic cytokine that can function as an autocrine or paracrine tumorigenic factor. The fact that IL-6 is a cytokine that participates in pituitary tumor development, in addition to the findings of its role in OIS, makes this cytokine an attractive candidate as an autocrine/paracrine stimulator of pituitary adenoma progression inducing OIS.

IL-6 maintains pituitary tumoral senescence by its autocrine action, providing a natural model of IL-6 mediated adenoma OIS, which explains the benign nature of these abundant adenomas.

DOI: 10.1530/endoabs.41.S3.1

S3.2

Pituitary stem cells: quest for hidden functions

Hugo Vankelecom

The pituitary is the 'master' endocrine gland, governing the fundamental processes of body growth, metabolism, reproduction and stress. The past decade, it progressively became clear that the pituitary, like many adult tissues, harbors a population of stem cells. While the molecular portrayal of these cells is continually expanding, their function remains essentially hidden. From recent studies, the picture is emerging that the stem cells of the adult pituitary are highly quiescent and only visibly wake up in pathological conditions.

Upon transgenic cell-ablation damage in the pituitary, the stem cell compartment is promptly turned on with expansion and expression of the missing hormone. This activation is accompanied by substantial regeneration of the lost hormonal cells, a restorative competence that was unexpected in the mature gland. The regenerative skill however rapidly disappears at aging, together with a decline in the number and fitness of the stem cells. One function of the adult pituitary stem cells may thus be hidden in the regenerative toolbox of the gland, at least during a specified and limited time window.

Recent work also showed activation of the pituitary stem cell compartment during tumor formation in the (mouse) gland. Moreover, pituitary tumors (from patients and mice) contain a candidate 'tumor stem cell' (TSC) population. The pathogenesis of pituitary tumors remains far from understood. A link between the tumor-driving TSC and the pituitary stem cells may shed new light on tumorigenesis in the gland.

To conclude, decoding the hidden functions of the pituitary stem cells will not only lead to better fundamental insights into their role but may also expose (novel) targets for treating pituitary tumors and for regenerative intervention in pituitary deficiency as caused by damage, tumors or aging. Yet, this functional unraveling has only just begun.

DOI: 10.1530/endoabs.41.S3.2

S3.3

Adamantinomatous craniopharyngioma: lessons from mouse models

Juan Pedro Martinez-Barbera
UK.

Adamantinomatous craniopharyngioma (ACP) is a paediatric pituitary tumour that is associated with high morbidity due to the tendency of the tumour to infiltrate locally into surrounding brain structures such as the hypothalamus and visual tracts. We have developed mouse models for human ACP, which we are using to better understand the pathogenesis of these human tumours as well as to test novel targeted treatments. Using advanced imaging techniques such as X-ray computed tomography (micro-CT) and magnetic resonance imaging (MRI), we show that mouse and human tumours display similar radiological features and reveal insights into the invasive properties of the human tumours. Complementing our initial molecular studies on murine ACP, we have now completed whole-transcriptomic analysis of 18 samples of human ACP (16 pediatric, one adult) and six control samples. Together, mouse and human studies indicate that the paracrine activities of senescent cells may be critical for tumour initiation and growth. The molecular studies have also identified several dysregulated pathways, offering potential new targets against human ACP, which are currently being investigated in ongoing pre-clinical trials. Of note, inhibition of the sonic hedgehog (SHH) pathway, activated in both murine and human ACP, provides no benefit to the treated mice. In contrast, pathway inhibition leads to faster progression of the tumours.

DOI: 10.1530/endoabs.41.S3.3

How to diagnose endocrine disease in obese patients? (*Endorsed by the European Journal of Endocrinology*)

S4.1

HPA axis abnormalities and metabolic syndrome

Eva Kassi
Greece.

MetS is a cluster of interconnected factors that directly increase the risk of cardiovascular atherosclerotic diseases, and diabetes mellitus type 2. Visceral obesity/insulin resistance have gained increasing attention as the core manifestations of the syndrome. HPA axis is one of the main stress response pathways. Apart from having a circadian activity also mediates the adaptive response to stressors. A growing body of evidence point towards a strong relationship between perturbations of HPA axis and metabolic syndrome.

Persistent over-stimulation of HPA axis by various stressors resulting to elevated circulating glucocorticoids can lead to metabolic syndrome components. Cortisol has been causally demonstrating to promote the accumulation of visceral adipose cells and visceral obesity. Moreover, acting through various pathways it increases the apetite, stimulates gluconeogenesis, glycogenolysis, lipolysis in subcutaneous fat tissue and over time causes insulin resistance, diabetes, hyperlipidemia. Importantly, disruption of fine tuning of the intracellular cortisol production - as it is regulated by 11β-HSD enzyme in specific adipose depots as well as in other essential metabolic organs also promotes metabolic syndrome phenotype.

Disrupted biological rythms such as those seen in sleep disorders and shift workers have been shown to increase the risk of metabolic disorders such as hyperglycemia, insulin resistance, central obesity and hypertension. Actually, loss of circadian rhythm and glucocorticoid excess conditions seem to develop similar metabolic disturbances; this indicate that the circadian CLOCK system and stress-responsive HPA axis strongly cooperate with each other in physiology and pathophysiology, however, details of such interaction at multiple levels remain largely unexplored.

Finally, epidemiological studies suggest a fetal programming of metabolic syndrome. It is now becoming increasingly accepted that intra-uterine and perinatal activation of HPA axis can cause epigenetic modifications which can lead to metabolic disturbances later in life.

Given that the prevalence of metabolic syndrome has reached epidemic levels, a better understanding of the role of HPA axis dysregulation in its pathophysiology and vice-versa will help us to better design prevention and treatment strategies.

DOI: 10.1530/endoabs.41.S4.1

S4.2

Male hypogonadism and obesity: how to differentiate cause and consequence

Felipe Casanueva
Spain

Male hypogonadism is generally associated with overweight or obesity and, in these situations androgen therapy partially, or totally, reverses the excess adiposity. However, the opposing situation, i.e., the role of overweight on a reduction of gonadal function has been scarcely studied. In fact, changes in body morphology are complex because several factors such as age, social and lifestyle influences, and the physiological response to stress can affect both problems, adiposity excess and gonadal function. At the end both factors will mutually interact. In a previous work, we have observed that obesity and overweight *per se*, exert a profound effect on male gonadal function in community dwelling individuals of middle-aged and elderly men. The situation of advanced age provides a good model because the age-associated decline in testosterone function is well described. Furthermore, the progressive reduction in gonadal function associated with aging vanishes if obese and overweight individuals are separated from the group. However, socioeconomic status, as well as lifestyle factors, has been demonstrated as causal factors in the development of obesity and increased waist circumference, and these factors, are at the same time inducers of gonadal dysfunction, acting at central level. Considerable more work is needed in order to clarify the interacting network of factors and, to understand if intervention to counteract one of them may provide a focus for health promotion and prevention, mostly at advanced ages.

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S4.3

Subclinical hypothyroidism and obesity: cause or consequence?

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Spain.

Levels of TSH respond to fluctuations in serum free T(4) (fT(4)) and remain in a very narrow individual range. There exists current controversy regarding the upper limit of normal serum TSH values above which treatment should be indicated. In a cohort of healthy men from the general population, both serum TSH and fT(4).TSH product were positively associated with fasting and postload insulin concentration and negatively with insulin sensitivity.It was concluded that thyroid function tests were intrinsically linked to variables of insulin resistance and endothelial function. It is possible that underlying factors lead simultaneously to increased serum TSH, insulin resistance, ensuing dyslipidemia, and altered endothelial function even within current normal TSH levels.
In fact, type I iodothyronine 5′-deiodinase (D1) gene expression and activity were found in adipose tissue of obese subjects, hinting at a role of 3,5,3′-triiodo-L-thyronine formed by D1 in response to leptin in the modulation of adipose tissue metabolism. On the other hand, recent observations disclosed that visceral adipose tissue μ-Crystallin was an adipose tissue factor linked to parameters of thyroid hormone action and might mediate the interaction of thyroid function and insulin sensitivity.
Additionally, total (t)- and a splice variant (v)-TSHβ were consistently detected in adipose tissue from euthyroid subjects, and positively associated with serum total- and LDL-cholesterol, the lipidomics and metabolomics profile of adipose tissue, and with adipose tissue, liver and circulating markers known to change with cholesterol levels TSHβ could be an adipose tissue marker of hypothyroidism, possibly produced to maintain energy storage during fasting.

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Adrenal incidentaloma guidelines

S5.1

Abstract unavailable.

S5.2

Abstract unavailable.

S5.3

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S5.6

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S5.7

Abstract unavailable.

Characterization and treatment of thyroid cancer

S6.1

Abstract unavailable.

S6.2

Abstract unavailable.

S6.3

Dynamic risk stratification in the follow up of thyroid cancer

Barbara Jarzab
Poland.

The discussion which prognostic factors are the most reliable to adequately assess the risk of cancer related death and relapse in differentiated thyroid cancers [DTC] is ongoing. To date, age at diagnosis and distant metastases were considered as the most important risk factors. Among other factors, that may influence both overall and disease free survival, were male sex, some histopathological features such as: tumor diameter, tumor grade, aggressive histotype, extrathyroidal extension, angioinvasion, and lymph node involvement. However, the results of different analyses, evaluating the role of any particular factor, are distinct. These divergent data were the reason leading to a significant change in the approach to DTC risk stratification. Currently, it is based on a continuous dynamic evaluation conducted through the whole follow-up, because a rigid risk assessment at DTC diagnosis does not reflect the real prognosis. The first evaluation, based according to the ATA criteria only on histopathological findings and TNM classification, stratifies a patient as low, intermediate or high risk. Next, during the further follow-up, the risk is re-stratified on the basis of the treatment outcomes (classified as one of the following categories: excellent response, incomplete biochemical response, incomplete structural response or indeterminate response). On the one hand, thanks to this re-stratification, patients demonstrating an excellent response to therapy have a minimal risk of DTC recurrence, regardless of an initial risk class. On the other hand, an incomplete response to initial therapy increases the probability of persistent disease or DTC recurrence. Thus, the new approach allows to avoid the over-treatment in subjects with an excellent response to the initial therapy and simultaneously to select patients requiring a more intensive monitoring due to a higher risk of DTC relapse.

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The chronic syndromes of patients with cured pituitary diseases (*Endorsed by the European Journal of Endocrinology*)

S7.1

Acromegaly: 10 years after cure

Johannes Romijn
The Netherlands.

Appropriate treatment of acromegaly results in biochemical control or cure and reduces signs and symptoms, morbidity and excess mortality. Nonetheless, many of these patients still have considerable decreases in quality of life parameters and suffer from increased morbidity due to combinations of factors, including pituitary insufficiency despite optimal endocrine substitution, irreversible effects of previous GH/IGF-1 excess with complex multisystem morbidity, and the effects of treatment modalities. Even during follow up after long term biochemical control or cure many of these patients suffer from the complications of previous GH/IGF-1 excess. These complications include sleep disorders, acromegalic cardiac manifestations, especially in older patients, acromegalic arthropathy (a distinct form of arthropathy) associated with arthralgias, aortic root dilatation, intracranial saccular aneurysms, dolichocolon, diverticular disease, and vertebral fractures despite normal bone density. Apparently, these long term manifestations of acromegaly have major irreversible components.

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S7.2

Cushing's disease: 10 years after cure

Elena Valassi
Spain.

Recent evidence suggests that resolution of hypercortisolism in Cushing's disease (CD) may not lead to complete remission of the clinical abnormalities associated with this condition. In particular, elevated cardiovascular risk may persist in 'cured' CD patients long-term after eucortisolism has been achieved. This is believed to be related with the maintenance of visceral obesity and altered adipokine secretory pattern which perpetuate features of metabolic syndrome, including impaired glucose tolerance, hypertension, dyslipidemia, atherosclerosis and hypercoagulability. Nephrolithiasis and incomplete recovery of bone mineral density have also been described in CD patients in remission. Moreover, previous exposure to excess cortisol may have irreversible effects on the structures of the central nervous system controlling cognitive function and mood. Thus, sustained deterioration of the cardiovascular system, bone remodelling and cognitive function along with neuropsychological impairment might be associated with high morbidity and poor quality of life in CD patients in remission for many years. Furthermore, relapse of hypercortisolism is not infrequent, occurring in up to 66% of patients within 10 years from successful surgery. This exposes the patients to the deleterious effects of glucocorticoid excess again.
Life-long monitoring is mandatory in CD patients to diagnose recurrence, control long-term complications of previous cortisol excess and, possibly, normalize life expectancy.

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S7.3

Craniopharyngioma: 10 years after cure

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Germany.

Childhood-onset craniopharyngiomas are rare intracranial embryonal malformations of the sellar region arising from remnants of Rathke's pouch that require life-long control and management of the endocrine, ophthalmological and neuropsychological deficits caused by the tumors and their treatment. Craniopharyngiomas show low-grade histological malignancy and frequently affect hypothalamic/pituitary regions and the optic chiasm due to their location. Hypothalamic involvement and/or treatment-related lesions to the above structures result in impaired physical and social functionality that includes severe neuroendocrine sequelae, mainly hypothalamic obesity, with major negative impact on quality of life in surviving patient. Quality of life in craniopharyngioma patients with hypothalamic involvement is impaired by physical fatigue, reduced motivation, dyspnea, diarrhea, and non-optimal psychosocial development.

Hypothalamic obesity in craniopharyngioma patients is associated with a severe increase in BMI during the early post-operative period. During long-term follow-up of >12 years, the degree of obesity is plateauing at high levels. Patients with craniopharyngiomas involving hypothalamic structures showed reduced 10-years overall survival rates, whereas overall and progression-free survival rates are not related to degree of resection. Accordingly, gross-total resection should be avoided in cases of hypothalamic involvement to prevent further hypothalamic damage, exacerbating sequelae.

As surgical expertise has been shown to have major impact on postoperative morbidity, medical societies should establish criteria of adequate professional expertise for the treatment and care of craniopharyngioma patients. Based on these criteria, health authorities should organize the certification of centers of excellence authorized for treatment and care of patients with this childhood craniopharyngioma.

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Primary aldosteronism

S8.1

Novel targets of mineralocorticoid receptor in human renal cells

Marc Lombes

Aldosterone exerts numerous pleiotropic functions, notably in the kidney where it controls hydroelectrolytic homeostasis and ultimately blood pressure. Aldosterone acts by activating the mineralocorticoid receptor (MR), a transcription factor that regulates target gene expression. Alteration of the mineralocorticoid signaling leads to various diseases including hypertension, cardiovascular, renal, metabolic or CNS disorders.

Aldosterone mechanism of action is extremely complex, involving several intricate aspects (1) whereby kinetic and cross-talk dynamics appeared to play a critical role in the control of transepithelial sodium transport. An overall assessment of MR genomic targets by new tools was therefore highly desirable. We setup the chromatin immunoprecipitation (ChIP) with a specific anti-MR antibody in highly differentiated human renal cells expressing GFP-MR. This approach coupled with the innovative high-throughput sequencing technology (ChiP seq, HiSeq) allowed identification of approximately one thousand direct genomic MR targets. Computational analysis of these genomic sites defined a specific MR response element (MRE) in which the AGtACAgxatGTtCt sequence was the most prevalent motif. Of interest, most genomic MR-binding sites (MBSs) (84%) are located at long distances (>10 kb and up to 150 kb) and various directions from the transcriptional start sites of corresponding target genes, either well-known or new mineralocorticoid-response genes. Specific aldosterone-induced recruitment of MR on genomic sequences was validated by ChIP-qPCR and correlated with concomitant and positive aldosterone-activated transcriptional gene regulation as assayed by RT-qPCR. Of note, most MBSs lacked MREs but harbored DNA recognition motifs for other transcription factors (FOX, EGR1, AP1, PAX5) suggesting functional interaction (2). Dynamics of MR recruitment and of its transcriptional co-regulators demonstrated that finerenone, a novel non-steroidal MR antagonist, prevents assembly of active transcriptional initiation complexes (3). These studies provide new insights into aldosterone, MR-mediated renal signaling. Many unanswered questions remain notably concerning specificity of corticosteroid receptor action yet opening germane perspectives for mineralocorticoid-related pathophysiology.

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S8.2

Revised guidelines for finding and treating primary aldosteronism

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Italy.

Primary aldosteronism is an endocrine form of hypertension which is highly prevalent among hypertensive population but its rate of detection is far lower than its real prevalence.

This might be due to lack of adequate information or expertise in general practitioners or even among hypertension specialists, other than endocrinologists. As PA is common, and has a much higher cardiovascular risk profile than age-, sex-, and blood pressure (BP)–matched essential hypertension, targeted treatment is of obvious benefit to at-risk patients with hypertension. Thus, the challenge of diagnosing this condition, correctly recognizing the subtype, and offering the optimal specific treatment was faced in 2008 by the Endocrine Society who published Clinical Guidelines for the Case Detection, Diagnosis, and Treatment of Primary Aldosteronism (PA). Since than, new insights in understanding the pathophysiology of PA and better diagnostic methods became available; on the other hand, it was recognized that, in spite of the world-wide diffusion of the Guidelines, an overwhelming majority of PA remain occult since most subjects with PA are never screened. To address these issues, it was decided to update the Guidelines, in the attempt either to incorporating insights from relevant studies over the past seven years but also to offer, in the explicit recognition that PA as a major public health issue, and not merely a matter of complex and expensive case detection, diagnosis and treatment of individual patients, a simplified approach to those hypertensives who are not fortunate enough to be studied in specialized Centers. The new Guidelines, which are expected to appear within the current year, build on and extend the previous ones in several points including: broader indications for screening to include subjects with sustained BP above 150/100 mmHg; recognition that the prevalence of PA varies from 5% (and more APA) to 10% (and more IHA) according as more or less stringent cutoffs for ARR and PAC are adopted; strengthening the case for timely diagnosis and treatment of PA, based on mounting evidence for cardiovascular and renal damage; report of new findings on molecular genetic of APA; suggestion of abbreviated work-up in patients with clear cut signs of PA and definition of the conditions in which AVS could be avoided; indication to tentatively treat with MR antagonist all cases with elevated ARR who are unwilling or unable to proceed in the confirmatory/subtype testing. The Guidelines will end with an outlook on the need of standardized Aldosterone and Renin assays, of more reliable confirmatory tests, of less invasive and more accessible imaging techniques, of new non-steroidal MR antagonists, of institution of registries and, above all, of providing to all clinicians involved in the field the ability to recognize PA as a possible (and treatable) cause of hypertension in their patients.

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S8.3

Adrenal lessons from next-generation sequencing

Maria-Christina Zennaro
France.

Primary aldosteronism (PA) is the most common form of secondary hypertension. In the majority of cases it is caused by unilateral aldosterone producing adenoma (APA) or by bilateral adrenal hyperplasia. Although the majority of cases of PA are sporadic, the disease may occur in the context of familial hyperaldosteronism where it is associated with specific germline mutations. Recent advances in genome technology have improved our understanding on the genetic basis of PA, allowing to identify and to characterize new familial forms of the disease as well as somatic mutations involved in APA and to establish a pathophysiological model of APA development. This talk will summarize our current knowledge on the genetic basis of PA and discuss the pathogenic mechanisms leading to increased aldosterone production and cell proliferation. Perspectives for clinical management of patients and open questions to be addressed by future research will be addressed.

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Bone marrow adipose tissue – A "novel" functionally active fat depot

S9.1

Bone Marrow Adipose Tissue and bone, a bad romance

Stephanie Lucas
France.

Bone Marrow Adipose Tissue (BMAT) has only recently become an emerging topic in both medical and basic research. As secretory cells found either packed or scattered within the BM, these adipocytes are likely contributors to haematopoiesis- or bone- related diseases. Indeed, clinical studies have consistently reported that BMAT amount is associated with bone loss in diverse types of osteoporosis such as that of ageing, post-menopause and anorexia nervosa. Since BM adipocytes and osteoblasts (the bone forming cells) arise from the resident Mesenchymal Stem Cells (MSC), the process of adipogenesis per se is often viewed as a competitive process for osteoblastogenesis. Indeed, various endocrine and local factors that usually alter osteoblastogenesis promote adipogenesis. However, studies from other groups and ours qualify this view. Moreover, the functional phenotype of BM adipocytes is also suggested to be a key determinant in bone fragility. As shown by us and others, coculture of osteoblasts with adipocytes compromises the phenotype, function or survival of osteoblasts. Owing to the impact of the adipokines adiponectin and leptin on bone formation, a few groups like ours have started to explore the capacity of BM adipocytes to release factors involved in bone remodeling. Indeed, compared to classical extramedullary adipocytes; primary mature BM adipocytes exhibit low expression levels of typical adipokines with high expression levels of anti-osteoblastogenic factors (such as Wnt signaling inhibitors) and pro-osteoclastogenic factors (such as RANKL). These first findings obtained both in human samplings and mouse models strengthen the detrimental involvement of BMAT in bone remodeling.

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S9.2

Distinct metabolic role of bone marrow adipose tissue

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Finland.

Bone marrow adipose tissue (BMAT) fills the majority of bone marrow space in adult long bones. Despite its wide presence the functions of BMAT in normal energy metabolism, bone turnover or in disease are largely unknown. Amount of BMAT does increase with age, upon failure of hematopoietic bone marrow and in anorexia nervosa but its amount also positively correlates with that of visceral fat. Work in animal models has suggested that BMAT would share characteristics with brown adipose tissue. Our research group is interested in the metabolic activity and functions of BMAT and its role in the whole body energy metabolism. To do this, we combine modern positron emission tomography (PET) imaging and molecular biologic approaches.

In healthy subjects under fasting conditions BMAT does uptake glucose (18F-fluorodeoxy glucose, FDG) similarly to subcutaneous and slightly less than visceral adipose tissue. However, insulin stimulates the glucose uptake more than in the other fat depots during hyperinsulinemic clamp. Interestingly, in morbidly obese patients and especially in obese with type II diabetes, fasting BMAT glucose uptake was higher than in controls but it was not stimulated by insulin indicating that BMAT may become insulin resistant. In type II diabetic patients BMAT insulin sensitivity could be improved by bariatric surgery-induced weight loss or by rosiglitazone. We also found that cold stimulation does not activate glucose metabolism in BMAT as it does in brown fat. Furthermore, we did not observe any expression of brown fat marker genes in BMAT, which together with PET data indicates that human long bone BMAT does resemble brown fat. Instead, BMAT did show a distinct gene expression pattern different from subcutaneous fat.

Taken together our data demonstrates that BMAT is metabolically active, insulin sensitive and molecularly distinct fat depot that likely has important but overlooked role in whole body energy metabolism.

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S9.3

Development, endocrine functions, and metabolism of marrow adipose tissues

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Marrow adipose tissue (MAT) accumulates in diverse clinical conditions but remains poorly understood. We have observed region-specific variation in MAT adipocyte development, regulation, size, lipid composition, gene expression and genetic determinants. Functionally, MAT is a disproportionate source of adiponectin. Early MAT formation in mice is conserved, whereas later development is strain dependent. Proximal, but not distal tibial, MAT is lost with 21-day cold exposure. Rat MAT adipocytes from distal sites have an increased proportion of monounsaturated fatty acids and expression of Scd1/Scd2, Cebpa and Cebpb. Humans also have increased distal marrow fat unsaturation. We define proximal 'regulated' MAT (rMAT) as single adipocytes interspersed with active haematopoiesis, whereas distal 'constitutive' MAT (cMAT) has low haematopoiesis, contains larger adipocytes, develops earlier and remains preserved upon systemic challenges. Loss of rMAT occurs in mice with congenital generalized lipodystrophy type 4, whereas both rMAT and cMAT are preserved in mice with congenital generalized lipodystrophy type 3. Consideration of these MAT subpopulations may be important for future studies linking MAT to bone biology, haematopoiesis and whole-body metabolism.

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Late Breaking News Session

S10.1

Abstract unavailable.

S10.2

Abstract unavailable.

S10.3

Abstract unavailable.

New Developments in subclinical thyroid disease

S11.1

Thyroid function and aging: what can we learn from animal models?

Edward Visser
The Netherlands.

Since thyroid hormone is a key regulator of metabolism, changes in thyroid hormone signaling have widespread effects. Thyroid state changes during aging and vice versa lifespan is affected by thyroid state. However, underlying mechanisms remain elusive. DNA damage importantly contributes to the process

of aging, as underscored by premature aging syndromes caused by defective DNA repair.
In different mouse models of premature (DNA-repair deficient animals) and normal aging, thyroid hormone signaling is attenuated in specific tissues. This is associated with tissue-specific induction of the thyroid hormone-inactivating deiodinase D3 and decrease of thyroid hormone-activating D1 activities. Also, the T3-receptor beta appears important in mediating the T3-effects on aging. From the current knowledge it can be speculated that tissue-specific attenuated thyroid hormone signaling may contribute to the adaptive survival response during aging. Future studies should reveal if decreasing thyroid hormone signaling improves survival and if interventions that (further) suppress TH signaling extend lifespan. Such studies on modulating thyroid hormone signaling may have important implications for future therapeutic strategies to promote healthy aging.
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S11.2

Subclinical thyroid disease and clinical outcomes: lessons from large individual participant-based analyses from the Thyroid Studies Collaboration
Nicolas Rodondi
Switzerland.

To clarify the risks associated with subclinical thyroid dysfunction, we built in 2008 the Thyroid Studies Collaboration and collected into individual participant data from 70 000 participants from 17 prospective cohorts. We first clarified the risks of coronary heart disease, heart failure and mortality and assessed the contribution of autoimmunity on the risks of cardiovascular diseases. We also assessed the risk of stroke associated with subclinical thyroid dysfunction. Then, we extended our study to assess the risk of fractures associated with subclinical thyroid dysfunction, as well as the impact on bone mineral density. We also explored what the most appropriate TSH levels in the euthyroid range, analysing the risks of clinical outcomes within the normal range. Results of all these studies will be presented at this session. We were able to clarify these risks, which could not be adequately addressed in previous study-level meta-analyses or in single cohorts performed in a more limited age group or without TSH stratification.
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S11.3

Subclinical hypothyroidism: when should we start treatment?
Leonidas Duntas
Greece.

Subclinical hypothyroidism (SCH), defined as a state of elevated TSH concentrations in the presence of normal free thyroxine and triiodothyronine concentrations, can be mild or severe according to the extent of TSH increase. The disease may be progressive or regressive, while the main cause of SCH is chronic autoimmune thyroiditis. However, treatment of SCH remains controversial, levothyroxine being the treatment of choice. It should be initiated in pregnant women and in patients with goiter and high titers of thyroid antibodies. High serum TSH concentrations (4.5–10 mU/l) are associated with increased cardiovascular risk, especially in patients younger than 65 years old, in whom treatment should be commenced. Once treatment is started, serum TSH needs to be rechecked 2 months later and dosage adjustments made accordingly. The aim is to reach a stable serum TSH in the lower half of the reference range (0.4–2.5 mU/l). A low dose of thyroxine is required in patients with diagnosed coronary artery disease. Recent data question any benefit of treatment in patients older than 65 years, while treatment is usually not recommended in older (above 75 years) and very old (above 85 years) patients. It is advisable to implement a wait-and-see strategy and to carefully follow up patients. Nevertheless, an individual approach and tailored therapy is preferable as we should treat the patient and not the disease. Overzealous therapy is strictly to be avoided.
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Novel insights of disorders in pubertal timing

S12.1

Pubertal timing is changing: possible role for genetic, epigenetic and environmental factors
Anders Juul
Denmark.

Puberty marks the transition period from childhood into adulthood with the attainment of adult reproductive capacity. Timing of puberty exhibit marked interindividual variation and depends on genetic and lifestyle factors. Onset of puberty has started earlier during the last 20 years, which cannot be attributed to genetic factors. Thus, lifestyle and environmental factors must be responsible for these worrying trends.
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S12.2

Environmental modulation of the pubertal timing and neuroendocrine regulation
Jean-Pierre Bourguignon
Belgium.

During the past decades, advancement in onset of pubertal timing has been observed. Recent changes also include a trend towards delay in completion of puberty, raising the question of environmental influences. Since pubertal timing appears to be 'programmed' during foetal and neonatal life, factors such as endocrine disrupting chemicals (EDCs) could possibly interfere at those early stages. As an example, the insecticide DDT could partly account for the increased prevalence of sexual precocity among children adopted from developing countries. Bisphenol A (BPA) is a ubiquitous EDC present in plastics and cans. Human data suggested no association between BPA exposure and pubertal timing or even delayed menarche whereas studies in rodents indicated possible early onset of puberty.
EFSA has currently set the level of safe daily BPA exposure to 4 µg/kg per day. Female rats were exposed to vehicle or BPA 25 ng/kg per day or 5 mg/kg per day from postnatal day 1 to 5 or 15. After 15 days of exposure to 25 ng/kg per day of BPA, vaginal opening (VO) was delayed following a delayed developmental acceleration of pulsatile gonadotropin-releasing hormone (GnRH) secretion. Inversely, exposure to BPA 5 mg/kg per day for 15 days resulted in early VO following a premature acceleration of GnRH secretion. On PND 20, the mRNA expression of hypothalamic genes involved in $GABA_A$ neurotransmission showed opposing changes depending on the dose of BPA. The study of GnRH secretion after BPA exposure in presence of $GABA_A$ receptor agonist/antagonist confirmed that a very low BPA dose leads to delayed puberty through an increased GABAergic tone whereas a high BPA dose leads to early puberty through reduced GABAergic tone. Thus, early postnatal exposure to BPA leads to opposing dose-dependent effects on the neuroendocrine control of puberty in the female rat. A very low and environmentally relevant dose of BPA delays maturation of the neuroendocrine control of puberty through alteration of GABAergic neurotransmission.
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S12.3

Novel regulatory molecules of pubertal timing
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Finland.

Puberty is a crucial developmental event in the lifespan of any individual, when reproductive competence is acquired and somatic and psychological maturation completed. As key maturational process, puberty is the end-point of a sophisticated developmental continuum, sensitive to numerous modifiers, and is subjected to precise regulatory networks, in which central and peripheral signals, as well as external cues, cooperate for the precise control of pubertal timing. In this presentation, we will summarize recent developments in our knowledge of the central mechanisms responsible for the activation of the reproductive axis at puberty, with special emphasis on the role of recently identified neuropeptide systems (epitomized by kisspeptins and neurokinin B), and their interaction with other central transmitters and metabolic hormones. In addition, we will present recent data concerning novel molecular regulators of puberty, including central epigenetic and microRNA regulatory pathways, as well as cellular energy sensors,

which operating at the hypothalamus appear to play a fundamental function in the precise control of puberty and its coupling with the body energy/metabolic status. All in all, we intend to provide an integral view of the state-of-the-art in this exciting area of neuroendocrinology, which will (hopefully) enhance the understanding of the physiology of puberty, as well as of the pathophysiological basis of the alterations of pubertal timing and their impact on other bodily systems.

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Management of Cushing's syndrome

S13.1

New developments in the medical treatment of Cushing's disease

Richard Feelders
The Netherlands.

Cushing's disease (CD), caused by a corticotroph pituitary adenoma, is associated with multi-system morbidity and when untreated or suboptimally treated with an increased mortality. Transsphenoidal adenomectomy is the first choice of treatment for CD. Medical treatment is an option in patients in whom surgery is not successful or not feasible. Medical therapy for CD can be classified into pituitary-directed drugs, adrenal-blocking drugs and glucocorticoid receptor antagonists. Dopamine and somatostatin receptors have been identified as targets for pituitary-directed drug therapy. The majority of ACTH-secreting pituitary adenomas express the dopamine receptor subtype-2 (DA2) and somatostatin receptor subtype-5. The DA2 agonist cabergoline can normalize cortisol production in $\pm 30\%$ of patients. Pasireotide, a universal somatostatin analog with high affinity for sst5, normalizes cortisol production in $\pm 25\%$ of patients. A study with longacting pasireotide in CD is underway. Combined targeting of DA2 and sst5 with cabergoline and pasireotide, which may have synergistic effects, showed promising results. Potential new therapeutic targets in corticotroph adenomas include cyclin-dependent kinases (CDK), epidermal growth factor receptor (EGFR) and heat shock protein 90 (HSP90). CDK are upregulated in corticotroph adenomas and can promote cell growth via deregulation of the cell cycle. EGFR signaling, in particular in adenomas with somatic mutations in the USP8 gene, is associated with POMC expression and cell proliferation. Overexpression of HSP90 contributes to glucocorticoid resistance of corticotroph adenomas. Preclinical studies on targeting CDK, EGFR and HSP90 with roscovitine, gefitinib and silibinin respectively showed promising results. Osilodrostat and levoketoconazole are recently developed inhibitors of steroidogenesis and are currently under investigation in multicenter trials. Mifepristone is the only available glucocorticoid receptor antagonist and was recently approved in the USA for treatment of hyperglycemia related to CD. Medical therapy for CD should be tailor-made and future studies should explore the optimal order and combination of medical treatment modalities.

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S13.2

Abstract unavailable.

S13.3

Rethinking familial adrenal Cushing's

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USA.

Primary adrenal Cushing syndrome is the result of cortisol hypersecretion mainly by adenomas and, rarely, by bilateral micronodular or macronodular adrenocortical hyperplasia. cAMP-dependent protein kinase A (PKA) signaling is the major activator of cortisol secretion in the adrenal cortex. Many adenomas and hyperplasias associated with primary hypercortisolism carry somatic or germline mutations of genes that constitute part of the cAMP–PKA pathway. We will discuss Cushing syndrome and its linkage to dysregulated cAMP–PKA signaling, with a focus on genetic findings in the past few years. In addition, we present the finding of germline inactivating mutations in ARMC5 that are associated with primary bilateral macronodular adrenocortical hyperplasia. This finding has implications for genetic counseling of affected patients; hitherto, most patients with this form of adrenal hyperplasia and Cushing syndrome were thought to have a sporadic and not a familial disorder. Other genetic syndromes including Li-Fraumeni, Beckwith Widemann, and Multiple Endocrine Neoplasia type 1 also are associated with familial Adrenal Cushing's. In adrenal adenomas and PBMAH, a spectrum of tumour growth exists as a result of variable genetic defects. Many of the genetic factors that underlie the development of cortisol-producing lesions of the adrenal cortex have been identified. If germline mutations of the Carney complex gene PRKAR1A are present, patients develop PPNAD and cortisol hypersecretion in adolescence or early adulthood. If alterations of the cAMP–PKA pathway occur at the somatic level, cortisol-secreting adenomas form, at any age. However, active research is still attempting to understand why cAMP activation at different points in the pathway yields different phenotypes. Advances in knowledge in the past few years have identified novel treatment targets for cortisol excess in Cushing syndrome, and highlight the importance of genetic testing in this condition.

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Hot topics on vitamin D

S14.1

Vitamin D and immunology

Chantal Mathieu
Belgium.

In recent years, great attention has been given to the pleiotropic effect of vitamin D, a vitamin well known from its role in bone and calcium homeostasis. Also in the immune system, modulating effects by vitamin D have been described. Receptors for vitamin D are present in cells throughout the immune system and a central role for the antigen presenting dendritic cell and the macrophage in the effect of vitamin D in the immune system is described. The latter cells not only carry receptors, but also contain the machinery to produce themselves the activated form of vitamin D, 1,25-dihydroxyvitamin D3. These data suggest a physiological role for vitamin D as an immune modulator. Epidemiology confirms this possible role, indicating correlations between vitamin D deficiency and adverse immune outcomes (more infections, more autoimmune diseases). Animal models confirm this detrimental effect of vitamin D deficiency on immune function and even point towards the possibility of exploiting these effects of vitamin D in a pharmacological way, using analogues of vitamin D as immune modulators or treating immune cells ex vivo. Clinical intervention studies using vitamin D or its activated form, 1,25-dihydroxyvitamin D3, have yielded confusing results. The place for vitamin D in a healthy immune system and in disease will be discussed.

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S14.2

Vitamin D and pregnancy – outcomes of mother and child

Christel Lamberg-Allardt
Finland.

Vitamin D deficiency is a global problem in many populations, but is a distinct problem for some groups e.g. pregnant women. A sufficient vitamin D status during pregnancy is important both for the mother, for the foetus and the newborn child. The serum 25-hydroxyvitamin D concentration (25OH)D of the infant at birth correlates with the maternal vitamin D status during pregnancy. Vitamin D metabolism is altered during pregnancy, but the regulation and impact is unclear, e.g. the maternal serum 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) concentration is increased. Moreover, the placenta has the ability to produce $1,25(OH)_2D$. A number of various health outcomes in the mother and the offspring have been linked to maternal vitamin D insufficiency during pregnancy. A low initial vitamin D status in the newborn predisposes to rickets. Research focus has been set on the relationship of vitamin D status during pregnancy and a number of adverse nonskeletal outcomes such as preeclampsia in the mother, preterm birth and growth related outcomes in the child. Vitamin D insufficiency in pregnancy has been associated with increased risk for e.g. gestational diabetes mellitus.

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S14.3

CYP24A1 mutations and human disease

Glenville Jones

Idiopathic infantile hypercalcemia (IIH) constitutes a broad group of diseases with a common outcome namely, hypercalcemia. It is now recognized that mutations of the vitamin D catabolic cytochrome P450, CYP24A1 represent one of the major causes of IIH. Patients often present in neonatal life with transient hypercalcemia, but adults with hypercalciuria, renal stones & nephrocalcinosis also appear with CYP24A1 defects. Recently, there have been reports that pregnant females with IIH can suffer hypercalcemic episodes during pregnancy, presumably due to increased synthesis of 1,25-$(OH)_2D_3$ by the placenta, that abate after pregnancy. Estimates of the frequency of CYP24A1 gene mutations suggest 1:100 carriers and a 1:40 000 incidence of IIH. While genetic analysis of the CYP24A1 locus represents the definitive diagnosis of this form of IIH, we have devised a rapid, screening test for detecting IIH patients with two defective CYP24A1 mutations. It consists of simultaneously measuring vitamin D metabolites: 25-OH-D_3 and 24,25-$(OH)_2D_3$ in serum by LC-MS/MS and then expressing the results as a 25-OH-D_3:24,25-$(OH)_2D_3$ ratio. Heterozygotes and normal individuals have ratios between 5-25 while IIH patients have ratios >80. Refinements of this approach have further resolved IIH patients from individuals with a high ratio due to vitamin D deficiency and patients with chronic kidney disease on dialysis. Loss-of-function CYP24A1 mutations cause hypersensitivity to dietary vitamin D, so reduction of dietary vitamin D or exposure to UV light is recommended. Further insights into the causes of hypercalcemic episodes in IIH should come from studies of the CYP24A1-null mouse. Reintroduction of a BAC clone representing the full wild-type human or mouse CYP24A1 gene into the CYP24A1 null mouse restores normocalcemia.

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In the rhythm of EYES: Let' dance!

S15.1

The Microbiome Waltz – cross-regulation of rhythmic oscillations at the host-microbiota interface

Christoph Thaiss
Israel.

All domains of life feature diverse molecular clock machineries that synchronize physiological processes to diurnal environmental fluctuations. However, no mechanisms are known to cross-regulate prokaryotic and eukaryotic circadian rhythms in multi-kingdom ecosystems. We discovered that the intestinal microbiota, in both mice and humans, exhibits diurnal oscillations, leading to time-specific compositional and functional profiles over the course of a day. The active phase of the host is dominated by microbial energy harvest, DNA repair, and cell growth, while detoxification and environmental sensing pathways dominate during the resting phase. These rhythmic fluctuations are governed by the circadian clock of the host, and ablation of host molecular clock components or induction of jet lag leads to loss of microbiota diurnal fluctuations and dysbiosis. Mechanistically, the host circadian clock controls feeding rhythms, which in turn drive diurnal microbiota oscillations. Scheduled feeding allows for phase reversal of microbiota diurnal activity and rescues loss of microbiota rhythms in mice deficient in the circadian clock.

Disruption of the circadian clock is a hallmark of the modern life style and has been associated with enhanced susceptibility to metabolic disease. We found that jet lag-induced dysbiosis in both mice and humans promotes glucose intolerance and obesity that are transferrable to germ-free mice upon fecal transplantation. Microbiota from jet-lagged humans or mice causes manifestations of the metabolic syndrome in germ-free recipients, while microbiota after recovery from jet lag does not.

Together, these findings provide evidence of coordinated meta-organism diurnal rhythmicity and offer a microbiome-dependent mechanism for common metabolic disturbances in humans with aberrant circadian rhythms, such as those documented in shift workers and frequent flyers.

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S15.2

Jive up your judgement! Density is not the destiny – the lessons from vertebral morphometry and bone turnover in acromegaly

Marko Stojanovic
Serbia.

Skeleton is an emerging target for systemic complications in acromegaly. The GH/IGF-1 excess is believed to cause an increased bone turnover and negative calcium balance. Observations on bone mineral density (BMD) in acromegalic patients are inconsistent, possibly in relation to skeletal site and method of BMD measurement or gonadal status. Reports on skeletal fragility are also conflicting but it is predominantly believed that an increase of vertebral fractures (VFs) risk is present in acromegaly. This results from deterioration of structural and biomechanical properties of bone, despite preserved BMD. VFs are often clinically silent yet associated with decreased survival and increased risk for subsequent vertebral and nonvertebral fractures. Since VFs are among the most invalidating complications of acromegaly, dedicated investigation of bone health is recommend. In patients with acromegaly, two dimensional BMD, measured by dual X-ray absorptiometry (DXA) is insufficient predictor of fracture risk. Osteoarthritic complications in acromegalics and excess cortical bone often cause BMD overestimation. Bone size enlargement potentially causes BMD underestimation. Vertebral morphometry (VFA) provides a useful tool for time and cost effective and low radiation screening for VFs. Comprehensive evaluation and monitoring of bone health is mandatory at diagnosis, through follow-up and even after successful treatment. Prevalence and progression of VFs are expected even after biochemical control of acromegaly. Duration of the disease is a crucial factor. Assessment of bone remodeling, through bone turnover markers is important throughout long term management of acromegaly. Elevated bone turnover markers are expected in the active disease. In cured and controlled patients monitoring of bone markers is needed to detect possible low-turnover osteoporosis, particularly in hypogonadal patients, warranting additional DXA BMD follow-up. Known skeletal health risk in acromegaly requires commitment to investigate and treat additional factors affecting bone in these patients, such as untreated hypogonadism, overreplaced hypocortisolism or concomitant diabetes mellitus.

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S15.3

Chemokine receptor CXCR4 – important role in human adrenal physiology and tumour disease?

Carmina Teresa Fuβ

Introduction

Chemokines are small secreted molecules that promote cell survival, proliferation and directional guidance of migrating cells in normal physiology and tumour pathophysiology. We have recently observed high CXCR4 mRNA expression both in normal human adrenals and in adrenocortical carcinomas. Furthermore, a PET tracer for selective molecular imaging of CXCR4-expression has recently been established.

Objective

To further investigate CXCR4 protein expression in the normal adrenal cortex and in benign adrenocortical tumours and to estimate its potential as a target for molecular imaging in primary hyperaldosteronism (PA).

Methods

CXCR4-expression was evaluated by quantitative PCR and by immunohistochemistry in paraffin-embedded sections of 2 normal adrenals (NA), 117 aldosterone producing adenomas (APA), 49 non-functioning adenomas (NFA), 52 cortisol producing adenomas (CPA). In addition, the expression of its ligand CXCL12 (SDF1), aldosterone synthase and 11-beta-hydroxylase was analyzed using specific antibodies. Furthermore, we performed *in vitro* binding studies of [68Ga]Pentixafor to frozen tumor tissue of APAs and NAs.

Results

In normal adrenals, strongest CXCR4 staining was found in the outer part of the adrenal cortex covering the CYP11B2 positive zona glomerulosa (ZG) and the outer part of the zona fasciculata while its ligand CXCL12 was particularly expressed in the inner cortical zone. Both qRT-PCR and immunohistochemistry further indicated high CXCR4 expression in most APAs which was significantly higher especially compared NFAs ($P=0.01$). [68Ga]Pentixafor exhibited strong binding to kryosections of APAs.

Conclusion

The expression pattern of CXCR4 and CXCL12 in normal adrenals suggests that it may play a physiological role in ultrastructural organization of the adrenal cortex. Because of the high expression in APAs compared to CPAs and NFAs and the strong binding of [68Ga]Pentixafor to APAs, CXCR4 may be a suitable target for molecular imaging of APAs in PA.

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Thyroid nodules

S16.1

Abstract unavailable.

S16.2

Pediatric thyroid nodules

Marianna Rachmiel

In a modern world of ultrasound (US) technology, thyroid nodules are diagnosed 5–10 times more frequently than used to be the case by palpation. Thus, the question of work-up and management is of major importance, especially in asymptomatic incidental findings. This question is very pertinent in pediatric cases, when imaging is performed for non-thyroid indications.

In the adult population, thyroid nodules are detected by US in 19 to 67% of the population. In the adolescents and young adult population, estimates from US examination suggest that 13%, and among young children, up to 5%, have thyroid nodules.

Although thyroid nodules are less common in children, it is of major concern that they are almost five-fold more likely to be malignant in children than in adults (26.4% vs. approximately 5%).

We must always keep in mind that a child and even an adolescent, is not simply a miniature adult, and thus approach and management are not identical.

The aim of this review is to discuss the major issues in evaluating and treating thyroid nodules in children and adolescents, and to compare pediatric evaluation and treatment with that of the adult population with thyroid nodules.

The following questions will be discussed: Do we need routine surveillance to detect thyroid nodules as early as possible in high-risk patients? Who are high risk pediatric patients? Do all nodules need FNA or are there clinical and sonographic features that will help to identify those in need of FNA? If the FNA appears benign, is this sufficient to allow life-long follow up without surgical removal? What if we incorrectly diagnose a thyroid cancer as a benign lesion: Will that negatively impact long-term survival? Do benign thyroid nodules in children become or predispose to malignant lesions later in life? Does size count? How should apparently benign lesion be treated in children?

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S16.3

Abstract unavailable.

Genetics and epigenetics of testicular failure

S17.1

Aberrations on the X-chromosome as cause of male infertility

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Germany.

Infertility affects 10–15% of couples and the causes of couple infertility are equally attributed to male and female (co-)factors. Male infertility is a genetically and clinically highly heterogeneous disease with a multitude of up to 1,500 genes supposedly involved in spermatogenesis. Thus, unravelling the underlying causes and the pathophysiology is challenging and candidate gene approaches, e.g. picking one or several genes known to cause infertility in mice, did not identify novel genetic causes of infertility in men.

The sex chromosomes are enriched for genes required for fertility and the Y-chromosomal AZF-microdeletions have been known for a long time to cause azoo- or severe oligozoospermia. However, X-chromosomal microdeletions and mutations in X-linked genes have only been analysed recently by utilising novel methods of genome-wide analyses. These have greatly expanded the toolbox for genetic studies and broadened the scope beyond single gene analyses. The power of such approaches is demonstrated by genome-wide array-Comparative Genomic Hybridisation (array-CGH) in groups of clinically well-characterised oligo- and azoospermic men. We were the first to report an excess of Copy Number Variations (CNVs) in infertile males especially on the sex-chromosomes. X-linked CNVs have also been proposed as recurrent cause for male infertility by others - comparable to the Y-chromosomal AZF-deletions.

Very recently, by using high-resolution array-CGH, we identified exon-deletions and nucleotide mutations in *TEX11* as the first common X-linked cause for meiotic arrest in about 15% of men with this phenotype. This breakthrough relied on phenotyping by testicular histology allowing specific selection of study subjects. Hemizygous mutations in *TEX11* were confirmed as an important cause for meiotic arrest already in another study.

Taken together, comprehensive screening for small deletions and sequencing of X-chromosomal genes will likely result in fast identification of novel genetic causes for male infertility.

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S17.2

Gene variants modulating testicular function

Maris Laan

Determinants of male reproductive system are highly complex. The palette of genetic variants modulating testicular function and fertility potential, are expected to be heterogenous. Our team has exploited complimentary study designs to provide novel insights and robust data on the contribution of genetic variation to testicular physiology and risk to impaired fertility in men. Firstly, I discuss our discovery studies utilizing the candidate gene approach and focusing on gonadotropin FSH and LH beta encoding genes FSHB and LHB. The discovered FSHB –211G/T (rs10835638) represents so far the only identified genetic variant with direct major effect on male serum FSH levels. Our and other groups have suggested its pharmacogenetic potential to identify the best responders to male FSH treatment. Our resequencing data of the LHB gene enables to assess the impact of previously suggested and novel variants on male reproductive physiology. Secondly, I address the robustness of genetic associations from published GWA studies for circulating testosterone and SHBG, and their contribution to testicular and sperm parameters. Thirdly, I talk about our ongoing screen for genomic structural variants (copy number variants, CNVs) in male idiopathic infertility. CNVs involving genes critical for the regulation of spermatogenesis are promising candidates responsible for strong or causative genetic effects. The majority of studies investigating the role of CNVs in male infertility have been focused on sex chromosomes. Our team aimed at characterisation of the genome-wide load and profile of CNVs among men with idiopathic infertility. Based on the study data, we propose an overall altered autosomal CNV profile as a considerable risk factor leading to male infertility and report novel genomic hotspots and recurrent CNVs as potential causes of impaired spermatogenesis. In perspective, uncovering the genetic contribution to testicular (mal)function is expected to lead to improved diagnostics, optimal treatment and perspective pharmacogenetic approaches in andrology clinics.

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S17.3

SEMA3A and SEMA3E: from mice to Kallmann syndrome

Anna Cariboni
Italy.

Gonadotropin releasing hormone neurons are a small group of scattered hypothalamic neuroendocrine cells that control reproductive functions in all mammals and many vertebrates.

Despite their position in the adult hypothalamus, during development they originate in the nasal placode and migrate along the vomeronasal nerve to reach the forebrain and attain their final position in the hypothalamus. Failure of GnRH neurons to migrate lead to Kallmann Syndrome, a genetic disorder characterised by absent/delayed puberty and anosmia. The genes underlying KS are largely unknown but the combination of genetically modified mouse models with exome sequencing may help to identify the unknown genes.

We have previously demonstrated that class 3 semaphorin (SEMA) 3A controls the positioning of the vomeronasal nerve and therefore the migration of GnRH neurons via Neuropilin (NRP1-2) receptors (Cariboni *et al.* Hum Mol Gen 2011).

Mice lacking SEMA3A display typical KS features including hypogonadism. Predicted by our findings on mouse models, mutations of the SEMA3A gene have been subsequently identified in patients with KS (Hanchate *et al.* PLOS Genet 2012).
In the search for additional SEMA3-mediated signalling pathways involved in this developmental process we found that PLEXIND1, which is the SEMA3E receptor, is expressed by GnRH neurons with a pattern of expression that is temporally complementary to NRP1. Specifically, we found that in the nasal compartment GnRH neurons express high levels of NRP1 and low levels of PLEXIND1, whereas once projecting into the forebrain they stop expressing NRP1 and express very of high levels PLXND1. Accordingly mice lacking PLXND1 show a reduction in the total number of GnRH neurons, and an increased number of caspase-positive cells in the forebrain in correspondence of GnRH neurons projecting to the medial preoptic area. This results in decreased size of their gonads and reduced fertility, both of mice lacking PlexinD1 or its SEMA3E ligand.
Predicted by our findings on mouse models, we found mutations in two siblings affected by KS in the SEMA3E gene, strongly supporting a role of SEMA3E/PlexinD1 genetic pathway in the aethiopathogenesis of KS.

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S18.1

Abstract unavailable.

S18.2

Current developments in classification of neuroendocrine neoplasia

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Switzerland.

According to the current WHO classification neuroendocrine neoplasias (NEN) are classified according to differentiation into well differentiated neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinomas (NEC). NEN are classified in addition to organ of origin and grade. More recent molecular data confirms this approach as the identified mutation spectrum differs according to differentiation and organ of origin. However, NEN might be more heterogeneous: Expression data of a large series of pancreatic NET indicates that biologically meaningful subgroups can be defined as in other malignant neoplasms, the clinical role regarding prognosis and prediction to therapy response of such a classification will need to be examined.
More recently, a subset of highly proliferative G3 NEN were described to differ morphologically and biologically from NEC G3 and are best designated as well differentiated NET G3. Morphology is able to identify a subset of these tumors and further studies will show if molecular classifications will be able to help.

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S18.3

Abstract unavailable.

Brown adipose tissue – a burning issue (*Endorsed by Endocrine Connections*)

S19.1

The role of brown and brite fat in energy balance regulation

Martin Klingenspor
Germany.

Three major observations triggered a revitalized interest in the role of brown fat in energy balance and the metabolic benefits of this thermogenic tissue in humans. Firstly, progenitors of brown adipocytes derive from the muscle lineage whereas recruitable brown-like adipocytes in white fat, termed brite (brown-in-white), can be of other developmental origin. Secondly, healthy adult humans have metabolically powerful brown/brite fat that is activated by acute cold exposure, β3-adrenergic receptor agonist treatment, or after ingestion of a meal. Thirdly, cold-induced metabolic activity of brown/brite fat in humans is negatively associated with body mass index and age, and is recruitable by cold-acclimation. Based on these findings human brown/brite fat has been reconsidered as a target for pharmacological or nutritional interventions in obese and diabetic subjects. The beneficial effects of brown/brite fat are attributed to the high capacity of brown/brite adipocytes to dissipate heat. Thermogenic capacity in these cells is determined by high lipolytic capacity, extraordinary mitochondrial density and expression of uncoupling protein 1 (UCP1). Located in the inner mitochondrial membrane, UCP1 is constitutively inactive, but upon lipolytic release of fatty acids dissipates proton-motive force as heat thereby causing extraordinary mitochondrial respiration rates. Enormous efforts are currently undertaken to identify treatments that stimulate the formation and maintenance of thermogenic brown/brite adipocytes, and activate UCP1 in these cells. Release of noradrenaline from sympathetic varicosities is the physiological trigger of UCP1 activation in brown/brite fat, but also de novo recruitment of thermogenic capacity. However, sympathomimetics selectively activating brown/brite fat thermogenesis without detrimental cardiovascular side-effects are currently not available. Therefore, the pros and cons for a significant role of brown/brite fat in human energy balance regulation and the evidence for non-adrenergic activators of brown fat thermogenesis will be critically addressed.

DOI: 10.1530/endoabs.41.S19.1

S19.2

Abstract unavailable.

S19.3

Role of brown adipose tissue activation in lipid metabolism and cardiometabolic health

Patrick C Rensen
The Netherlands.

Activated brown adipose tissue (BAT) combusts high amounts of intracellular lipids into heat. In the past few years, we have investigated the consequences of BAT activation for lipid metabolism and cardiometabolic health. Initially, we showed that South Asians, a population characterized by dyslipidemia and prone to develop type 2 diabetes and cardiovascular disease compared to white Caucasians, have low BAT activity correlating with low energy expenditure (Lancet Diab Endocrinol 2014). In search for pharmacological strategies to activate BAT, we then set out to understand the physiology of BAT. Using preclinical models we elucidated that BAT activation enhances selective uptake of lipoprotein-triglyceride-derived fatty acids by BAT thereby generating lipoprotein remnants that are taken up by the liver (J Lipid Res 2015; Circ Res 2016). Next, we discovered novel pharmacological targets that modulate BAT activity with respect to uptake of plasma triglyceride-derived fatty acids, both directly (e.g. AMPK, BMP7R, CB1R, USF-1) and via neural control (e.g. MC4R,

GLP-1R, ADRB3) and showed that BAT activation improves dyslipidemia and hyperglycemia and reduces type 2 diabetes and atherosclerosis (e.g. FASEB J 2014; Diabetes 2014; Nat Commun 2015; Sci Transl Med 2016). Recently, we also demonstrated that disruption of the central biological clock predisposes to adiposity by reduced sympathetic outflow to BAT (PNAS USA 2015) and we identified a strong circadian rhythm in the uptake of plasma lipids by BAT, explaining a circadian rhythm in postprandial lipid responses as well as plasma lipid levels (unpublished). Based on these collective data, we recently started (timed) human intervention studies in prediabetic individuals from South Asian vs white Caucasians origin aimed to activate BAT activity and to improve cardiometabolic health.

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Hitchhiker's guide to the microsmos of GPCRs

S20.1

Location, location, location: spatial programming of GPCR signalling
Aylin Hanyaloglu

An archetypal view of GPCR signalling depicts cell surface localized receptors activating specific heterotrimeric G-protein signal pathways, which in turn converge on to common downstream pathways. How such signals are translated into the highly diverse cellular and physiological responses that are controlled by this superfamily of receptors has been a long-standing biological question. This question has driven our more current understanding of the complexity of these receptor-signalling systems, yet how such functional pleiotropy in GPCR signalling is decoded to specific downstream cellular responses is unknown. One mechanism that regulates both signal specificity and diversity is membrane trafficking, a system deeply integrated with cell signalling. Our recent studies with the gonadotropin hormone receptors, provides an unprecedented view of how GPCR activity can be regulated at a spatial level. We have demonstrated that specificity in signalling of distinct internalized GPCRs can be achieved by regulated endosomal targeting of receptors upstream of the classic early endosome, a compartment we term the very early endosome (VEE). Importantly, GPCR activation of cAMP-PKA signalling drives its own post-endocytic sorting via a unique VEE recycling mechanism, and spatially restricts endosomal cAMP and MAPK signalling. Spatial encoding of receptor signalling provides a mechanism for reprogramming GPCR activity by altering receptor location across distinct endosomes to create highly regulated and distinct signalling profiles. Such mechanisms may also be altered pathophysiologically and that perturbed gonadotropin-activity in recurrent miscarriage may be due to altered spatial control of GPCR signalling.

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S20.2

Tethered Agonism: a common activation mechanism of glycoprotein hormone receptors
Torsten Schöneberg
Germany.

Glycoprotein hormone receptors (GPHRs) have been cloned about 25 years ago and, since then, the glycoprotein hormones TSH, LH/hCG and FSH are considered as the agonists for their respective receptors. Additionally to TSH, the TSH receptor for example, can be activated by mutations and autoantibodies causing hyperthyroidism and Graves' disease, respectively. The mode, how the receptors integrate the activating actions of glycoprotein hormones, mutations and autoantibodies to trigger receptor's signal transduction, is a still unsolved mystery. We recently showed that a short peptide sequence in the C-terminal part of the extracellular N terminus functions as a tethered agonist for all glycoprotein hormone receptors *in vitro* and *in vivo*. Our data support a scenario where, upon structural changes within the ectodomain due to extracellular ligand binding, this intramolecular ligand most probably isomerizes and activates the 7-transmembrane helix domain triggering G-protein activation. The identification of the internal agonist sequence for GPHRs now allows for characterization of its agonist binding pocket followed by rational ligand design. Such ligands could be therapeutically useful for blocking TSHR activation due to autoantibodies in Graves' disease and activating mutations in GPHRs.

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S20.3

Innovative approaches for the control of class C GPCRs activity
Jean-Phillippe Pin
France.

G protein-coupled receptors play key roles in cell-cell communication processes, and, not surprisingly, are the main targets for therapeutic drugs. Among these, those of the class C are the receptors for neurotransmitters, glutamate and GABA (mGlu and $GABA_BRs$), for the umami and sweet taste compounds (T1Rs), and for calcium and basic amino acids (CaSR and GPRC6a). Class C GPCRs are much more complex proteins than the class A and B GPCRs. They are made of two subunits covalently linked by a disulfide bridge, each being composed of a venus flytrap domain (VFT) where agonists bind, connected via a cystein-rich domain to a heptahelical membrane domain responsible for G protein activation. Such a large protein complex undergoes major conformational changes upon ligand binding in the VFT, leading to the activation of one 7TM domain.
During this presentation, I will summarize our view of the activation mechanism of these receptors, and illustrate the multiple possibilities offered to develop innovative molecules able to specifically regulate them. These include orthosteric as well as allosteric compounds acting within the 7TM. Recently, photo-switchable compounds have been developed that allow to control receptor activity where and when needed. Using such compounds identified for mGluRs, we demonstrated that it is possible to perfectly control the response to pain in living animals.
The important conformational changes accompanying class C receptor activation offers the possibilities to develop antibodies that can regulate their activity. We identified llama single chain antibodies (nanobodies) that act as positive allosteric modulators of mGlu2 subtype. These nanobodies control mGlu2 activity in brain slices, enhancing the presynaptic inhibitory effect of mGlu2 agonists. In addition, injection of these nanobodies in the hippocampal area enhance to inhibitory action of mGlu2 agonists of the context fear memory.
These findings illustrate the numerous possibilities offered by the class C GPCR complex structure to modulate their activity.

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An update on hyperparathyroidism

S21.1

Primary hyperparathyroidism: what is new?
Camilla Schalin-Jäntti

Primary hyperparathyroidism (PHPT) is a common endocrine disorder, with a prevalence of 1–4 per 1000, that increases to 21 per 1000 in age groups 55–75 years. PHPT may be cured in only one way: by surgical excision of the abnormal parathyroid tissue, which in ∼85% of patients is due to a parathyroid adenoma. Double adenomas are found in ∼4% of cases and parathyroid carcinoma in 1%. There is consensus that patients with markedly increased serum calcium concentrations, symptomatic kidney stones and osteoporosis should undergo surgery. In 5–10% of cases, PHPT is part of a genetic syndrome, such as multiple endocrine neoplasia type 1 or 2, hyperparathyroidism-jaw tumor syndrome (HPT-JT), familial isolated hyperparathyroidism (FIHP), or familial hypocalciuric hypercalcemia (FHH).
To date, exciting topics within PHPT include the evaluation of neurocognitive symptoms and health-related quality of life (HRQoL). Such symptoms are commonly reported in PHPT, and there is a need for a sensitive tool applicable for the assessment of such symptoms in the out-patient clinic. The value of symptoms as prognostic factors regarding who benefits from surgery has so far been poorly studied. Whether HRQoL in PHPT improves after surgery is a matter of debate. I will discuss some of the studies available on HRQoL in PHPT, and the outcome of surgery on HRQoL.
An increasing amount of genetic defects underlying PHPT have been identified over the years, and I will go through some of the recent findings in HPT-JT, FIHP, and familial hypocalcuric hypercalcemia (FHH).
Last but not least, the incidence of parathyroid carcinoma seems to be increasing world-wide. I will shortly review this topic, and also share some novel data from the Finnish Parathyroid Carcinoma Cohort with you.
Other topics discussed in this session include the relationship between primary hyperparathyroidism, hypertension and hyperaldosteronism, and novel data regards available preoperative imaging techniques in PHPT.

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S21.2

Hyperparathyroidism, hypertension and hyperaldosteronism
Evelyn Asbach

Primary aldosteronism (PA) is the most frequent cause of endocrine arterial hypertension. PA is known to cause a higher cardiovascular morbidity, which is reduced by specific therapy of PA. Numerous studies suggest that mineralocorticoid excess may influence mineral homeostasis. On the other side, parathyroid hormone excess has been linked to cardiovascular disease. Increasing evidence supports a bidirectional interaction between aldosterone and PTH which might lead to a higher cardiovascular risk.

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S21.3

What is new in imaging and surgery for hyperparathyroidism
Marko Hocevar

During last few decades primary hyperparathyroidism (PHP) evolved from the disease of 'bones, moans, stones and groans' to a disorder that is most commonly asymptomatic and incidentally diagnosed with increasing biochemical screening. At the same time different localization studies of the abnormal parathyroid gland(s) emerged. Because PHP is caused in more than 85% of patients with a single gland adenoma which can be reliably localized preoperatively, there has been a major paradigm shift in the management of PHT. The traditional approach to parathyroid surgery, consisted of bilateral neck exploration with the cure rates around 95%, was replaced by a more focused minimally invasive approach based on pre-operative localization and intraoperative parathyroid hormone testing (ioPTH). Minimally invasive approach is critically dependent on the preoperative localization studies and their imperfection represents its major limitation.
Ultrasound is the most frequently used anatomic imaging modality with the lowest cost and reported sensitivity of 70% to 100% for detecting enlarged parathyroid glands. It is highly operator-dependent and in the presence of thyroid gland abnormalities its sensitivity decreases.
Sestamibi scanning is the most frequently used functional imaging modality with reported sensitivity of 54–100% for identifying single gland adenoma. Addition of single photon emission computed tomography can further improve the sensitivity.
Recently our group reported a study of ^{18}F-fluorocholine PET/CT as a promising, effective imaging method for localization of hyperfunctioning parathyroid tissue with higher sensitivity than sestamibi scanning.
Use of ioPTH is a highly effective intraoperative adjunct telling a surgeon when to conclude the operation during focused minimally invasive parathyroidectomy. However, the benefit of ioPTH may be marginal in the presence of a highly sensitive preoperative localization study and patients with a single adenoma can safely undergo a focused parathyroidectomy without ioPTH testing.

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New mechanisms to induce and protect from ovarian insufficiency

S22.1

Genetic aspects of folliculogenesis
Kui Liu
Sweden.

In humans and other mammalian species, follicular development is a complicated process. The pool of resting primordial follicles serves as the source of developing follicles and fertilizable ova for the entire length of female reproductive life. In recent years, molecular mechanisms underlying follicular activation and development have become more evident, mainly through the use of genetically modified mouse models. Recently reported mutant mouse models have shown that a synergistic and coordinated suppression of follicular activation provided by multiple inhibitory molecules is necessary to preserve the dormant follicular pool. Several molecules and pathways operating in both the somatic primordial follicle granulosa cells (pfGCs) and oocytes have been shown to be important for primordial follicle activation and development. In this presentation, we will summarize both historical and recent studies on mammalian primordial follicular activation and focus on the up-to-date knowledge of molecular networks controlling this important physiological event. These advances may provide a better understanding of human ovarian physiology and pathophysiology for future clinical applications.

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S22.2

Cohesin ring, meiosis and primary ovarian insufficiency
Reiner Veitia

Primary ovarian insufficiency is a disorder resulting in the loss of ovarian function. It is a multifactorial condition characterized by amenorrhea, estradiol deficiency and high FSH levels before the age of 40 years. Most POI cases are idiopathic. Although genes encoding factors involved in meiosis and DNA repair have been considered as obvious candidates to explain POI cases, it is only recently that whole-exome sequencing explorations have incriminated causal mutations in genes such as *STAG3*, *SYCE1*, *MCM8*, *MCM9, HFM1*, etc. These findings will be discussed in the context of POI but also from the perspective of male (in)fertility.

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S22.3

Ovarian protection during cancer treatments
Richard Anderson
UK.

Recent years have seen a dramatic rise in interest in preserving fertility in women facing treatment for cancer and other serious diseases, and fertility preservation is rapidly becoming a mainstream part of reproductive medicine. This approach, however, serves to remove oocytes or ovarian tissue before cancer treatment, rather than directly protecting the ovary itself. Some chemotherapies and radiotherapy have well known adverse effects on follicle number, although the details of the effects and their magnitude for chemotherapeutic agents are often poorly characterised. Thus, emerging evidence suggests that different agents can have differential effects on the oocyte itself, the surrounding granulosa cells, and the ovarian stroma including the ovarian vasculature. This may mean that different protective strategies may be needed for different chemotherapeutic agents. There have been studies for many years investigating the potential protective effect of GnRH agonists on the ovary administered during chemotherapy. Initial studies were underpowered and often uncontrolled, but recently larger well powered RCTs have shown a consistent beneficial effect in reducing the risk of premature ovarian insufficiency after chemotherapy for early breast cancer. Smaller studies have also been undertaken in other cancers, particularly lymphoma, but these have not shown a clear benefit. This may reflect the specific treatment regimens involved in those studies, rather than being a feature of the diagnoses. Non-hormonal approaches have also been investigated, although largely confined to animal studies. These have often focused on the potentially beneficial effects of sphingosine-1-phosphate, and the tyrosine kinase inhibitor, Imatinib. Generally, conflicting results have been reported, thus, there is a need for greater understanding of potential mechanisms of action before introduction to clinical trials.

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Indications of incretin based therapies

S23.1

GLP-1 in type 1 diabetic patients
Thomas Dejgaard
Denmark.

The treatment of type 1 diabetes is currently restricted to insulin therapy. However, achieving and maintaining strict glycaemic control is a demanding task for many patients and increases the risk of hypoglycaemia and weight gain. This makes new treatments complementary to insulin of interest. In type 2 diabetes, the combination of insulin and a GLP-1 receptor agonist improves glycaemic control, induces weight loss and reduces daily insulin dose needed. However, only little evidence exists about the efficacy and safety of the combination in patients with type 1 diabetes.
Mechanistic studies suggest that GLP-1 enhances endogenous insulin secretion in patients with preserved beta cell function. Furthermore, it improves postprandial glucose control through a reduction in gastric emptying rate and an inhibition of postprandial glucagon secretion, regardless of residual beta cell function in type 1 diabetes. Nevertheless, the clinical data are conflicting in regard to the effect on HbA1c. Improvements have been reported in small-scale, non-randomised and/or retrospective studies. Recently the first two randomised, controlled trials were published reporting similar improvements in HbA1c in liraglutide and placebo treated patients. Reductions in insulin dose and body weight are consistently

reported in all studies. Furthermore, episodes of mild hypoglycaemia were reduced compared with placebo in one study.
Adverse events in all trials were common and predominantly gastrointestinal, i.e. nausea, obstipation and vomiting, often transient and most pronounced when initiating therapy. No serious or unknown side effects have emerged so far.
Currently GLP-1 receptor agonists are not approved for the treatment of type 1 diabetes. Further research is needed on both short- and long-acting agonists to improve knowledge about the therapeutic potentials. The effect in new onset type 1 diabetes is also of major interest.

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S23.2

GLP-1 in type 2-diabetic patients

Michael Nauck

GLP-1 is one of the two known incretin hormones (the other one being GIP), which have the ability to stimulate insulin secretion whenever glucose concentrations are above a certain permissive threshold. The incretin effect (greater stimulation of insulin secretory responses with oral as compared to matched intravenous glucose administration) is reduced in patients with type 2 diabetes, thus the question needed to be addressed, whether there is hyposecretion or impaired action of incretin hormones in patients with type 2 diabetes. Initial findings suggested lesser secretion of GLP-1 in patients with type 2 diabetes, however, with multiple studies available that address this question, no consistent deficiency has been found in meta-analyses. GIP has lost most of its insulinotropic activity in patients with type 2 diabetes, probably related to the overall deficiency in β-cells typical for this condition. Some effectiveness of GLP-1 is preserved in type 2 diabetes, although strictly speaking, the effects of GLP-1 in such patients are reduced, if compared to healthy subjects with normal glucose tolerance. Nevertheless, the effects elicited by GLP-1 or other agents interacting with GLP-1 receptors (GLP-1 receptor agonists) are sufficient to elicit clinically meaningful effects, reducing glucose concentrations in hyperglycaemic patients with type 2 diabetes. Because of the nature of the interaction with β-cells in the islet of Langerhans, GLP-1 receptor stimulation does not trigger hypoglycaemia, and therapy with incretin-based glucose-lowering medications is not complicated by hypoglycaemia, even if near-normal glucose concentrations are achieved. In addition, GLP-1 receptor agonists induce weight loss, the extent of which, however, is highly variable. As an injctable treatment, GLP-1 receptor agonists are as effective as simple insulin regimens in terms of reducing HbA1c. GLP-1 receptor agonists can be used in conjunction with insulin. Novel approaches use fixed-dose combinations of basal insulin and a GLP-1 receptor agonist.

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S23.3

The role of GLP-1 in body weight regulation: lessons from human trials

Arne Astrup
Denmark.

In 1996, we showed that GLP-1 is a satiety hormone in humans, and increased post-prandial GLP-1 levels following high protein meals have shown to be at least partially responsible for the high satiating effect of protein. The natural ligands to stimulate GLP-1 release seem to be peptide fragments and monoacylglycerides.
The once-daily GLP-1 analogue liraglutide at doses up to 3.0 mg was compared with placebo or orlistat over 104 weeks as adjunct to diet and exercise in 564 obese individuals with without diabetes. After 52 weeks, mean weight loss was greater with liraglutide 3.0 mg (7.8 kg) vs placebo (2.0 kg) or orlistat (3.9 kg) [both $P \leq 0.0001$].
In the SCALE Obesity and Prediabetes 160-week double-blind trial, 2254 individuals with prediabetes and obesity or overweight with comorbidities, were randomized 2:1 to liraglutide 3.0 mg ($n = 1505$) or placebo ($n = 749$). The primary objective was to evaluate the proportion of patients with type 2 diabetes at 160 weeks. Time to onset of diabetes was 2.7 times longer with liraglutide 3.0 mg ($n = 1505$) vs placebo ($n = 749$) [95% CI: 1.9–3.9, $P < 0.0001$] (HR: 0.2). At week 160, mean weight loss from baseline was 6.1% with liraglutide 3.0 mg vs. 1.9% with placebo ($P < 0.0001$).
Liraglutide 3.0 mg was well-tolerated, with mild or moderate gastrointestinal side effects being the most frequently reported. Serious adverse events occurred in 15.1% of individuals in the liraglutide group vs, 12.9% with placebo. Gallbladder-related events (2.9 vs 1.2/100 patient years of observation (PYO)) and confirmed pancreatitis (0.29 vs 0.13 events/100 PYO) were low, but more frequent with liraglutide 3.0 mg vs placebo.
In summary, GLP-1 is an endogenous satiety hormone involved in appetite regulation and GLP-1 receptor agonists can reduce body weight and diabetes risk over 3 years.

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Endocrine neoplasias: new associations (*Endorsed by the European Journal of Endocrinology*)

S24.1

Abstract unavailable.

S24.2

Abstract unavailable.

S24.3

Abstract unavailable.

What's new and exciting in nuclear receptor action?

S25.1

Abstract unavailable.

S25.2

Ligand independent activities of vitamin D receptor

Gilles Laverny

The bioactive form of Vitamin D [1,25(OH)2D3] plays a major role in calcium homeostasis. Moreover, it has potent anti-inflammatory and anti-proliferative properties, and thus is a potential pharmacological agent to treat various refractory diseases. Nevertheless, the doses required to elicit such effects induce hypercalcemia. The activity of 1,25(OH)2D3 is mediated by the vitamin D receptor (VDR), a member of nuclear receptor superfamily. A number of patients with rickets carry mutations of VDR impairing either its DNA- or ligand- binding, but only mutations impairing DNA binding induce alopecia.
In order to dissociate the calcemic activities of 1,25(OH)2D3 from its anti-inflammatory and antiproliferative properties, more than 3000 analogs were synthesized. The resolution of the VDR ligand binding domain 3D structure facilitated the design of such analogs, but no potent agonists devoid of hypercalcemic activities have been obtained.
Based on VDR structural data, we generated mice expressing a point-mutated VDR (VDRgem), unresponsive to 1,25(OH)2D3, but the activity of which is

induced by gemini ligands. We have shown that these mice present clinical signs of rickets that their mineral ion and bone homeostasis are more impaired than in VDR-null mice, and that unliganded VDR has repressive activities. As VDRgem mice have a normal hair cycle in contrast to VDR-null mice, these results indicate that skeletal defects might be more severe in patients expressing a ligand binding deficient VDR than in those with full receptor deficiency. Thus, these results might facilitate the stratification of patients with Vitamin-D dependent rickets.
In addition, we have shown that administration of gemini ligands to VDRgem mice normalizes their serum calcium levels, demonstrating that the activity of VDRgem can be induced in-vivo. Further analysis of VDRgem mice should help to unravel both liganded and unliganded VDR signaling.

DOI: 10.1530/endoabs.41.S25.2

S25.3

Molecular battles between corticosteroid receptors in the heart
John Cidlowski

Heart failure is a leading cause of death in man, and stress is increasingly associated with adverse cardiac outcomes. Glucocorticoids are primary stress hormones, but their direct role in cardiovascular health and disease is poorly understood. To determine the *in vivo* function of glucocorticoid signaling in the heart, we generated mice with cardiomyocyte-specific deletion of the glucocorticoid receptor (GR). The cardioGRKO mice appear normal early in life but die prematurely due to spontanious heart failure. In contrast, knockout of the cardiomyocyte mineralocorticoid receptors (MR) does not lead to cardiovascular disease. To investigate whether glucocorticoid activation of cardiomyocyte MR contributes to the pathology in the cardioGRKO mice, we generated mice lacking both GR and MR in cardiomyocytes. Strikingly, the cardioGRMRKO mice are protected from the development of heart failure. These findings reveal that cardiomyocyte MR signaling, when unopposed by GR signaling, plays a major role in the progression of cardiac disease. Moreover, they suggest that combining GR agonists with MR antagonists may represent an improved therapeutic approach for treating heart disease.

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An update on bone homeostasis and osteoporosis (*Endorsed by the European Journal of Endocrinology*)

S26.1

Genetics of human bone formation
Wim Van Hul

Bone mineral density (BMD) and bone mass are quantitative traits that are the result of the two balanced processed of bone resorption and bone formation. Often they are used as a surrogate phenotype for the diagnosis of osteoporosis, characterized by an increased fracture risk due to a decreased bone mass and deterioration of the microarchitecture of the bone.
Variation in BMD is determined by both environmental and genetic factors with 50–85% of the variance being controlled by genetic factors. In a minority of the cases, abnormal BMD can be explained by one mutation in one gene with a large impact. These mutations can result in monogenic bone disorders with either an extreme high or low BMD. However, in most cases the genetic factors contributing to variation in BMD are highly polygenic. Identification of these genetic factors regulating bone mass has been a challenge in the last decades. So far, over 70 loci have been identified explaining around 6% of the genetic variation.
Identification of the disease causing genes in monogenic diseases increased the knowledge on the regulation of bone mass and highlighted important signaling pathways. Especially the identification of the essential role of Wnt signaling in bone formation turned out to be a major breakthrough. Interestingly, a large number of genes from this pathway turned out to play a role, not only in conditions with extremely low or high bone density but genetic variants in these genes also contribute to the variation of BMD in the general population. Since only 6% of the genetic variation is yet identified, additional studies with different study design are needed to identify all genes involved in bone formation and the regulation of bone mass.

DOI: 10.1530/endoabs.41.S26.1

S26.2

Sex steroids and bone metabolism
Marie Lagerquist
Sweden.

Fractures are associated with suffering and increased mortality in patients and great costs for society. It is well established that sex steroids are important regulators of skeletal growth and bone metabolism and estrogen is known to protect against bone loss and prevent fractures. Estrogen not only protects the female skeleton, but is also associated with bone mass and fracture risk in the male skeleton. However, the use of this hormone as a therapeutic drug against bone loss is restricted due to severe side-effects, such as increased risk of breast cancer and stroke. It is therefore important to increase our knowledge regarding the mechanisms underlying the protective effects of estrogen on the skeleton in order to provide the possibility to develop new bone-specific treatment options which can separate the positive, bone-protective, effects from adverse estrogenic effects. Estrogen exerts its effects via estrogen receptors and ERα is an important mediator of the protective estrogenic effects on bone, both in the female and the male skeleton. In experimental studies, using different genetically modified animal models, our research group is working on determining i) the importance of estrogen signaling in different specific celltypes and ii) the role of different signaling pathways in cells, including the importance of different posttranslational modification sites in the ERα. The aim is to provide a summary of what is known regarding sex steroids and their impact on bone metabolism with focus on target cells for estrogen and estrogen receptor signalling pathways.

DOI: 10.1530/endoabs.41.S26.2

S26.3

New bone-forming treatments for osteoporosis
Socrates Papapoulos
The Netherlands.

Most currently available agents for the treatment of osteoporosis decrease bone resorption and turnover to varying degrees but do not stimulate the formation of new bone that is essential for the management of patients with severe disease. Teriparatide, the most extensively studied bone -forming treatment stimulates not only bone formation but also resorption, acts mainly at sites undergoing active remodeling and increases cortical porosity. The newly developed PTHrP analogue, abaloparatide, has similar but less pronounced effects on bone remodeling and increases hip BMD significantly more than teriparatide. Combination treatment with teripatatide and the resorption inhibitor denosumab increased BMD at all skeletal sites significantly more than either monotherapy after one year suggesting that for optimal therapeutic outcome bone formation and resorption should be modulated in opposite directions. The recognition of the role of Wnt signaling pathway in bone formation by osteoblasts provided a number of potential targets for the development of novel pharmaceuticals (eg. sclerostin, Dkk1 and LRP4). The restricted expression of sclerostin in the skeleton and the lack of abnormalities of organs other than the skeleton in humans and animals with sclerostin deficiency made this protein the most attractive target. Inhibition of sclerostin in animals stimulated cancellous and cortical bone formation, that was mainly modeling-based, and increased bone mass and strength while bone resorption was decreased suggesting a functional uncoupling of bone formation and resorption. Two humanized antibodies to sclerostin, blosozumab and romosozumab were investigated in clinical phase I and II studies. These antibodies given subcutaneously once every 4 weeks induced marked increases in BMD of the spine and the hip associated with rapid transient increases in bone formation markers and decrease of bone resorption markers. On-going phase III studies with romosozumab with fracture outcomes will also provide information about the long-term safety and tolerability of sclerostin inhibitors, essential for the introduction of any new treatment into clinical practice.

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Why do we gain weight; homeostasis and rewards of ingestive behaviour

S27.1

Obesity medication reduces the reward value of food
Lora Heisler

Obesity is a primary healthcare challenge of the 21st century. Medications increasing the bioavailability of the neurotransmitter serotonin (5-hydroxytriptamine; 5-HT) have historically been used for obesity treatment. 5-HT primarily influences appetite via action at the 5-HT2C receptor (5-HT2CR); the clinical significance of which has recently been realized with the launch of the 5-HT2CR agonist lorcaserin for obesity treatment in the USA. Efforts to delineate the underpinnings of 5-HT2CR appetite suppression have largely focused upon action within the hypothalamus, a crucial brain region modulating energy homeostasis. However, another neuroanatomical population of 5-HT2CRs is located within the ventral tegmental area (VTA), a primary node within reward circuits. To examine the physiological significance of 5-HT2CRs within the VTA, we utilized designer receptors exclusively activated by designer drugs (DREADD) technology to probe the discrete function of VTA 5-HT2CRs in the reward value of food. Designer Gq receptor (AAV8-hSyn-DIO-hM3Dq-mCherry) was bilaterally injected into the VTA of 5-HT2CR-Cre mice producing 5-HT2CR-Cre:hM3Dq-expressing neurons exclusively within the VTA. The selective activation of these neurons by designer drug clozapine-N-oxide (CNO) significantly suppressed home cage laboratory chow intake. Further analysis indicated that this was related to a reduction in food reward. Specifically, discrete simulation of 5-HT2CRs within the VTA significantly suppressed operant responding for food reward (chocolate pellets), both when mice were motivated to eat through food restriction and in the free feeding condition. To evaluate the translational significance of this finding, we next examined whether human obesity medication 5-HT2CR agonist lorcaserin influences the reward value of food. The same concentrations of lorcaserin that reduced ad libitum home cage food intake also significantly reduced operant responding for food reward. Thereby, these data suggest that a component of lorcaserin-induced appetite suppression is due to a reduction in food reward and identify that the little studied population of VTA 5-HT2CRs are sufficient to mediate this effect.

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S27.2

Brain systems involved in food intake – a neuroimaging approach

Stefanie Brassen
Germany.

As part of the Transregional Collaborative Research Centre TR-SFB134 we study central insulin effects on hedonic food processing across the life-span. So far, 48 younger participants across a wide weight-range (BMI: 18–38) were investigated with functional magnetic resonance imaging (fMRI) during a hedonic food processing task after receiving intranasal insulin (160UI) or placebo in a cross-over design after an overnight fast. Imaging results during the placebo session reveal a robust activation pattern of homeostatic (ventral hypothalamus) and reward-related (ventral tegmental area, ventral striatum, amygdala, ventromedial and orbitofrontal cortex) neurocircuits. Behaviorally, insulin application reduced food liking only in participants with normal insulin-sensitivity, as indicated by an insulin resistance index HOMA-IR of ≤ 2 ($N=28$). Only in participants with an increased HOMA-IR > 2 ($N=20$), plasma insulin levels during placebo predicted food liking, i.e. participants with a moderate endogenous insulin level demonstrated reduced food liking while elevated levels were related to high food liking scores. On the neural level, behavioral insulin effects were paralleled by activation changes in the hypothalamus and regions of the reward system. In our ongoing analyses we are now focusing on group- and insulin-effects on connectivity patterns between homeostatic and dopaminergic brain regions as well as on non-linear insulin effects on behavior and brain function. Given recent animal data on differential central insulin action in different areas of the dopaminergic reward system, our approach might be useful to translate and extend current hypotheses to the human brain.

DOI: 10.1530/endoabs.41.S27.2

S27.3

How hypothalamus senses and stimulates food intake

Tamas L Horvath
USA.

Emerging evidence indicates that the hypothalamus is a key regulator of the adaptation of the central nervous system (CNS) to the changing environment in support of survival, with subsets of hypothalamic neurons acting as upstream regulators of brain regions classically considered as master determinants of CNS function, such as the cortex and hippocampus. The regulatory role of the hypothalamus in cortical and hippocampal functions is mediated via classical neuronal pathways and by the regulation of peripheral tissue output in the form of hormones and nutrients. Here, we argue that when the relationships between these brain regions and peripheral tissues are reconsidered based on these driving principles of health and survival, it is challenging to envision that long-lasting successful strategies to combat obesity can emerge from propagation of satiety and energy expenditure. We also argue that many hypothalamus-driven metabolic principles will have important implications for neurological and psychiatric conditions.

DOI: 10.1530/endoabs.41.S27.3

Adrenal Insufficiency: Causes and management

S28.1

Abstract unavailable.

S28.2

Genetics of adrenal insufficiency

Christa Flück
Switzerland.

Genetic defects causing primary, central secondary or tertiary adrenal insufficiency (AI) belong to the group of rare diseases that involve multiple candidate genes. In primary AI adrenal defects lead to hormonal deficiencies. Underlying genetic mutations may be found either in genes involved in the development of the adrenal gland (e.g. DAX1/NR0B1) or in genes that are essential for the signaling, regulation (e.g. MC2R, MRAP) or the biosynthesis of steroid hormones (e.g. StAR, CYP11A1 etc.) and their cofactors (e.g. POR) and mitochondrial partners (e.g. NNT).
Genetic defects causing isolated, secondary (central) AI due to corticotropin deficiency are very rare and include TPIT, while genetic mutations of PCSK1 and POMC not only cause AI but also manifest with massive obesity, hypogonadotropic hypogonadism and abnormal glucose homeostasis. In addition, AI may also be part of the clinical spectrum of developmental defects of the pituitary gland leading to multiple pituitary hormone deficiency (e.g. HESX1, LIM4, PROP1).
This symposium lecture will cover the genetics of human mutations causing AI and elucidate what we learnt from those experiments of nature.

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S28.3

Abstract unavailable.

New insights into the pathogenesis of PCOS

S29.1

Metabolic dysfunction in a rodent model of PCOS

Jenny Visser
The Netherlands.

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women in their reproductive age. Based on the Rotterdam criteria PCOS is diagnosed by at least two out of the following three criteria: hyperandrogenism, oligo/anovulation, and polycystic ovaries. To date, the underlying cause of PCOS remains unknown, although the elevated androgen levels are suggested to play an

important role in the development of PCOS. In addition to ovarian dysfunction, women with PCOS display metabolic disturbances, such as obesity and insulin resistance. The accompanied elevated insulin levels can stimulate the ovary causing ovarian androgen production to increase even further. Thus, the elevated androgen and insulin levels may constitute a detrimental vicious circle between ovarian and metabolic dysfunctioning.
Animal models may aid in getting a better understanding of the development of PCOS and its the long term health consequences. To date, naturally occurring animal models are unknown. Therefore, androgenisation of animals is most frequently used to induce the reproductive and metabolic symptoms resembling PCOS.
We have developed a mouse PCOS model through chronic exposure of prepubertal mice to the non-aromatizable androgen DHT. At the end of the 90-day treatment period, DHT-treated mice were anovulatory and their antral follicles had a cyst-like structure. These mice also displayed increased adiposity and became glucose intolerant. In addition, analysis of their aortic vessels revealed the presence of a vascular phenotype since DHT-treated mice had decreased endothelial function. This suggests that exposure to DHT can induce several reproductive and metabolic characteristics associated with PCOS in women.
By applying this treatment regimen to transgenic mice, we can decipher the interaction between androgens and other factors, such as gonadal growth factors, to PCOS.

DOI: 10.1530/endoabs.41.S29.1

S29.2

Energy balance and androgens

Colin Duncan
UK.

PCOS is associated with increased androgens, elevated insulin and obesity. As obesity and androgens promote insulin resistance and hyperinsulinemia increases ovarian androgen production, and the likelihood of obesity, the interaction between these factors is complex. We investigated the development of insulin resistance, hyperandrogenism and obesity using a clinically realistic ovine model of PCOS. Exposure of the pregnant ewe to increased testosterone from d62 to d102 of gestation (d147) programs female offspring to develop a PCOS-like condition. These offspring have normal external genitalia and a normal birthweight. However in adulthood they become obese with hyperinsulinemia, increased ovarian and adrenal androgens and anovulation. Increased androgen and insulin concentrations are manifest in adolescence when the sheep are ovulatory and of normal weight. However there are fetal antecedents of hyperinsulinemia in the pancreas and of hyperandrogenism in the ovary. This suggests that insulin and androgen dysregulation develop in parallel, with fetal origins, as a consequence of prenatal androgen action. Androgen administration to control adult females reduced insulin sensitivity to that of the PCOS-like adults while androgen treatment of PCOS-like sheep did not cause any further deterioration. Metabolic assessment of prenatally programmed PCOS-like adult sheep demonstrated a reduction in postprandial thermogenesis, not seen in weight matched control sheep with intake-driven obesity, which was correlated with insulin resistance. This was associated with molecular alterations in subcutaneous adipocyte function, which could first be detected in adolescence before the development of obesity. Androgens alter energy balance in females but in PCOS it is likely that prenatal exposure to increased androgens, rather than ongoing postnatal exposure, is a major factor in the dysregulated energy balance. Women with PCOS have reduced post-prandial thermogenesis and this is recapitulated in the ovine model of PCOS. This suggests that women with PCOS have a driver towards obesity with developmental origins.

DOI: 10.1530/endoabs.41.S29.2

S29.3

Abstract unavailable.

Disorders of development and function of neurohypophysis

S30.1

Copeptin in the differential diagnosis and prediction of diabetes insipidus

Mirjam Christ-Crain
Endocrinology, University Hospital Basel, Basel, Switzerland.

Copeptin and arginine vasopressin (AVP) derive from a common precursor molecule and show equimolar secretion and response to osmotic, haemodynamic and stress-related stimuli. Plasma concentrations of copeptin and AVP in relation to serum osmolality are highly correlated. In contrast to AVP, which can be difficult to measure, copeptin is stable in plasma and can be easily measured with a sandwich immunoassay. For this reason, copeptin has emerged as a promising marker for the diagnosis of AVP-dependent fluid disorders. This talk will focus on copeptin in the differential diagnosis of diabetes insipidus and primary polydipsia and on the prediction of diabetes insipidus in patients undergoing pituitary surgery.

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S30.2

Role of TBI in the development of neurohypophyseal disorders

Mark Sherlock
Republic of Ireland.

Disorders of salt and water homeostasis are common following traumatic brain injury. Diabetes insipidus is a well-recognized complication of TBI. Polyuria occurs immediately after significant brain injury in up to 22% of cases, nearly always occurring within the first 2–3 days. The great majority of cases resolve spontaneously, and cross-sectional studies of long-term survivors of TBI report low rates of chronic diabetes insipidus. It is likely that in the absence of formal diagnostic assessment of AVP secretion, many patients with "subclinical" diabetes insipidus remain undiagnosed and maintain normal plasma osmolality through increased water intake.
Approximately 15% of patients recovering from TBI develop hyponatremia in the acute recovery phase. In over 80% of these cases, hyponatremia is due to SIADH. The natural history is for resolution of hyponatremia after recovery from the neurological acute insult. Although ACTH deficiency may occur in the acute recovery phase of TBI, hyponatremia is only rarely due to glucocorticoid deficiency in this context, but cases do occur and a high index of suspicion is required.
This talk will discuss the clinical management of neurohypophseal disorders following traumatic brain injury.

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S30.3

SIADH: current and future management options

Chris Thompson
Republic of Ireland.

SIADH is the commonest cause of hyponatraemia in hospital practice SIADH must be distinguished from hypovolaemic and hypervolaemic hyponatraemia, and a diagnosis of euvolaemic hyponatraemia is established, the main differential is between SIADH and glucocorticoid deficiency.
Not all cases of SIADH require active management. Drug induced SIADH usually responds to drug withdrawal, though active management may speed up return to eunatraemia if the drug has a long half life. Mild hyponatraemia which accompanies reversible conditions such as lobar pneumonia, often need no treatment other than treatment of the underlying condition. However, as evidence accumulates that hyponatraemia is associated with increased morbidity and mortality, interest has grown in the opportunity to reduce morbidity and mortality with active management.
Chronic hyponatraemia. The evidence base for the success of active management is sparse. Most clinical guidelines recommend fluid restriction (FR) as first line therapy, though the evidence base for success of therapy is limited. A number of parameters, such as urine osmolality $>$ 500 mOsm/kg and Furst equation $>$ 1 predict poor response to FR. Patients find FR difficult for long term treatment. Demeclocycline is unreliable, unlicensed, has no evidence base, and had significant side effects. Urea has a limited, poor quality evidence base, and there is

no available compound for clinical use. Vasopressin receptor antagonists have the backing of well-designed prospective studies, and undoubted clinical efficacy, though the cost of therapy deters many clinicians.

Acute hyponatraemia. Acute symptomatic hyponatraemia is a medical emergency associated with high mortality which can be reduced substantially by active management. New guidelines have been altered to recommend an initial rise in plasma sodium of 4–6 mmol/l over the initial 4–6 hours, as opposed to a steady rise in plasma sodium; the use of bolus hypertonic saline compared with continuous infusion to achieve this goal will be discussed.

DOI: 10.1530/endoabs.41.S30.3

New Scientific Approaches

NSA1

Abstract unavailable.

NSA2

Engineering an ovary bioprosthesis

Monica M Laronda
USA.

Patients with gonadotoxicity due to disease treatment, or who face primary gonadal insufficiency as a result of genetic causes, have limited options for long-term endocrine and fertility support. Current fertility options, such as egg or embryo banking, exclude women with hormone-responsive cancers and pre-pubertal children. This highlights the urgency of addressing this currently unmet need with innovative engineering solutions. Our objective is to create an ovary bioprosthesis that can restore function. We have implanted a bioinspired, scalable 3D-printed scaffold in an ovariectomized mouse that models human disease.

To better understand the natural ovarian environment, we decellularized, or removed all of the cells, from bovine ovaries or human ovary slices and examined the remaining organ skeleton. Through scanning electron microscopy, we identified defined regions where quiescent primordial follicles reside in the cortex and where large growing follicles reside in the medulla. The extracellular matrix of the cortex contained stiffer laminin fibers and the medulla contained more flexible fibronectin fibers, as both regions contained mostly collagen. This natural ovary skeleton composition, architecture and mechanical properties inspired our design for an ovarian implant. We developed a new method for printing gelatin, a collagen-derived biomaterial, into scaffolds for the purpose of creating a self-supporting ovary bioprosthesis skeleton. Using this method, we created scaffolds with bioinspired pore structures and a stiffness after cross-linking (compressive elastic modulus ~30 kPa) similar to that of the ovary (elastic modulus 5–20 kPa). We tested several scaffold designs to optimize ovarian follicle survival and function. Our criteria were to maintain high mechanical properties of the implant for desirable surgical handling while creating space from scaffold porosity to enable follicle expansion, ovulation and release of an egg, vascularization and passage of follicle paracrine signals. Our intersecting 30° and 60° advancing angle designs, that allow for multiple strut contacts, supported folliculogenesis at a significantly higher rate than scaffolds created with a 90° advancing angle containing through-pores (30°, 78.6% ±3.6 survival; 60°, 75.9% ±4.0 survival; 90°, 48.5% ±8.3, $P=0.01$). The 30° and 60° scaffolds supported two or more follicle contacts at a higher rate than the 90° scaffolds. These additional contacts were essential for sustained follicle health over the 8-day culture (74.3% ±6.5 survival with two or more strut contacts versus 33.2% ±11.3 with one strut contact, $P=0.01$). Three-dimensional confocal analysis confirmed that the follicles were supported within the manufactured follicle niche structures of the 30° and 60° scaffolds and interacted with the struts. Follicular somatic cells robustly expressed vinculin, a focal adhesion protein, along the pore struts and spread those struts. The length of spreading was significantly less with more contacts, which provided support for the follicle's spheroid structure as the basement membrane was maintained (average contact length when contacting one strut 198.7 μm ±42.8; two struts 104.8 μm ±14.0; three struts 59.5 μm ± 5.4; $P<0.005$). Follicles within the intersecting scaffold designs stained positive for 3β hydroxysteroid dehydrogenase, released estradiol over an 8-day *in vitro* culture, and upon exposure to human chorionic gonadotropin, ovulated and released MII eggs through the open porosity without mechanical or enzymatic manipulation of the follicular cells or scaffold. The implantable ovary bioprosthesis was constructed by down-selecting to a 60° 3D printed scaffold and seeded with green fluorescent protein (GFP)-positive quiescent primordial and growing primary and secondary murine follicles. The bioprostheses were implanted into the native organ site in ovariectomized GFP-negative mice. These follicle-seeded bioactive scaffolds supported vascular infiltration without the addition of angiogenic factors, restored the estrous cycle (as observed through vaginal cytology) and produced live offspring. These healthy offspring were supported by the lactating implant recipient mother until weaning.

These data underscore the importance of the bioactive scaffold architecture in supporting folliculogenesis and demonstrate a functional ovary bioprosthesis. This research expands beyond the current state of tissue engineering toward developing a common scheme for complex soft tissue replacement through bioinspired-manufacturing of bioactive scaffolds.

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NSA3

Abstract unavailable.

NSA4

Single cell transcriptomics in endocrine system physiology: example from the pancreas

Stefan Kubicek
Austria.

The specialized endocrine cell types of pancreatic islets of Langerhans are essential for maintaining glucose homeostasis. Bulk approaches to characterize islets in normal and diabetic conditions are challenging, as both cell-type specific gene expression changes, changes in the composition of islets, and changes in cell types including de- and trans-differentiation can contribute. Furthermore, technologies to isolate specific cell types from human islets are often lacking, and where available prone to induce gene expression changes in the purification process.

Therefore, we applied single-cell RNA sequencing on cells sorted from human primary islets. We show that using this technology we can validate previously described and discover novel marker genes at for individual cell types. Furthermore, we identify key differences between human and rodent islets, and we observe islet-cell specific expression of diabetes risk genes identified from genome-wide association studies.

In summary, the establishment of single cell transcriptomics opens up numerous possibilities to characterize islets in normal and diabetic conditions, but also to clarify islet-cell type specific effects of therapeutic intervention.

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NSA5

Abstract unavailable.

Debate

The use of NSAIDs in endocrine cancers: the case of Celecoxib

D1.1

Abstract unavailable.

D1.2

The use of NSAIDs in endocrine cancers: the case of Celecoxib: FOR

Joan Carles
Spain.

NSAIDs inhibit cyclooxygenase activity and thereby reduce prostaglandin synthesis. Two genetic isoforms of COX have been characterized: COX 1 constitutively produced in most tissues and COX 2 is not expressed in most normal tissues which is induced by pro inflammatory and mitogenic stimuli. Chronic inflammation and oxidative stress are key players in COX2 dependent carcinogenesis and it is important to point out that this type of inflammation has been associated with cancer in different tumors including endocrine tumors, such as prostate and breast cancer.
Preclinical and clinical evidence suggest that COX2 is an attractive target for the treatment or prevention of different endocrine tumors. It has been shown that COX2 is overexpressed in breast and in prostate cancer tissue.
Different mechanisms of action have been postulated: promote tumor specific angiogenesis, inhibit apoptosis, modulation of IL6, IL8 modulation of cholesterol and the final hormones (testosterone and estradiol). Also COX2 inhibitors can minimize certain typical side effects of chemotherapy such as mucositis, diarrhea and other inflammatory toxic effects.
Results from different clinical trials in will be reviewed endocrine malignancies during the meeting.

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D1.3

The use of NSAIDs in endocrine cancers: the case of Celecoxib AGAINST

Andrea Sacchetti
The Netherlands.

The antitumor properties of non-steroidal anti-inflammatory drugs (NSAIDs), with respect to both cancer prevention and therapy, have raised considerable interest in the last two decades, leading to well consolidated evidences in gastrointestinal cancers, especially colorectal cancer. NSAID action has been proposed to occur through two independent modes: a COX-dependent one, mainly involving the inhibition of COX-2-mediated PGE2 production, and a COX-independent one, mainly involving direct toxicity to tumor cells. Among NSAIDs, Celecoxib is considered particularly promising as antitumor drug because of both selective COX-2 inhibition and powerful COX-independent toxicity on tumor cells.
However, I have recently demonstrated that the direct toxicity of Celecoxib, mostly observed *in vitro*, relies on precipitate-dependent cell damage rather than molecular effects (Sacchetti, *J Cell Biochem*. 2013 Jun; 114(6): 1434–44) and requires concentrations of the drug much higher than those observed during therapy, with the exception of some regions of the gastrointestinal tract. If, in the latter, COX-inhibition may be effectively potentiated by COX-independent actions from Celecoxib and/or its (COX)-inactive metabolites, leading to relevant antitumor effects, on non-gastrointestinal tumors the action of Celecoxib is probably limited to COX-2 inhibition and, as a matter of fact, its efficacy is less pronounced and still controversial.
Overall, because of the misleading toxicity observed *in vitro*, the potential of Celecoxib as antitumor agent has been probably overestimated in comparison with other NSAIDs, while limited beneficial effects must be accurately weighted against unwanted risks, in particular cardiovascular toxicity associated with COX-2 inhibitors. For what concerns endocrine cancers, it is early to draw conclusions, considering the heterogeneity of these tumors and the limited literature on the subject. However, the available evidences do not support the idea of testing Celecoxib as a first choice in prevention or therapy, but suggest considering other NSAIDS as well, or combinations of NSAIDs, in pre-clinical models and clinical trials.

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Should we treat subclinical Cushing's syndrome?

D2.1

Abstract unavailable.

D2.2

Are we ready for pharmacological therapy of obesity?: AGAINST

Uberto Pagotto
Italy.

The ongoing obesity epidemic is one of the main concerns worldwide and for this reason preventive strategies to reduce the future global health and the economic costs of this disease are urgently needed. Diets for weight loss and physical activity represent the cornerstone of treatment for patients who are overweight and/or obese, in particular to improve the frequent comorbid conditions associated with obesity. Now and in the past multiple medications have been approved for chronic weight management in order to pharmacologically treating obesity like other chronic diseases. However, still a number of doubts has been attributed to the use of drugs to curb obesity mainly due to a series of factors:
i) The modest efficacy of the current medications options often limited to 5–10% body weight loss
ii) The lack of long-term studies clearly demonstrating a final beneficial effects of anti-obesity drugs when compared to bariatric surgery with respect to the cardiovascular events
iii) The previous experience of serious safety inducing a risk-to-benefit ratio no longer favourable toward anti-obesity drugs
iv) The limited possibility to provide an individualized pharmacotherapy in consideration of the heterogeneity featuring obesity phenotype
v) The economical cost of the drugs for the national Agencies when reimbursement is approved or for the single patient when not
All these reasons supporting the idea that we are not yet ready for pharmacological therapy of obesity will be critically revised during the lecture.

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Strengths and weaknesses of hormone immunoassays and mass spectrometry: what the clinician should know

D3.1

Strengths and weaknesses of hormone immunoassays and mass spectrometry: what the clinician should know: mass spectrometry

Brian Keevil
UK.

Liquid chromatography–tandem mass spectrometry (LC–MS/MS) is a powerful tool that is changing the way we analyse steroids in the clinical laboratory. It offers positive compound identification to enable the unequivocal identification of a compound free from interference. LC–MS/MS is already opening up the field of steroid analysis in endocrinology and is providing new applications for individual steroids and panels of steroids in different clinical conditions. LC–MS/MS is now well-accepted technology and is increasingly being used to replace problematic immunoassay methods because of greater sensitivity and specificity. Improved sample preparation, modern chromatography methods and sensitive, faster scanning mass spectrometers have all played a role in improving LC–MS/MS. LC–MS/MS is also playing a key role in improving the quality of assays through the development of reference measurement procedures, characterisation of reference materials and multi-site calibration programmes. There is increasing interest in multiplexing steroid assays into panels of diagnostic tests to aid and improve the diagnosis and monitoring of disease.

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D3.2

Abstract unavailable.

Are we ready for pharmacological therapy of obesity?

D4.1

Abstract unavailable.

D4.2

Should we treat subclinical Cushing's syndrome?

Paul M Stewart
UK.

The term subclinical Cushing syndrome arose at the turn of the millennium with the description of large Italian study of adrenal incidentalomas. Of 1096 patients from 26 centres, 9.2% had 'subclinical Cushing's' (JCEM, 2000; 85:637-644). Since then over 300 publications have detailed this newly discovered endocrine diagnosis, and herein lies the main issue. The definition of Cushing's syndrome is not in doubt – a 'constellation of symptoms and signs that reflect prolonged and inappropriately high exposure of tissues to glucocorticoids'. No single test has 100% sensitivity or specificity, which is why the guidelines suggest numerous screening tests including urinary free cortisol (UFC), late night salivary cortisol (LNSC) or a 1mg overnight dexamethasone (DEXA). Sensitivity is high to avoid missing the 'killing disease' at the expense of specificity so that a false positive result is 50× more commoner than a true positive. False positives are common in patients with 'physiological' cortisol hypersecretion, such as those with diabetes, obesity and depression.

Adrenal incidentalomas have a prevalence rate of 7% in subjects over 70 years, where prevalence rates for diabetes are 25%, hypertension 65%, obesity 35% and osteoporosis 16% (male) and 47% (female). Papers describe abnormalities in a host of variable diagnostic tests that have included random cortisol, loss of circadian rhythm, DHAS, blunted ACTH response to CRF in addition to the 'guidelines' screening tests of UFC, LNSC and o/n Dexa in variable doses. No wonder that 9% of such patients have abnormal results – the specificity of these tests predicts exactly that!

Within the 'subclinical' literature, and our own personal experiences there are undoubtedly patients with adrenal incidentalomas who do have inappropriate cortisol hypersecretion, the hallmark of which must be suppressed ACTH. With the current lack of evidence base for treating what is usually 'mild disease', in a patient who may lack many of the discriminatory features of Cushing's syndrome, the physician will be guided by end organ effects of cortisol (BMI, BMD, glucose tolerance, lipids, BP) in deciding whether or not to proceed to laparoscopic adrenalectomy – but in doing so must accept that there is nothing 'subclinical' in this scenario.

'Subclinical Cushing syndrome' currently comprises a majority of patients with age related diseases and false positive abnormalities in HPA axis testing who DO NOT have inappropriate cortisol hypersecretion. A small number of cases with suppressed ACTH and inappropriate cortisol production causing low BMD, BP, CVS risk and diabetes may need therapy, but then by definition are very much 'clinical' in nature.

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Meet the Expert Sessions

MTE1

Gynaecomastia in adult men is frequently a symptom of other diseases; the Copenhagen experience

Niels Jørgensen
Denmark.

Breast development in boys and men, gynaecomastia, is a common condition. The incidence peaks three times through life: neonatally in the first weeks after birth; pubertally, usually around genital stage 3 to 4 and in adulthood with increasing incidence after the age of 50 years.
Using a standardized diagnostic approach a cause for gynaecomastia developed in adulthood can be detected in the majority of men, and gynaecomastia may be the first presenting symptom of an underlying treatable pathology. The Copenhagen experience is that when excluding men where gynaecomastia developed due to abuse of anabolic steroids, an underlying reason might be detected in up to 70% of the remaing men; in ~30% it was due to medical treatment due to comorbities, in ~30% it was due to testosterone deficiency and in another 10% it was due to other treatable caused. Furthermore, more than one reason was present in many and a diagnostic approach ought to take that into account. The results emphasize the importance of a thorough andrological–endocrinological examination in patients presenting with gynaecomastia.

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MTE2.1–MTE2.2

Difficult thyroid cases

Carla Moran & Luca Persani

In clinical practice, most thyroid disease is due to thyroid gland dysfunction and so can be detected by measurement of TSH alone. This is because the negative feedback of thyroid hormones on the hypothalamus and pituitary gland result in TSH levels that are closely, and inversely, correlated with circulating free thyroid hormone (FT_4, FT_3) levels. However, several conditions are exceptions to this rule and can be very hard to diagnose also due to a certain lack of awareness.
Examples of situations when measurement of TSH alone might be misleading include:
– interference in TSH and/or FT_4 measurements
– central hyperthyroidism due to TSH-secreting pituitary adenomas
– central hypothyroidism
– resistance to thyroid hormone action (RTHα or RTHβ)
– disorders and drugs interfering in thyroid hormone transport and metabolism
In addition, depending on the type of thyroid hormone being taken excessively by patients, exogenous thyrotoxicosis can present with variable abnormalities of thyroid function tests, making the diagnosis of such cases very challenging.

DOI: 10.1530/endoabs.41.MTE2.1–MTE2.2

MTE3

Abstract unavailable.

MTE4

Treatment of osteoporosis; treatment goals and duration of therapy

Osteoporosis is a prevalent condition mainly involving the elderly with an increased risk of fractures, morbidity and mortality. Partly due to ageing of the population there is an increase in the prevalence of osteoporosis and fractures. It is estimated that one in five men will experience a fragility fracture after the age of 50 years. Apart from lifestyle factors such as increasing physical exercise, adequate status of calcium and vitamin D, the cessation of smoking and moderation of alcohol intake, there are multiple treatment options for the prevention of osteoporotic fractures including antiresorptive agents such as bisphosphonates and denosumab and anabolic therapy with recombinant human parathyroid hormone (rhPTH) analogues.
The ultimate goal in the treatment of osteoporosis is the reduction in fracture risk with an increase in BMD and restoration in bone microarchitecture. With current available drugs the reduction in risk of fractures is much higher for vertebral than for non-vertebral fractures. No therapy with osteoporosis drugs will be able prevent all fractures and the definition of treatment failure is lacking. An important issue among clinicians is when to stop therapy and when to consider switching drug. These issues will be discussed during this workshop, illustrated with clinical cases.

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MTE5

Abstract unavailable.

MTE6

MEN syndromes

Valeriano Leite
Portugal.

Multiple endocrine neoplasia (MEN) syndromes are classically defined as the occurrence of two or more endocrine tumours in a patient, and include two major forms, characterized by development of tumours within specific endocrine glands, referred to as type 1 (MEN1) and type 2 (MEN2). These disorders are due to mutations in the *MEN1* gene in MEN1 (parathyroid, pituitary or pancreatic tumours), and in the *RET* gene in MEN2 (which comprises three types: MEN2A with medullary thyroid carcinomas, pheochromocytomas, and hyperparathyroidism; MEN2B with medullary thyroid carcinomas, pheochromocytomas, mucosal neuromas, ganglioneuromas and marfanoid habitus; and isolated familial medullary thyroid carcinoma). Additionally, *CDKN1B* gene mutations are detected in MEN 4 (parathyroid and pituitary tumours), the rarest form of MEN diseases. However, tumours occurring in MEN syndromes may also have a non-endocrine origin such as lipomas and facial angiofibromas in MEN1 syndrome. In addition, there are other hereditary endocrine syndromes in which there is only one type of endocrine tumour occurring either in an isolated form (familial isolated pituitary adenomas) or, eventually, associated with tumours from other tissues (hyperparathyroidism-jaw tumour syndrome and paraganglioma/pheochromocytoma syndrome). On the other hand, endocrine neoplasias may also be a component of hereditary syndromes characterized by a predominance of non-endocrine tumours such as Cowden syndrome, Carney complex, familial adenomatous polyposis or von-Hippel–Lindau disease.
Hereditary endocrine neoplasias are usually inherited as an autosomal dominant trait and are due to mutations in tumour suppressor genes, except for MEN2/FMTC in which the causative gene, the *RET* gene, is a proto-oncogene.
Individually, each of these syndromes has a low incidence/prevalence but, due to their multiplicity, Endocrinologists, in particular those working in referral centers for endocrine tumours, are frequently requested to evaluate and treat patients with such neoplasias.
Illustrative cases of some of these syndromes will be presented and discussed in this MTE session.

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MTE7

New ATA recommendation for differentiated thyroid cancer management from the point of view of European endocrinologist

Furio Pacini
Italy.

The American Thyroid Association has recently developed updated guidelines for the management of thyroid nodules and thyroid cancer. Compared to previous editions, this new guidelines give important new recommendation on several issues.

Initial treatment for thyroid cancer is total thyroidectomy. After total thyroidectomy, patients are treated with ^{131}I activities aimed at ablating any remnant thyroid tissue. Radioiodine ablation is recommended in high-risk patients and in some low risk patients, while there is no indication in very low risk patients. The method of choice for preparation to perform a radioiodine ablation is based on the administration of recombinant human TSH.

After thyroid ablation, aim of follow-up is the early discovery and treatment of persistent or recurrent disease. At 6 to 12 months the follow-up is based on physical examination, neck ultrasound, rhTSH stimulated serum Tg measurement. At this time nearly 80% of the patients will belong to the low risk categories and will disclose normal neck ultrasound and undetectable (<1.0 ng/ml) stimulated serum Tg in the absence of serum Tg antibodies. These patients may be considered in complete remission.

The few patients with persistent disease, require imaging techniques for the localization of disease. Included in this category are the 5–10% of DTC patients that presented with local or distant metastases at diagnosis and an additional 5–10% that develop recurrent disease during follow-up. When appropriately treated, 2/3 of those patients with local disease and 1/3 of those with distant disease may achieve complete remission. Lung macro-nodules may benefit from radioiodine therapy but the definitive cure rate is very low. Bone metastases have the worst prognosis. Whenever radioiodine therapy is not effective and the disease progress, patients are candidate to treatment with tyrosine kinase inhibitors which have been recently approved after successful outcome of several clinical trials.

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MTE8

Abstract unavailable.

MTE9

Treatment of male hypogonadism

Dimitrios G Goulis
Greece.

Traditionally, male hypogonadism is classified into hypogonadotrophic (the archetype being Kallmann syndrome) and hypergonadotrophic (the archetype being Klinefelter syndrome). Late-onset hypogonadism (LOH) constitutes a separate entity that can be defined as the state where men of advanced age demonstrate low serum testosterone (T) concentrations in combination with a spectrum of symptoms reminiscent of those of 'classic' male hypogonadism (e.g. reduced sexual function, loss of vigor, muscle weakness and depression). In obese men, hypogonadism can further worsen the metabolic profile.

The cornerstone of the treatment of male hypogonadism is testosterone replacement therapy (TRT) in the form of intramuscular injections or transdermal preparations (gel, patches). Important TRT issues include:

- Indications (undisputable diagnosis of hypogonadism).
- Contra-indications (absolute: prostate cancer breast cancer; relative: sleep apnea syndrome, benign prostate hyperplasia with obstructive symptoms).
- Adverse effects (polycythemia, prostate hyperplasia, gynecomastia, alteration of serum lipid profile, liver toxicity, impairment of spermatogenesis).
- Follow-up program [recording of clinical (e.g. symptom improvement including sexual function, natural history of sleep apnea, blood pressure, digital rectal examination) and biochemical (e.g. PSA, fasting lipid profile, complete blood count, liver function tests) parameters on pre-determined time intervals].

TRT is expected to re-establish sexual functioning and libido, improve mood and muscle mass, prevent osteoporosis and maintain mental acuity and virilization. A most debated issue is that TRT in LOH. Despite the evidence TRT may increase the incidence of cardiovascular disease, a critical review of the available literature suggests that TRT is effective and safe treatment for male hypogonadism, when applied in carefully selected populations. In symptomatic men with LOH, metabolic impairment and obesity, the combination of TRT with lifestyle modifications can result in better outcomes.

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MTE10

Systems medicine: the impact on endocrine practice

Eugenia Resmini
Spain.

Systems Medicine is an interdisciplinary field of study that deals with systems of the human body as part of an integrated whole, incorporating biochemical, physiological, and environment interactions. Systems Medicine draws on systems science and systems biology, and considers complex interactions within the human body with a patient's genomics, behavior and environment perspective. The earliest uses of the term systems medicine appeared in 1992, it is a modern approach which produces improvement of patient health through systems-based approaches and practice.

A distinctive challenge of Systems Medicine is that it means different things for different people and that different societies and communities use different approaches and languages.

Clinicians always have integrated clinical observation, empirical knowledge and information from medical tests in order to diagnose and treat patients. This is a proven and successful concept. However, the success of this approach is challenged by the steep increase in the amount of different pieces of information to integrate and the sheer size and complexity of large datasets, such as genome sequences, which we are able to produce. Computational and mathematical analysis and modeling methods used in Systems Medicine offer a unique and effective opportunity to fill this gap. These methods open new horizons and will extend medicine's ability to help by harnessing an enormous amount of patient and disease relevant information that is available and will become available in the future. Systems Medicine provides a systematic and tractable approach that is reproducible, scalable and evolvable, ensuring that the increasing volume of highly complex patient data will be accessible and intelligible. Systems Medicine will give clinicians a new tool that will step change the capabilities of the clinician to diagnose and treat patients faster, better and more effectively. The Coordinating Action Systems Medicine (CASyM) is a multidisciplinary European consortium that joins forces to develop an implementation strategy for Systems Medicine. This new and innovative concept integrates multiple disciplines, whereas a significant part of this is clinical medicine, from clinical trials through public health and medical economics. The CASyM road map is driven by clinical needs: It aims to identify areas where a systems approach will address clinical questions and solve clinical problems. The Instituto de Salud Carlos III (Institute of Health Carlos III, ISCIII) is the main Public Research Entity funding, managing and carrying out biomedical research in Spain. The Institute has been conducting research and providing key services in the life and health sciences for over 20 years. It is also the responsible for managing Spain's Health Research and Development Strategy. Its key mission is to support the development of scientific knowledge in the health sciences and to contribute to innovation in healthcare and the prevention of disease throughout Systems Medicine. Putting patients at the heart of all its activities and objectives, the Institute promotes and coordinates biomedical research and provides scientific and technical services of the highest quality in partnership with all the organizations forming part of the Spanish System of Science, Technology and Innovation. In order to create a network of research excellence, it created the Centros de Investigación Biomédica en Red (Biomedical Research Networking Centre, 'CIBER') by setting up consortia, with their own legal personality, which are designed to conduct research on a specific broadly defined disease or health problem. CIBER are formed through the association of research groups linked to the National Health System to help form the scientific basis of the programs and policies of the National Health System. The purpose of creating and maintaining CIBER is to promote research excellence in biomedicine and health sciences conducted in the National Health System and in the system of science and technology. Systems Medicine is an appealing concept, it still is in the phase of its active development and not implemented in clinical practice. For this reason clinical needs and opportunities for the implementation of Systems Medicine in clinical endocrinology will be discussed. The aim of the discussion will be to explore innovative approaches in the characterization and management of endocrine disorders, where new discoveries and new technologies are challenging scientists for the development of research, as well as for the clinical practice.

Participants will be asked for their main field of expertise and any present and/or previous experience in the Systems Medicine area. Moreover, their interest toward Systems Medicine and their feeling about the add-on value of Systems Medicine in their own area of research and in general, will be evaluated. Types of Systems Medicine based applications which are more appealing in clinical endocrinology would be identified. Targeted therapies, clinical trials, neuroendocrine databases, diabetes and quality of life emerged as very appealing for System Medicine in clinical endocrinology. Systems approaches may also fulfill the unmet needs which include the necessity of prognostic parameters, validated treatment algorithms, identification of pathway-specific compounds and identification of patient heterogenei

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Oral Communications

Adrenal – Basic & Clinical

OC1.1

Genetic landscape of sporadic unilateral adrenocortical adenomas without PRKACA p.Leu206Arg mutation

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Genetic alterations affecting the PKA/cAMP pathway are commonly found in cortisol-producing adrenocortical adenomas (ACAs), while activating mutations in the gene coding for β-catenin (*CTNNB1*) have been reported in both adenomas and carcinomas. However, the molecular pathogenesis of most ACAs is still unclear. Aim of the study was a comprehensive genetic characterization of sporadic ACAs and the identification of novel molecular markers involved in adrenal tumorigenesis and steroid autonomy.

Whole-exome sequencing was performed on DNA of adrenocortical tumors and corresponding blood samples of 99 patients with ACAs (39 associated with overt Cushing's syndrome, 35 with subclinical hypercortisolism and 25 endocrine inactive) negative for the p.Leu206Arg *PRKACA* mutation.

In total, 706 protein-altering somatic mutations were detected in 88/99 ACAs (median: 6 mutations per sample, range: 0–55). Several altered genes could be recognized as part of the Wnt/β-catenin pathway (*CTNNB1, APC, APC2, PKP2*, and different members of the protocadherin superfamily), being associated with larger tumor size and endocrine inactivity. Moreover, many components of the cAMP/PKA pathway were affected by somatic mutations, including three new mutations in the *PRKACA* gene, mutations in metabotropic glutamate receptors (*GRM3, GRM4, GRM6*) and others (*GNAS, PRKACA, PRKAR1A, CREB1, CREBBP, ADCY3*), and associated with female gender and overt Cushing syndrome. Finally, more surprisingly, we also observed several alterations in genes involved in the Ca^{2+} signaling (*CACNA1C, CACNA1E, RYR1, RYR2, RYR3, GRIA1, GRID1, GRIK2, GRIN1, GRIN3B, GRIP1, GRIA2*).

In conclusion, this study represents the most comprehensive genetic characterization of unilateral ACAs, including inactive adenomas. We thereby identified somatic alterations affecting signaling pathways known or potentially involved in the adrenal tumorigenesis.

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OC1.2

Focal DNA methylation measurement in adrenocortical carcinoma is a prognostic marker independent from tumor stage and Ki67; an ENSAT study

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Recent pan-genomic analyses of tumor DNA identified specific patterns of DNA methylation –e.g. CpG islands hypermethylation in the promoter regions of genes- as pejorative prognostic markers in adrenocortical cancer (ACC). Integrated genomics clearly shows that ACC with such an hypermethylation belongs to specific subgroups of ACC with increased driver genes alterations and a poor survival.

Aim

To confirm the prognostic value of this methylation pattern on an independent cohort using a commercially available kit, and to confront methylation to tumor stage and Ki67, the two main prognostic factors validated so far.

Patients and Methods

DNA methylation was measured by methylation-specific multiplex-ligation-dependent probe amplification (MS-MLPA) in the CpG islands of 27 genes using the ME002-B1 kit (MRC-Holland). MS-MLPA marker was set up in a training cohort of 50 ACC, then validated in an independent cohort of 203 ACC from 21 ENSAT centers. The validation cohort included 64% females, median age 50 years, 80% localized tumors (ENSAT stages I–III). Univariate and multivariate survival analyses were performed with Cox models.

Results

The mean methylation of 4 genes (PAX5, GSTP1, PYCARD, PAX6) correlated well with methylation arrays (Pearson correlation coefficient 0.81). The mean methylation was a strong predictor of survival, with a hazard ratio (HR) for recurrence of 1.013 ($P<10^{-6}$) and a HR for death of 1.012 ($P<10^{-4}$) per 1% increase of methylation. In a multivariate model including ENSAT stage and Ki67, the mean methylation remained significant for predicting recurrence ($P<10^{-3}$) and death ($P<10^{-3}$).

Conclusion

Focal measurement of tumor DNA methylation is a high and independent predictor of recurrence and death in ACC patients. MS-MLPA is readily compatible with clinical routine, and should therefore complete the clinical and pathological prognostic markers for precision medicine.

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OC1.3

Hormone replacement therapy with prednisolone is associated with a worse lipid profile than replacement with hydrocortisone in patients with adrenal insufficiency: a matched analysis of data from the EU-AIR

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Introduction

Prednisolone is the standard treatment for most inflammatory conditions. However, it is also used in hormone replacement therapy in adrenal insufficiency (AI) for historical reasons or due to its longer half-life and once-daily application. Recent data indicate that daily prednisolone could be associated with lower bone mineral density than daily hydrocortisone in patients with AI. However, data on risk factors for cardiovascular disease in patients with AI treated with prednisolone are scarce, despite cardiovascular disease being the major cause of death in patients with AI. Therefore, we analyzed real-world data from the European Adrenal Insufficiency Registry (EU-AIR).

Design
EU-AIR with 19 centres across Germany, the Netherlands, Sweden and the UK started enrolling patients with AI in August 2012. Patients on dexamethasone or modified-release hydrocortisone were excluded from this analysis, as were patients with congenital adrenal hyperplasia. Patients receiving prednisolone (3–6 mg/day) or hydrocortisone (15–30 mg/day) were included, resulting in 50 patients on prednisolone and 909 on hydrocortisone. We performed a 1:3 matching regarding sex, age, duration of disease and aetiology of AI.
Results
After matching, we found significantly higher total cholesterol (6.3 ± 1.6 vs 5.4 ± 1.1 mmol/l; $P < 0.05$) and LDL levels (3.9 ± 1.4 vs 3.2 ± 1.0 mmol/l; $P < 0.05$) in 47 patients on prednisolone compared to 141 patients on hydrocortisone. HbA1c, HDL and triglyceride levels were not different between groups, neither were BMI (27.2 ± 3.9 vs 27.8 ± 5.3 kg/m^2), systolic and diastolic blood pressure ($128 \pm 18/78 \pm 9$ vs $131 \pm 18/79 \pm 10$ mmHg), and waist circumference (99.0 ± 13.8 vs 96.1 ± 13.9 cm). No differences in the frequency of hypertension or diabetes mellitus were detected between groups.
Conclusions
This is the first matched analysis comparing cardiovascular risk factors in patients with AI on prednisolone and hydrocortisone. Significantly higher LDL levels in patients treated with prednisolone than hydrocortisone could predict a higher relative risk of cardiovascular disease for these patients.

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OC1.4

Urine steroid metabolomics is a highly sensitive tool for post-operative recurrence detection in adrenocortical carcinoma

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Context
Adrenocortical carcinoma (ACC) is an aggressive malignancy with high recurrence rates. Regular post-operative follow-up imaging is essential, but associated with high radiation exposure and frequent diagnostic ambiguity. Urine steroid metabolomics has been described as a novel diagnostic tool for the detection of adrenocortical malignancy. Here we present the first clinical study assessing the performance of this innovative approach in the follow-up of patients with complete (R_0) ACC resection.
Patients and Methods
We included 142 ACC patients from 13 centres registered with the European Network for the Study of Adrenal Tumours (ENSAT). We selected all patients recorded 2008-2015 fulfilling the following criteria: 1) recorded on the ENSAT registry as confirmed ACC with R_0 primary tumour resection; 2) availability of at least two postoperative 24-hour urines, one whilst disease-free and the other after recurrence. The urine steroid metabolome was analysed by gas chromatography-mass spectrometry, with quantification of 38 distinct steroid metabolites. Biochemical detection of ACC recurrence was judged both by expert review and a machine learning-based computational algorithm.
Results
Recurrent disease was detected by imaging in 28 of 142 patients after a median of 21 (IQR 5–28) months following R_0 resection. Steroid metabolome analysis diagnosed disease recurrence at the time of first abnormal imaging or earlier in 19/28 cases. The sensitivity of this approach was highest in patients who had provided a pre-operative urine sample (10/11 cases diagnosed correctly). Similarly, ACC recurrence was detected correctly in 11/12 patients not receiving adjuvant mitotane. By contrast, in patients on adjuvant mitotane, and hence downregulated global steroidogenesis, sensitivity was reduced (8/16 detected). In 8 patients, biochemical recurrence detection pre-dated the first radiological evidence of recurrence by >2 (range 3–10) months.
Conclusion
Our study provides proof-of-principle evidence for urine steroid metabolomics as a sensitive diagnostic tool for the prediction of ACC recurrence following R_0 resection.

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OC1.5

Is biochemical assessment of pheochromocytoma necessary in adrenal incidentalomas with magnetic resonance features non-suggestive of pheochromocytoma?

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Objective
It is not currently well known whether pheochromocytomas can be ruled out based on low intensity on T2-weighted sequences and signal loss on out-off phase magnetic resonance imaging (MRI) sequences. Hence, in this study we aimed to investigate whether biochemical screening for pheochromocytoma in patients with adrenal incidentalomas (AI) showing MRI features not suggesting pheochromocytoma would prove beneficial.
Methods
We performed MRI for 300 adrenal incidentalomas in 278 consecutive patients. All patients were screened for pheochromocytoma with plasma metanephrine and normetanephrine. Patients with high plasma levels of metanephrine and normetanephrine were also assessed for pheochromocytoma by urinary metanephrines.
Results
Hyperintensity was detected on T2-weighted MRI sequences in 28 (9.3%) of the 300 AI. Among these 28 incidentalomas, pheochromocytoma was diagnosed in 13 (46.4%) of the cases by histopathological analysis. Hyperintensity on T2-weighted MRI was significantly higher in pheochromocytomas compared to the remaining AI ($P < 0.001$). All 13 pheochromocytomas were characterized with hyperintensity on T2-weighted sequences and the absence of signal loss on out-of-phase sequences on MRI. Pheochromocytoma was not detected in any of the 272 AI, which appeared hypointense or isointense on T2-weighted MRI sequences and in 250 cases with signal loss on out-of-phase sequences.
Conclusion
The results of this study suggest that AI, which appear hypointense or isointense on T2-weighted MRI sequences and those with signal loss on out-of-phase sequences, may not require routine biochemical screening for pheochromocytoma. Further studies including a higher number of pheochromocytomas are required to confirm our results.

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Receptors & Signalling

OC2.1

3-T1AM signaling in the rat thyrocyte cell line PCCL3

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The endogenous decarboxylated thyroid hormone (TH) metabolite 3-Iodothyronamine (3-T1AM) exerts partially TH antagonistic effects in rodents and was shown to suppress the hypothalamic pituitary thyroid axis in rats after single dose application. Therefore, it might play a role in maintaining TH homoeostasis. Among the molecular targets of 3-T1AM are G protein-coupled receptors like the trace amine associated receptor 1 (TAAR1) and adrenergic receptors. Furthermore, 3-T1AM was shown to activate the cold-sensitive transient receptor potential melastatin 8 channel (TRPM8). By acting on these target structures 3-T1AM modulates cAMP and Ca^{2+} signaling in several cell lines in vitro. We recently obtained experimental evidence that 3-T1AM (1 μM for 1 – 3 h) interferes with the TH synthesis machinery and energy metabolism in

the rat thyrocyte cell line PCCL3. To elucidate the mechanism underlying these effects we analyzed the activation of signaling pathways by 3-T1AM and well established receptor ligands in PCCL3 cells. Levels of cAMP were measured with a competitive assay and cytosolic free Ca^{2+} was analyzed with the calcium indicator fura-2/AM and fluorescence imaging. 3-T1AM (0.1 – 1 μM) incubation did neither modify basal nor TSH-stimulated cAMP concentration. Incubation of PCCL3 cells with phenylethylamine or norepinephrine/isoprenaline, endogenous ligands of TAAR1 and adrenergic receptors, respectively, left cAMP unaltered indicating absent expression or functional inertness of the receptors to these agents. In contrast, 3-T1AM induced a strong increase in cytosolic free calcium in PCCL3 cells within minutes, which was abolished by co-incubation with the TRPM8 blocker BCTC. In conclusion, Ca^{2+} signaling via TRPM8 rather than TAAR1- or adrenergic receptor-dependent cAMP signaling is considered as a candidate mechanism that might mediate the metabolic and functional effects of 3-T1AM in PCCL3 cells.

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OC2.2

Expression levels of thyroglobulin processing proteases are reduced upon trace amine-associated receptor 1 deficiency in mice

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The function of the thyroid gland is to maintain thyroid hormone (TH) levels in the blood circulation. Thyroid epithelial cells liberate TH from the precursor molecule thyroglobulin (Tg) by the combined proteolytic action of the cathepsin B, K, L, and S. Cathepsin L-deficiency in mice results in impaired processing of Tg and remnants of dead cells in the follicle lumen. Recently, we have shown that Trace amine-associated receptor 1 (Taar1) is localized on the primary cilia of mouse thyrocytes. Interestingly, Taar1-deficient mice are characterized by remnants of dead cells in the follicle lumen; a phenotype shared with cathepsin L-deficient mice. Thus we investigated the possible link between expression and function of Taar1 and the activity of cathepsins B, K, L and S *in vitro* and *in vivo*. Pharmacological knock-down (Cathepsin L inhibitor III) of cathepsin L activity in FRT cells resulted in reduced immunoreactivity of Taar1 on their primary cilia. In mice ($n=6$) lacking Taar1, the expression *in situ* of cathepsin B, D and L was measured and cathepsin D and L expression levels were found to be reduced in 12 month old Taar1-deficient mice. We interpret these data to suggest that signalling mediated by Taar1 on the cilia of thyrocytes is critical for thyrocyte maturation and survival because it is involved in regulating the expression and activity of the cathepsins including cathepsin L that is critical to thyrocyte survival, TH processing and follicle maturation.

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OC2.3

PRKACA mutations in adrenal Cushing impair association with the PKA regulatory subunit

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In a previous study we found mutations in the main catalytic subunit of protein kinase A (PKA Cα) to be responsible for cortisol-secreting adrenocortical adenomas (ACAs). These mutations interfere with the formation of a stable holoenzyme, thus causing constitutive PKA activation. More recently, we identified additional mutations affecting PKA Cα in ACAs associated with overt Cushing syndrome: Ser213Arg_Leu212_Lys214insIle-Ile-Leu-Arg, Cys200_Gly201insVal, Trp197Arg, del244-248 + Glu249Gln, Glu32Val.
Here, we have performed a functional characterization of these new PKA Cα mutations. Specifically, we evaluated the basal association between PKA regulatory and catalytic subunits using co-immunoprecipitation as well as PKA activity with a kemptide assay.
All analyzed mutations with the exception of Glu32Val showed a reduced interaction with the regulatory (RIIβ) subunit. The interaction with the regulatory (RIα) subunit was affected also for all mutants except Glu32Val and Trp197Arg. The control of cAMP on the dissociation of the regulatory and the catalytic subunit was not affected. Two mutations (del244-248 + Glu249Gln and Trp197Arg) caused an increased basal PKA activity. Two mutations (Cys200_Gly201insVal and Ser213Arg_Leu212_Lys214insIle-Ile-Leu-Arg) were apparently inactivating, at least using kemptide as a substrate. The Glu32Val mutation did not affect the interaction with the regulatory subunit and showed a slightly increased PKA activity.
These findings suggest that interference with the formation of a stable PKA holoenzyme is a main mechanism leading to constitutive PKA activation in cortisol-secreting ACAs. Further studies are required to investigate the biological relevance and mechanisms of activation of the variants associated with decreased PKA activity.

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OC2.4

Link between cell cycle, steroidogenesis and PKA in adrenocortical tumors cells

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The cyclic AMP/PKA signalling cascade and PKA subunits are involved in the pathogenesis of a subset of cortisol-secreting adrenocortical tumors (ACT). In addition, steroid excess causes morbidity of all types of ACT.
The PKA regulatory subunits *PRKARIA, PRKARIIb* control proliferation/apoptosis in the H295R adrenocortical cell line. Their inactivation enhances the accumulation of cells in the G2 phase, increases steroidogenesis and activates the PKA and MAPkinases pathways.
The goal is to study the correlation between the cell cycle phases and the steroid secretion, and its control by PKA in H295R cells.
Methods
Using pharmacologic drugs, cells were synchronized at specific cell cycle check point (G1 phase), (S phase) and (G2 phase). We analysed the cell cycle distribution (Cytometry), the expression, of cyclins and cdks, the PKA subunits and cell signalling pathways, the expression of StAR and steroidogenic enzymes. We studied the effect of PKA activation by *PRKARIA* inactivation and *PRKACAa* overexpression along the cell cycle synchronization.
Results
The synchronization of H295R cells at G2 phase increased the expression of the steroidogenic enzymes and steroid secretion. Arresting H295R in G1 phase decreased the *steroidogenic enzymes* expression resulting in a decrease of cortisol secretion. PKA subunits distribution and PKA activity were modulated during the cell cycle progression.
Moreover the *PRKARIA* inactivation counteracted the decrease of steroidogenesis by enhancing StAR/luc reporter gene activity only in cells arrest in G1 phase, and enforced their progression in G2 phase. While *PRKACAa* overexpression increased the StAR/luc reporter gene activity, independently of the cell cycle check point arrest.
In Conclusion; we have demonstrated a tight link between the cell cycle check points and the regulation of steroidogenesis, where the *PRKARIA* subunit had a role as a key regulator of cell cycle and steroidogenesis in low steroidogenic G1 phase arrested cells.

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OC2.5

11β-HSD1 is a regulator of brown adipose tissue function and mediates stress adaptation in glucocorticoid excess

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Glucocorticoids (GC) are critical to stress adaptation but in excess (Cushing's syndrome) drive metabolic dysfunction. 11β-hydroxysteroid dehydrogenase type 1(11β-HSD1) amplifies intracellular GC signaling with 11β-HSD1KO mice

protected from the side-effects of GC excess. Brown adipose tissue (BAT) function is impaired by GC's, which repress UCP1 and beta-adrenergic stimulated thermogenesis. Identifying mechanisms regulating BAT function is important as humans have metabolically useful BAT, with more active BAT associated with enhanced energy dissipation. We postulated 11β-HSD1 plays a novel role in controlling BAT GC exposure, moderating thermogenic capacity. To test this 11β-HSD1KO mice were administered corticosterone over 4-weeks mimicking GC excess and BAT function assessed. Cultured BAT adipocyte energy metabolism was assessed measuring Oxygen consumption rates (OCR) ± GC ± beta-adrenergic stimulation. Profiling by qPCR and immunoblot for metabolic and mitochondrial function was conducted. GC excess increases 11β-HSD1 and impairs BAT in WT mice which display decreased UCP1 protein, expression of BAT-specific markers (PGC1a, PPARg, TFAM), and reduced OxPhos complexes content. Conversely, 11β-HSD1KO mice retained UCP1 to untreated control levels, resisted suppression of BAT expression markers and maintained expression of OxPhos complexes. GC exposed primary brown adipocytes from 11β-HSD1KO resisted suppression of UCP1 and of BAT genes. KO cells also demonstrated enhanced adaptation to cold stress at 30°C. Also KO cells have 30% higher basal OCR, which is not supressed by GC. Finally, beta-3 adrenergic stimulation of the BAT thermogenic program was enhanced in 11β-HSD1KO by 20%, and again was not supressed by GCs. We show that 11β-HSD1 regulates BAT energy metabolism and cell autonomous control of the thermogenic program in response to cold stress and beta-adrenergic stimulation. BAT may contribute to the metabolic derangements seen in GC excess through suppression of its capacity to dissipate energy, suggesting inhibition of 11β-HSD1 in BAT in the context of Cushing's syndrome may be beneficial.

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Diabetes prediction & complications

OC3.1

Identification of a spliceosome-associated fingerprint with potential to predict development of type 2 diabetes in high-risk patients

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Prevalence of metabolic syndrome (MetS) and type-2 Diabetes (T2D) is growing dramatically worldwide. Loss of phenotypic flexibility, i.e. the difficulty to cope with different stressors to maintain metabolic homeostasis, contributes critically to the development of MetS/T2DM. Thus, it is essential to identify the key modifiers of phenotypic plasticity that define an individual's susceptibility to develop T2DM. In this scenario, emerging evidence indicates that, under adverse metabolic conditions, the splicing machinery is markedly dysregulated in many tissues. We hypothesized that such a dysregulation could contribute to loss of phenotypic flexibility, and, as gene expression pattern in PBMCs commonly reflects disease-characteristic expression patterns, we reasoned that changes in spliceosome components of PBMCs might serve as biosensor/early indicators of MetS/T2D. To test this notion, expression of selected components of the major ($n=13$) and minor spliceosome ($n=4$), and associated splicing factors ($n=28$) was evaluated in PBMCs from 40 patients, who were initially non-T2D but in high-risk to develop T2D, and had suffered a prior cardiovascular event (CORDIOPREV study). Actually, during the 3-year follow-up, 20 individuals developed T2D and 20 did not (controls). PBMCs were isolated from basal and 4-h post-prandial blood, at the inclusion in the study and after 3-years. Results revealed that initial expression of relevant splicing factors and spliceosome components was altered in PBMCs from individuals who subsequently developed T2D. However, the most remarkable changes were observed during the post-prandial response, wherein expression of several splicing factors (e.g. Magoh, SRSF2, SRSF4, Tra2beta) was drastically induced in T2D-developing individuals compared to control patients, not developing T2D after 3-years of follow-up. These results reveal the existence of pre-TD2 development-associated spliceosome alterations, which could be related to the loss of phenotypic flexibility, and could help to predict, as a "splicing fingerprint", development of T2D in high-risk patients.

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OC3.2

Glucose-dependent insulinotropic peptide (GIP) stimulates Glucagon-like peptide (GLP)-1 from human and mouse pancreatic islets partly via alpha-cell-derived IL-6

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Introduction
Glucose-dependent insulinotropic peptide (GIP) induces the cytokine interleukin (IL)-6 in adipocytes. IL-6 enhances insulin secretion from β-cells via L- and α-cell-derived GLP-1.Therefore we hypothesized that GIP regulates Glucagon-like peptide (GLP)-1 as well as glucose control via IL-6.
Methods/Design
Basic research study on isolated human and mouse pancreatic islets and FACS-sorted human α-and β-cells that were treated with GIP in vitro. For in vivo studies, GIP effects on GLP-1 and insulin secretion as well as glucose homeostasis were evaluated in mouse models with pharmacologic and genetic ablation of IL-6.
Results
GIP induced IL-6 in mouse and human pancreatic α-cells, leading to GLP-1 and insulin secretion in pancreatic islets. This effect was impaired in the absence of IL-6 and modulated by IL-1β which stimulated IL-6 but directly impaired GLP-1 production. Furthermore, inhibition of the sodium glucose transporter (SGLT)2 with dapagliflozin - enhanced GIP-induced GLP-1 release. *In vivo*, GIP increased plasma GLP-1 and insulin, and improved glucose tolerance, which was potentiated by lipopolysaccharide and strongly decreased in IL-6-deficient mice or in the presence of a blocking anti-IL-6 antibody. In diabetic mice, IL-1β and IL-6 were massively upregulated in isolated islets and GIP lost its effects on glycaemia control and GLP-1 induction.
Conclusion
These data indicate that GIP induces GLP-1 and insulin via α-cell-derived IL-6, and that this effect is modulated by IL-1β and SGLT2 inhibtion. During diabetes, the prevailing inflammation may attenuate GIP effects. These findings further support the concept that the immune system plays an integral role in the regulation of metabolism in physiology and pathology.

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OC3.3

Reproducibility of fasting and oral glucose tolerance test derived parameters of glucose metabolism in non-diabetic postmenopausal women.

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Introduction
Given the importance of establishing a reliable diagnosis of impaired glucose metabolism and diabetes mellitus (DM), knowledge on accurate and reproducible parameters is needed. However, little is known on the reproducibility of fasting and oral glucose tolerance test (OGTT) derived parameters, especially with respect to the 2-hour derived parameters.
Objectives
To determine reproducibility of parameters of glucose metabolism in a non-diabetic postmenopausal population.
Materials and methods
Thirty seven non-diabetic postmenopausal women (54 ± 3 years, BMI 24.9 ± 4.5 kg/m^2) underwent two 75 g OGTTs with a 6 week interval. Serum C-peptide

and insulin were determined using the immunoanalyzer COBAS e411 (Roche). Glucose was analysed by the hexokinase method (COBAS, Roche). Fructosamine was determined on the P-modular (Roche). To investigate reproducibility, coefficient of variation (CV), reported as median (Q1-Q3), was calculated and compared using a Mann-Whitney U test. The least significant difference (LSD) was calculated as $t_{0.05/2.DFw} * (MSw * 2/n)\hat{}(0.5)$.

Results

Fructosamine (CV = 1.98 (0.87–4.73)%, LSD = 8.53 µmol/l) and fasting glucose (CV = 3.33(0.88–6.38)%, LSD = 5.67 mg/dl) showed high reproducibility. In contrast, fasting C-peptide (CV = 9.27(5.07–13.14)%, LSD = 0.40 µg/l) and fasting insulin (CV = 16.64(7.21–26.67)%, LSD = 3.46 mU/l) had low reproducibility compared to fructosamine and fasting glucose (all $P < 0.001$). Reproducibility of 2 h-glucose (CV = 8.53(3.79–17.21)%, LSD = 19.4 mg/dl), 2 h-C-peptide (CV = 17.46(5.18–23.73)%, LSD = 1.78 µg/l) and 2 h-insulin (CV = 25.13(17.51–49.19)%, LSD = 27.54 mU/l) were lower compared to fasting values (all $P < 0.05$). Time-dependent parameters, such as early insulinogenic (CV = 23.34(13.50–42.86)%) or early peptidogenic index (CV = 13.17(7.19–38.12)%), generally showed lower reproducibility.

Conclusion

Whereas fasting parameters of glucose metabolism, especially fructosamine and glucose, show high reproducibility in a non-diabetic postmenopausal population, this is not the case for fasting insulin and particularly the 2-hour OGTT derived parameters. This is clearly reflected in their respective LSD, which should be kept in mind in both clinical practices as well as in interventional studies.

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OC3.4

Association of neutrophil to lymphocyte ratio with vitamin D levels in type 2 diabetes mellitus

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Introduction

Increased neutrophil to lymphocyte ratio (NLR) is an inflammatory marker and an indicator of cardiovascular risk. Recent studies demonstrated that the NLR values of the diabetic patients were significantly higher than the healthy controls. Vitamin D (25OHD) deficiency has been associated with diabetes mellitus and cardiovascular diseases. Studies established a significant negative correlation between 25(OH)D and HbA1c levels. Aim of this study is to evaluate the association between 25(OH)D status and inflammation by using NLR.

Methods

Diabetic patients who admitted to our outpatient clinic between January-December 2015 were assessed retrospectively. Patients with cardiac comorbidity including hypertension, any acute or chronic inflammatory disorder and cigarette smokers were excluded. A total of 248 cases (151 female, 97 male; mean age 55.81 ± 8.86) were included in the study. Anthropometric and laboratory findings were recorded. Patients were grouped according to 25(OH)D levels (Group 1 = 25(OH)D < 30 ng/ml and group 2 = 25(OH)D > 30 ng/ml).

Results

Groups were age, sex and BMI-matched. Duration of diabetes were similar in both groups (4.69 ± 3.9 vs 6.33 ± 5.62 years; $P = 0.107$). There is no association between 25OHD and HbA1c levels ($P = 0.854$). Triglyceride levels were higher (182.53 ± 120.17 vs 151.44 ± 58.00 mg/dl) and HDL levels were lower in group 1 (44.89 ± 15.71 vs 49.73 ± 12.69 mg/dl) but these differences didn't reach the statistical significance ($P = 0.11$ and $P = 0.06$ respectively). In the 25(OH)D insufficient group, NLR were significantly higher than the adequate group (2.05 ± 0.67 vs 1.59 ± 0.42; $P = 0.000$).

Conclusion

Our results established higher NLR values in 25(OH)D insufficient diabetic patients and emphasized the increased cardiovascular risk in 25(OH)D deficiency.

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OC3.5

Improvement in diabetic neuropathy after metabolic surgery a comprehensive electrophysiological follow up study

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Aim

In the present study, we aimed to analyze the incidence of diabetic neuropathy (DN) via electrophysiological testing of type 2 diabetes mellitus (T2DM) patients scheduled for laparoscopic diverted sleeve gastrectomy with ileal transposition (DSIT). At a mean of 8 months after surgery, the electrophysiological tests were repeated and differences in electrophysiological parameters were evaluated to investigate the effects of the operation on outcomes related to diabetic neuropathy.

Methods

This cross sectional, non-blinded, prospective, pilot study included 55 severely diabetic non-responders, who fail to achieve adequate glycemic control despite appropriate medical treatment. Autonomic tests including motor and sensory nerve conduction studies (NCS), sympathetic skin response (SSR) and R-R interval analysis of patients scheduled for metabolic surgical treatments were performed pre- and postoperatively. The differences in metabolic and electrophysiological parameters were also analyzed. SPSS 15.0 for windows was used for statistical analysis. χ^2 test, a non-parametric test, was used to analysis the difference in the data obtained from the all groups.

Results

Patients had mean diabetes duration of 13.4 ± 7 years. Preoperative values of mean HbA1c, body weight and Body Mass Index (BMI) were 9.6 ± 2%, 94.0 ± 14.7 kg and 34.0 ± 5.1 kg/m^2 and decreased to 6.6 ± 1%, 71.7 ± 13.3 kg and 26.1 ± 3.5 kg/m^2 postoperatively ($P < 0.001$, each). Preoperative NCS evaluation revealed presence of polyneuropathy in 27 (49%) individuals; however, postoperative NCS measures showed decreased distal conduction time in 61%, increased response amplitudes in 40% and increased conduction velocity in 57% of patients for motor nerves. As for sensory nerves, decreased distal conduction time was found in 55% and increased response amplitudes in 57% of patients. In addition, significant improvements were observed in the of SSR and R-R interval analysis postoperatively.

Conclusion

Beyond the improvements in metabolic parameters and BMI in our diabetic patients who underwent DSIT, we also observed improved NCS results. Improvement in NCS variables may be interpreted as a result of better glycemic control.

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Thyroid - Clinical

OC4.1

Additional measurement of hCG distinguishes physiological high-normal thyroid function and reveals large differences in the risk of developing preeclampsia

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Context

Preeclampsia is a leading cause of maternal and perinatal morbidity and mortality worldwide, affecting 2–8% of all pregnancies. We have previously shown that women with high-normal levels of FT4 during early pregnancy have a 2.1-fold increased risk of preeclampsia – but there was no apparent association with low TSH. However, the thyroid is stimulated by human chorionic gonadotropin (hCG) during early pregnancy and therefore we hypothesized that women with high-normal thyroid function due to high hCG levels would have a different risk of preeclampsia as compared to women with high-normal thyroid function and low hCG.

Design, Setting, and Participants
In 5153 women TSH, FT4, hCG and TPO-antibody levels were measured during early pregnancy ($<18^{th}$ week). The association of high-normal FT4 (5^{th} quintile) or low TSH with preeclampsia was analysed using multivariable logistic regression stratified per 20.000 IU/l hCG (up to >60.000). All analyses were adjusted for gestational and maternal age, smoking, education, ethnicity, parity, BMI and fetal gender.
Results
The combination of high-normal FT4 levels with low hCG (<20.000 IU/l) was associated with an 11.1-fold increased risk of preeclampsia ($P<0.05$).
The combination of low TSH with low hCG (<20.000 IU/l) was associated with an increased risk of preeclampsia ranging between a 9.2-fold increased risk for TSH <0.1 mU/l, to an 8.7-fold increased risk for TSH $<5^{th}$ percentile and to an 3.8-fold increased risk for TSH <0.4 mU/l (all $P<0.05$).
The combination of high-normal FT4 and hCG > 20.000 or low TSH and hCG>20.000 was not associated with an increased risk of preeclampsia. All analyses remained similar after exclusion of TPOAb positive women.
Conclusion
The additional measurement of hCG in women with high normal thyroid function tests markedly improves the identification of women at high-risk of developing preeclampsia. This is likely to be due to the fact that hCG measurements allow for distinguishing physiologically high thyroid function caused by high hCG levels from pathophysiological high thyroid function due to autonomous production and/or TSH receptor stimulation antibodies.

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OC4.2

Molecular fingerprint of experimental thyrotoxicosis on human metabolism: combined metabolome and proteome study

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The functional state of the thyroid is usually determined by thyrotropin (TSH), whose serum levels depend on circulating thyroid hormone (TH) levels. This feedback mechanism is tightly controlled in the individual and contrasts broad reference range for TSH in the general population, leading to the concept of subclinical thyroid disease. We studied a model of experimental thyrotoxicosis in humans employing an untargeted metabolome and proteome approach. This allowed us to gain a comprehensive picture of TH action on human metabolism as well as to derive metabolic surrogates for thyroid function.
Levothyroxine was prescribed to sixteen healthy young men at a dose of 250 µg/day for 8 weeks. Plasma was samples were obtained every 4 weeks, starting before the treatment and ending 8 week after stopping the application. Mass spectrometry was used to determine protein and metabolite levels. Serum free thyroxine (FT_4) concentrations were associated with metabolite/protein levels by means of mixed-effect linear regression models in a subsampling setting. Predictive character of a bio-molecule signature for thyrotoxicosis was assessed by a random forest via a two-stage cross-validation procedure, separating training and validation.
Strong molecular alterations were observed despite no indication of clinical symptoms. Metabolites and proteins were affected to a similar amount (~60 each). TH action on lipid and amino acid metabolism could be confirmed and extended. Novel findings included a strong, positive association with γ-glutamyl amino acids. Significantly associated proteins were aggregated into pathways and revealed established TH targets, e.g. coagulation cascade and apolipoproteins, but also novel associations related to the complement system. A signature of 15 metabolites/proteins attained promising (AUC=0.86) discrimination between thyrotoxicosis and euthyroidism.
The use of untargeted OMICS approaches allowed us to reveal novel pathways of TH action and possess ability to identify new molecular signatures, beyond TSH and FT_4, for diagnosis and treatment of thyroid disorders.

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OC4.3

Antibodies against human eye muscle tissue fractions bind to type 2 5'deiodinase and inhibit the lymphocyte MAPK activation derived from hyperthyroid patients with Graves' disease

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Type 2 5'-deiodinase (DIO2) is a common enzyme between thyroid and eye muscle tissues involving in T_4 conversion to T_3. The role of DIO2 has been demonstrated in the development of skeletal muscle. Increased DIO2 activities was connected to eye muscle enlargements in hyperthyroid Graves' ophthalmopathy. In this study, the presence of antibodies against human eye muscle tissue fractions with the binding to DIO2 peptide was investigated and measured their inhibiting effects on lymphocyte mitogen-activated protein kinase (MAPK) activation.
Antibodies against DIO2 peptide (aa 123–143) and human eye muscle membrane (EyeM) and cytosol (EyeC) fractions were measured in 74 patients with Graves' disease and 32 controls using ELISA assay. Thyroid hormones and antibiodies against thyroid peroxidase and thyroglobulin were detected by chemilimunescence assay. TSH receptor antibodies and MAPK activation were measured by radio-immune assays.
Hyperthyroid Graves' patients without ophthalmopathy ($n=30$) showed more frequent binding to DIO2 peptide than patients with ophthalmopathy ($n=23$): 5 cases (37.5%) vs none for anti-EyeM IgG out of 8; 6 cases (20%) vs none for anti-EyeC IgG out of 30; $P<0.02$; 3 cases (25%) vs none for anti-EyeC IgM out of 12. Correlation was demonstrated between anti-EyeM IgG ($P<0.01$, $r=0.3507$) or anti-EyeC IgM ($P<0.02$, $r=0.3178$) and anti-DIO2 peptide antibodies. In hyperthyroidism, anti-DIO2 peptide antibodies correlated positively with TSH ($P<0.01$, $r=0.3498$) and inversely with FT_4 ($P<0.05$, $r=-0.2757$) levels. Hyper-thyroid Graves' patient sera with cross reactivity to DIO2 peptide inhibited lymphocyte MAPK activations after 0 and 120 minutes compared with those using control sera.
The results highlighted a cross reactivity between anti-EyeM or –EyeC and anti-DIO2 peptide antibodies. Anti-DIO2 peptide antibodies demonstrated inverse correlation with FT_4 levels and inhibited lymphocyte MAPK activations. Therefore, anti-DIO2 peptide antibodies may be responsible for lower FT_4 levels via decreased MAPK activation highlighting their protective roles against the development of ophthalmopathy.

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OC4.4

Thyroid function and glucose metabolism in adults after hematopoietic stem cell transplantation

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Aim
Endocrine and metabolic disorders are among the most common complications in survivors after hematopoietic stem cell transplant (HSCT). The aim of this study was to evaluate thyroid function and glucose metabolism in patients treated with HSCT.
Material and methods
This was a retrospective study which included 257 adult patients (173 males and 84 females) who underwent allogeneic HSCT between 2002 and 2014 in an Irish University Hospital. All patients were preconditioned with chemotherapy and total body irradiation (TBI). 121 patients received HSCT from unrelated donor, with 52.9% receiving HCST from related donors. Thyroid function was assessed early post HSCT (0–3 months), in the intermediate period (3–12 months) and late post HSCT (>12 months) with screening for diabetes at a median of 10 months (S.D. 18.21)
Results
The median age at diagnosis was 33 years (SD 10.45), with a median age at treatment of 35.3 years old (S.D. 10.27). The most common indication for HSCT was acute lymphoblastic leukaemia (39.68%) and the most used preconditioning regime was TBI/Cyclophosphamide (90.27%). 25 patients had thyroid function assessment in the early period of whom 32% had thyroid dysfunction. In the intermediate period, 86 patients were assessed, 19.76% of whom had thyroid abnormalities. In the late period, 172 patients had thyroid function assessment with 38.95% having an abnormal test. The 2 most frequent abnormalities were

subclinical hypothyroidism, and a low FT4 with an inappropriately low or normal TSH. 45 patients had HbA1c testing, with 48.88% being diagnosed with diabetes (HbA1c > 6.5%) and 11.11% with pre-diabetes.
Conclusion
Our study provides evidence that the incidence of thyroid dysfunction and glucose metabolism abnormalities is higher post HSCT than in the general population. This emphasizes the need for long term screening for thyroid dysfunction and diabetes in the post HSCT population.

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OC4.5

Risk factors of relapse in Graves' disease? Results from a systematic review and meta-analysis

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Context
Identification of risk factors predicting relapse in patients with hyperthyroidism of Graves' disease after the first cycle with standard thyreostatic therapy [ATD] is important to guide therapeutic options.
Objective
We performed a systematic review and meta-analysis to study predictors for risk of relapse after the first treatment episode with ATD in patients with Graves' disease induced hyperthyroidism.
Data sources
Based on a pre-specified protocol, we searched PubMed, EMBASE and Cochrane in July 2015 for case-control, controlled, and randomized-controlled trials analyzing risk factors for relapse after ATD treatment. The endpoint was relapse of disease until follow-up.
Data extraction
PRISMA and SIGN statements were used for reviewing the data and assessing quality of included trials.
Data synthesis
We included 54 trials with totally 8206 participants. Most trials were small with moderate to high risk for bias. Gene data were only qualitatively assessed. 31 trials were assessed quantitatively. There were 2053 relapses in 4398 patients. By random-effects meta-analysis (standardized mean difference - Hedges' g; 95% CI) orbitopathy (1.16; 1.08; 1.25), goiter (0.18; 0.07; 0.30), smoking (1.13; 1.02; 1.25), thyroid volume by sonography (−0.58; −0.90; −0.18), fT4 (−0.16; −0.28; −0.05), tT3 (−0.25; −0.46; −0.04), TRAb (−0.33; −0.62; −0.04), TBII (−0.36; −0.63; −0.09), TSAb (−0.26; −0.45; −0.06) did show a significant predictive value, whereas male (1.08; 1.0; 1.18) or female (0.98; 0.93; 1.02) sex, age (0.14; −0.07; 0.35), and tT4 (0.04; 0.23; 0.31) did not.
Conclusions
This analysis found several risk factors to predict relapse in Graves' disease which can be combined in a risk score. Prospective studies should evaluate the prognostic accuracy of such a score to guide treatment decisions.

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Neuroendocrinology

OC5.1

The Drosophila AIP orthologue is essential for actin cytoskeleton stabilisation and cell adhesion

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Introduction
Tumours with *aryl hydrocarbon receptor interacting (AIP)* mutations often show an unusually aggressive and invasive clinical course as up to 80% of AIP positive pituitary adenomas have a certain degree of extrasellar extension. The exact mechanisms by which AIP inactivation promotes an aggressive behaviour remain unknown. The majority of adenohypophysis is composed of sinuous cords of epithelial cells and consequently, molecules that can induce remodelling changes in the epithelial tissue of the normal pituitary gland are of a particular interest.
Methods
The *Drosophila melanogaster* AIP orthologue gene *CG1847* encodes for a protein with a similar size and structure. To study *CG1847*, we generated loss of function flies using two independent methods: RNA-interference and gene knockout via *P*-element imprecise excision. We specifically addressed *CG1847* function in the developing *Drosophila* wing, a tissue consisting of only two epithelial layers. We evaluated the resulting phenotypes in 2 stages of development: at pupal stage and at adulthood.
Results
Silencing or deletion of *CG1847* caused wing blisters in adults. Analysis of developing wings at pupal stage revealed a marked deregulation of the actin network in the wing epithelium, which resulted in loss of adhesion between the two cell layers. Furthermore, actin dysregulation resulted in wing vein widening as vein cells failed to form a lumen, enhancing the loss of adhesion phenotype.
Conclusions
In conclusion, the study of *CG1847,* the *Drosophila* orthologue of human AIP, revealed an exciting novel role for this protein in cell adhesion. The mechanism of CG1847 involvement in cell adhesion is via actin cytoskeleton deregulation, supported also by the wing vein widening. This novel possible interaction with cytoskeletal proteins suggests a putative involvement of AIP in cell motility and tumour invasiveness as cytoskeletal disorganisation is an important feature of epithelial-mesenchymal transition, a process leading to increased migratory capacity resulting in a more aggressive phenotype.

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OC5.2

Analysis of signal transduction in mice overexpressing mutant versus intact IGFBP-2 identifies a plethora of IGFBP-2 dependent mechanisms in different tissues and suggests permissive or regulatory effects of the RGD-sequence

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IGFBP-2 represents a multifunctional protein with effects on growth, reproductive development, aging, and metabolism. For the expression of these diverse effects *in vivo*, IGFBP-2 has a number of binding sites for IGFs, integrins, and proteoglycans. In order to assess the relative contributions of these binding sites to the multiple effects of IGFBP-2, we have developed transgenic mouse models overexpressing intact or mutant IGFBP-2. Here we discuss functions of the RGD-sequence present in the IGFBP-2 molecule and that has been demonstrated to mediate integrin binding *in vitro* and *in vivo*. Overexpression of intact IGFBP-2 in transgenic mice (D-mice) significantly ($P < 0.05$) slowed down glucose clearance in the oral glucose tolerance test (GGT). By contrast, overexpression of mutant IGFBP-2 lacking the RGD sequence in transgenic mice (E-mice) did not affect glucose tolerance if compared to non-transgenic littermates (C-mice). We therefore may assume that the effects of IGFBP-2 on glucose clearance after GTT are dependent on the RGD-sequence. While the effects of the RGD-motif for glucose clearance were present both in male and female mice, the RGD-sequence mediates higher life expectancy or long term survival only in female but not in male mice. For somatic growth presence or absence of the RGD-sequence has no effect in both genders. Now we performed a comprehensive analysis of signal transduction (integrin signaling, MAPK and PI3K signaling pathways) in different tissues of our experimental system. Interestingly, intact and mutated IGFBP-2 disrupted intracellular cell signaling in a number of tissues. Depending on age, sex and tissue specific effects of the presence or absence of the RGD domain have been observed. We may thus assume that the RGD-sequence has both permissive and regulatory functions for intracellular signaling. By using transgenic mice overexpressing normal or mutated IGFBP-2 we provide evidence that the pleiotropic network can be assessed on a mechanistic level.

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OC5.3

Development of a long-acting growth hormone antagonist for the treatment of acromegaly

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Background
The UK acromegaly register reported that <60% of acromegalics on medical therapy had controlled disease (1). Pegvisomant, a growth hormone antagonist (GHA), controls disease in >95% cases, but is not cost-effective and requires high dose daily injections (2). We have developed a fusion technology for making a cost-effective long-acting GH molecule (3), and generated a GHA by linking mutated growth hormone to its binding protein (GHBP).
Design of GHA
A mutation (G120R) within site 2 of GH produces a receptor antagonist and mutations in site 1 enhance binding creating a super antagonist. Linking to GHBP delays clearance but site 1 in GH can bind to GHBP reducing activity. We hypothesised that the W104A mutation in GHBP would prevent intramolecular binding and generate a potent antagonist.
Methods
Four target molecules were gene synthesised to include either site 2 mutation (GHA1), site 1 & 2 mutations (GHA2), site 2+W104A mutations (GHA3) and site 1 & 2+W104A mutations (GHA4). In vitro bio-potency of CHO purified protein was measured using GH-specific bioactivity assays.
Pharmacokinetics
Rats were given 1 nMole/kg (i.v) of GHA1-4. GHA from serum was quantified using an in-house GH ELISA.
Pharmacodynamics
Rabbits were given 2 mg/kg (s.c). GHA from serum was quantified using an in-house GH ELISA. IGF-I levels were analysed using an automated assay.
Results
Median IC50s of 45 nM (GHA1); 133 nM (GHA2); 40 nM (GHA3) and 16 nM (GHA4) were obtained. GHA4 antagonist activity was comparable to Pegvisomant. GHA1, 2, & 4 had similar terminal half-life's >20 h. Only GHA4 induced a reduction in IGF-I in rabbits of 14% with an associated reduction in weight gain.
Conclusions
GHA4 has the potential to be a long-acting potent GHA with no requirement for post-translational modification and is likely to be a cost-effective treatment for acromegaly.

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OC5.4

CNS IL-6 Trans-Signaling is enhanced in obese mice to improve anorexigenic and glucoregulatory effects of IL-6

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Introduction
Interleukin (IL)-6 can activate signal transducer and activator of transcription (STAT)3-dependent signaling similar to leptin in neurons. Here we demonstrate that central application of IL-6 suppresses feeding and improves glucose tolerance in mice. Furthermore, we found that central IL-6 trans-signaling is enhanced in obese mice to improve anorexigenic and glucoregulatory effects of IL-6.
Methods/design
Glucose tolerance and insulin sensitivity as well as food intake and pSTAT3 expression were investigated upon central application of IL-6 or hyper-IL-6, a fusion protein of IL-6 and its soluble receptor, in high-fat diet-fed and chow-fed control mice as well as in mice lacking the IL-6R in the whole body or in distinct areas of the hypothalamus (Nkx2.1-Cre;IL-6Rα-flox mice) or the forebrain (CamKIIα-Cre;IL-6R-flox mice). IL-6 trans-signaling in the central nervous system (CNS) was inhibited by intracerebroventricular administration of soluble gp130 (sgp130Fc), an inhibitor of soluble IL-6Rα (sIL-6R) complexed with IL-6. Furthermore, the concentration of endogenous sIL-6R was assessed in cerebrospinal fluid (CSF) and plasma of obese and lean mice.
Results
In contrast to leptin, the action of which is attenuated upon obesity development, the ability of IL-6 to suppress feeding is enhanced in obese compared to lean mice. Surprisingly, IL-6 suppresses feeding in the absence of classical IL-6-receptor (IL-6R)-dependent signaling in neurons of mice lacking the IL-6R either specifically in hypothalamic or in all forebrain neurons. Accordingly, obese mice exhibit increased concentrations of the soluble IL-6 receptor in the CSF, and blocking IL-6-trans-signaling via central injection of sgp130Fc abrogates the ability of IL-6 to suppress feeding. Similarly, central injection of hyper-IL-6 suppresses feeding in mice completely lacking expression of the membrane bound IL-6R.
Conclusion
Collectively, these experiments indicate that in obesity IL-6-trans-signaling is enhanced in the CNS of obese mice, allowing IL-6 to exert its beneficial metabolic effects even under conditions of leptin resistance.

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OC5.5

Zebrafish tool for the study of prokineticin receptor 2 (PROKR2) pathway on GNRH3 neuronal development

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The G protein-coupled receptor PROKR2 play an important and not fully understood role in GnRH-secreting neurons physiology. Indeed, mutations of PROKR2 in humans are known to cause Congenital Hypogonadotropic Hypogonadism (CHH) although with an important reproductive and olfactory phenotypic heterogeneity. The attempt to mimic PROKR2 human allelic variants in mouse model has so far failed to give insights into the mechanisms involved. The zebrafish (ZF), due to its amenability to genetic manipulation and imaging, has proved to be an ideal model organism for studying the early migration of GnRH neurons and the formation of the GnRH network. Nevertheless, only few data are available in the literature concerning the prokineticin-receptors in ZF. We performed bioinformatics analysis using public databases (Pubmed, ZFIN and ENSEMBLE) and bioinformatics tools (UCSC BLAT alignment, Genomicus) unmasking the presence of two well-conserved loci in the ZF genome, on chr1 and chr13, named prokr1a and prokr1b respectively. In order to correlate their expression with GnRH3 neuronal development we performed whole mount *in situ* hybridization (WISH) and qRT-PCR experiments. WISH experiments revealed peculiar pattern of expression for prok-receptors. Indeed, prokr1a is mainly expressed in midbrain-hindbrain boundary at 36 and 48 hpf and later in development in liver; while prokr1b presented a strong signal in olfactory placode and hypothalamic GnRH neurons starting from 36 hpf. The qRT-PCR results underline how prokr1b displayed higher expression level compared to prokr1a but, most interesting, the expression level start to increase at 24 hpf until 72 hpf, consistently with the migration pattern of GnRH3 fibers. In conclusion, our results suggest that prokr1b is the potential candidate involved in the GnRH-secreting neurons migration process from olfactory placode to their final hypothalamic destination. These data open the possibility to characterize the role of ZF prokineticin-receptors in physiological and pathological conditions thus giving novel insights into the pathogenesis of human CHH due to mutations in the PROKR2 gene.

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Diabetes therapy & complications

OC6.1

Choroidal thickness in diabetes mellitus type 1 without clinical diabetic retinopathy

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Purpose
To determine the changes of the choroidal thickness (CT) in diabetes mellitus (DM) type 1 patients without clinical diabetic retinopathy (DR).

Methods
We evaulated 50 patients with DM type 1 (50 eyes) and 50 healthy controls (50 eyes) in İzmir Military Hospital from January 2012, through January 2013. DR status was evaluated by indirect fundoscopy and included the study if they have no clinical diabetic retinopathy. Age, gender, duration since diagnosis of diabetes, fasting glycose level and serum glycosylated hemoglobin (HbA1c) were gathered from the patient charts. Right eyes of the each study and control groups were examined with spectral domain optical cohorens tomography (SD-OCT). Average macular thickness, central foveal thickness were calculated in macula map. Choroidal thickness was measured at 7 points for each patient: subfoveal, at 500, 1000, 1500 μm nasal and temporal by using the Nidek SD-OCT software. Age, sex, spherical equivalent (SE), intraocular pressure (IOP) and axial length (AL) were compared among groups by means of analysis of variance (ANOVA). Groups compared with Student *t* test.
Results
The mean HbA1c was 8.9±0.9% in the diabetic group. Mean duration of the diabetes was 6.1±2.8 years in study group. There were no statistical differences in age, gender, SE, AL, and IOP between groups ($P>0.05$). Subfoveal CT was 266.3±36.5 μm in study group and 278.9±32.8 μm in control group. It was significantly decreased in diabetic group versus control ($P<0.05$). Nasal 500, 1000, 1500 μm CT were decreased in study group ($P<0.05$). Temporal 500, 1000, 1500 μm CT were decreased in diabetic group. There was no differences according to the central macular thickness between groups.
Conclusions
Results of our study suggest that the general decrease of CT in patients with no retinopathy caused by early choroidal vasculopathy of DM. This results may guide the development of protective therapeutic strategies for avoiding the complications of DM in the future.
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OC6.2

Cortical bone size deficit in adult patients with type 1 diabetes mellitus
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Background
Impaired bone geometry and/or aberrant bone matrix formation may underlie the increased fracture risk observed in patients with type 1 diabetes mellitus (T1DM). Although reduced areal and volumetric bone mineral density (aBMD, vBMD) have been observed in pediatric and adolescent T1DM patients, few studies have confirmed these observations in adults. Moreover, data on bone geometry in T1DM remain scarce.
Objective
To compare areal and volumetric bone parameters and cortical bone geometry in adult T1DM patients and gender- and age-matched controls.
Methods
In 64 adult T1DM patients (39 men, 41.1±8.1 years) and 63 controls, areal and volumetric bone parameters and bone geometry were assessed using DXA and pQCT (radius: 4% and 66% regions).
Results
Median diabetes duration was 23.1 years, with a mean HbA1c of 63±5 mmol/mol over the last 10 years. In age-, height-, weight- and gender-adjusted analyses, T1DM was associated with lower aBMD and bone mineral content at the total hip (−5.14%, $P=0.011$ and −6.72%, $P=0.013$) and femoral neck (−7.43%, $P=0.003$ and −9.04%, $P<0.001$) and with lower femoral neck bone area (−2.82%, $P=0.014$). Cortical vBMD was higher in T1DM patients as compared to controls (+2.06%, $P=0.004$), but total vBMD was lower (−5.19%, $P=0.020$) and T1DM patients showed a cortical bone size deficit with smaller cortical thickness (−6.21%, $P=0.035$) and trends towards lower cortical area (−4.64%, $P=0.060$) and increased endosteal circumference (+5.29%, $P=0.074$). Furthermore, T1DM was associated with lower trabecular vBMD and higher trabecular area (−9.00% and +7.62%, $P=0.013$). Except for trabecular area, which was higher in male but not female T1DM patients as compared to controls, no major interactions between health status and gender were observed.
Conclusion
Besides decreased aBMD and trabecular vBMD, adult T1DM patients present with a cortical bone size deficit characterized by lower cortical thickness and higher endosteal circumference. This might contribute to the higher fracture risk observed in diabetic patients.
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OC6.3

TRAIL treatment reduces high-fat diet-induced hyperglycemia and hyperinsulinemia
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Introduction
Recent studies suggest that a circulating protein called TRAIL (TNF-related apoptosis-inducing ligand) may have an important role in the treatment of type 2 diabetes mellitus (T2DM). It has been shown that TRAIL deficiency worsens T2DM and that TRAIL delivery, when it is given before disease onset, slows down T2DM development. This study aimed at evaluating whether TRAIL had the potential not only to prevent, but also to treat T2DM.
Methods/design
30 male C57bl6J mice aged 8 weeks were randomly assigned to a standard diet (CNT, $n=10$), or a high-fat diet (HFD, $n=20$), providing 60% of calories from fat. After 4 weeks, HFD-fed mice were further randomized to receive either placebo (HFD, $n=10$) or TRAIL (HFD + TRAIL, $n=10$), which was delivered weekly by intraperitoneal injection. Body weight, food intake, fasting glucose and insulin were measured at baseline and every 4 weeks. GTT (glucose tolerance test) and ITT (insulin tolerance test) were performed at 6 and 12 weeks. After 12 weeks of study, the distribution of Cy5.5-labelled TRAIL was evaluated by whole-body scan. Then, mice were sacrificed and bloods and tissues (pancreas, quadricep, liver, adipose tissue) collected for further analyses.
Results
Cy5.5-labelled TRAIL gave the highest signal a few hours after being injected. Not with standing its rapid clearance, at the end of the study, TRAIL reduced body weight gain, without affecting food intake. Moreover, TRAIL reduced the hyperglycemia and the hyperinsulinemia displayed by the HFD-fed mice both at fasting and during the 12-week GTT, and it also significantly lowered glucose levels during the 12-week ITT, indicating an improvement in the peripheral response to insulin.
Conclusion
This study confirms the ability of TRAIL to significantly attenuate the metabolic abnormalities induced by a HFD, and shows that TRAIL is effective also when it is given after disease onset.
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OC6.4

LEA29Y expression in transgenic porcine islets prevents islet graft rejection in humanized mice without systemic immunosuppressive therapy
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Transplantation of pancreas or isolated Langerhans islets can cure type 1 diabetes. Xenografts from transgenic pigs represent a promising source to overcome the shortage of organ donors. We investigated the immunosuppressive effect of local LEA29Y expression (a high-affinity variant of CTLA4-Ig) by transplantation of neonatal porcine islet-like clusters (NPICCs) from *INS*LEA29Y transgenic pigs into humanized mice. NPICCs from 1–5 day-old pigs expressing LEA29Y under the control of the porcine insulin promoter (LEA-tg) or from wild-type pigs (wt) were transplanted under the kidney capsule (Tx) of streptozotocin-diabetic NOD-scid IL2Rgamma^{null} (NSG) mice (Tx-LEA-tg; Tx-wt). Xenorejection was investigated after transfer of human PBMCs (PBMC-NSG mice). Long-lasting effects of local LEA29Y expression were assessed by Tx in mice carrying a stable human immune system (transfer of hCD34$^+$ cells) (HSC-NSG mice). In PBMC-NSG mice, 80% of mice transplanted with wt-NPICCs ($n=5$) developed overt diabetes within 30 days after transfer of a human immune system indicating xenograft rejection. LEA-tg NPICCs were completely protected from rejection ($n=5$). In HSC-NSG mice, normalization of blood glucose levels (66.6%) and post-transplant glucose tolerance was comparable in Tx-LEA-tg ($n=12$) and immunodeficient control mice ($n=13$). All Tx-wt HSC-NSG mice remained hyperglycemic ($n=11$). In both animal models, graft-bearing kidneys revealed

destruction of wt-NPICCs with massive leukocyte (hCD45$^+$) and lymphocyte infiltration (CD4$^+$, CD8$^+$), which was absent in PBMC- and HSC-NSG mice transplanted with LEA-tg NPICCs. This is the first study providing evidence that beta-cell specific LEA29Y expression has a long-lasting protective effect on inhibition of human anti-pig xenoimmunity. This finding may have important implications for the development of a low-toxic protocol for porcine islet transplantation in patients with type 1 diabetes.

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OC6.5

Dapagliflozin added to lixisenatide in type 2 diabetic patients

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Introduction
Type 2 diabetes represents an important health problem and is designated by a progressive course. Since the vast majority of type 2 diabetic patients are overweight, there is a need not only to avoid weight gain but to lower body weight. Therefore, the usage of drugs that have the potential to lower body weight (GLP1 RA and SGLT2 -inhibitors) should with metformin be preferred initial therapy in the obese and overweight type 2 diabetic patients.
The aim of the study was to determine the efficacy of combination of dapagliflozin and lixisenatide in terms of glucose control and body weight change in type 2 diabetic patients.
Patients and Methods
62 uncontrolled diabetic patients on metformin + DPP-IV inhibitor ± SU (32 male, 30 female, mean age 62.5 ± 5.6 years, HbA1c 8.3 ± 0.8%, BMI 38.7 ± 3.2 kg/m^2 diabetes duration 7.2 ± 3.2 years) were randomised to metformin + lixisenatide (31 patients) or metformin + lixisenatide + dapagliflozin (31 patients) and followed for 6 months.
Results
A difference was observed in mean weight change −8.5 ± 4.2 kg in the group treated with metformin + lixisenatide + dapagliflozin, and −5.1 ± 4.7 kg in the metformin + lixisenatide group ($P = 0.09$). No difference between the lixisenatide and lixisenatide + dapagliflozin group was observed concerning the percentage of subjects reaching HbA1c < 7% (47% vs 50%). No difference was found in reduction of HbA1c (1.27% vs 1.21%).
Conclusion
Combination of lixisenatide and dapagliflozin represents highly potent treatment option in obese and overweight patients.
Combination of lixisenatide and dapagliflozin resulted in significant reduction of weight in comparison to lixisenatide alone with metformin. Interestingly, no difference in HbA1c level between the two groups was found. These results suggest that effect on weight loss is additive, but without effect on glucose control.

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Cardiovascular endocrinology

OC7.1

Lipoprotein lipase DNA methylation: cause or consequence of metabolic disorders

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Introduction
DNA methylation is one of the epigenetic mechanisms existing to regulate gene expression. It is believed that methylation of DNA is susceptible of change by environmental and nutritional factors. Thus, epigenetics provides a mechanism which may explain the etiology of some metabolic disorders and obesity.
Aim
The aim of this study is to analyze the DNA methylation level of several lipoprotein lipase (LPL)-promoter-CpG island in human visceral adipose tissue (VAT), as well as the gene and protein expression of this gene.
Material and methods
A total of 90 VAT samples were obtained during bariatric or hiatal hernia surgeries. Biochemical parameters from these patients were measured, and samples were assigned to two groups attending their BMI (BMI < 30, BMI > 30). We also assigned the samples according to glucose status in pre-diabetic/diabetic subjects (NG < 100 mg/dl, P/D > 100 mg/dl). Methylation level was measured through pyrosequentation, using the Pyromark technology and predesigned CpG methylation assays (Qiagen). The results were analyzed using the CpG methylation software (Qiagen) and the statistical package SPSS.
Results
We found higher levels of DNA methylation in P/D respect to NG subjects, while the gene expression was inverse. There was also a significant difference between subjects with BMI < 30 and subjects with BMI > 30, being lower the DNA methylation and higher the gene expression respectively. There was the same tendency in protein expression, with lower levels in PD subjects and lower levels in subjects with BMI > 30. Furthermore, LPL methylation and LPL gene expression correlated negatively. LPL methylation correlated positively with insulin, glucose, triglycerides, and HOMA-IR. There was a negative correlation between LPL gene expression with BMI and glucose.
Conclusion
LPL gene expression is related to the methylation level in its promoter. LPL methylation and LPL gene expression is associated to metabolic profile and BMI.

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OC7.2

Cardiovascular and metabolic morbidity in adult patients with classic congenital adrenal hyperplasia

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Background
Several studies suggest health problems in adult patients with CAH. However, data is inconsistent and based on small and relatively young cohorts.
The aim of this study was to analyze the metabolic and cardiovascular health in a cohort of 90 adult patients with classic CAH.
Subjects and methods
Participants included 90 patients with classic CAH: age range 18–62 years (mean 32.9 ± 10.5, median 29.2) 39 male, 51 female, 61 salt wasting, 29 simple virilising and 90 healthy controls matched for age, sex, BMI and smoking-habit. Anthropometric, metabolic, and subjective health status was evaluated (including measurement of intima media thickness of the common carotid artery, analysis of the body composition by bioimpedance analysis (BIA) and 24 hour ambulatory blood pressure).
Results
There was no significant difference in intima-media-thickness of the common carotid artery between patients and healthy subjects (median 0.60 ± 0.08 mm versus 0.64 ± 0.09 mm, $P = 0.067$ for the right side and median 0.060 ± 0.10 mm versus median 0.61 ± 0.09 mm, $P = 0.653$ for the left side). Patients showed increased BMI (mean 27.0 kg/m^2 versus 25.9 kg/m^2) compared to the general German population. Patients were significantly shorter (median 1.64 ± 0.09 m versus 1.73 ± 0.09 m, $P \leq 0.001$), both male and female had increased body fat mass in proportion to lean body mass (median 0.41 ± 0.22 versus 0.29 ± 0.10, $P \leq 0.001$ for male and median 0.61 ± 0.24 versus 0.49 ± 0.19, $P = 0.008$) compared to the control group. 24-hour blood-pressure measurements showed an impaired nocturnal drop, 54% of patients showed increased nocturnal systolic blood pressures, 17% had elevated systolic and diastolic blood pressures during the night time and were classified as non-dippers (systolic nocturnal drop: median 9.8 ± 5.3%, diastolic nocturnal drop: median 15.7 ± 6.6%)
Conclusion
Patients with classic CAH are at substantially higher metabolic and cardiovascular risk compared to a healthy control group. Better prevention strategies need to be employed.

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OC7.3

Muscle strength in Cushing's syndrome: cross-sectional evaluation of the German Cushing's registry

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Background
Endogenous Cushing's syndrome (CS) is rare with an estimated yearly incidence of 1–3 patients/million. CS describes a group of diseases that have in common an excess secretion of glucocorticoids which results in a characteristic clinical phenotype. Severe courses of Cushing's syndrome are characterized by a break-down of protein catabolism translating into clinical consequences including muscle weakness. While remission of CS is achievable by surgical removal of the ACTH- or cortisol-producing tumour, the effect of biochemical cure on muscular function is yet unclear.
Objective
The aim was to analyze parameters of muscular function in Cushing's syndrome.
Methods
We performed a cross-sectional, prospective study (as part of the German Cushing's registry) analysing 289 consecutive patients in 4 centres of the Cushing's registry. Patients with CS were studied during the active phase of the disease (ACS) or being in remission after successful treatment (CSiR, remission time 2 to 53 years). Rule-out CS patients were used as controls (RO). The following parameters were analysed: hand grip strength using a hand grip dynamometer and the chair rising test as measure of proximal muscular function. Hand grip was standardized to age and gender.
Results
We included 47 patients with ACS (64% female), 149 CSiR (82% female) and 93 RO (72% female). The age and gender corrected normally distributed hand grip strength was significantly lower in ACS compared to the RO group (dominant hand $P=0.002$, non-dominant hand $P=0.003$). Similarly, lower limb muscular function was impaired in ACS ($P=0.001$). The CSiR group showed age and gender corrected reduced hand grip strength (94% for non-dominant hand, $P=0.007$; 92% for dominant hand $P<0.001$ compared to normal reference values). 20% of CSiR performed a chair rising test of ≥ 12 seconds, a threshold associated with adverse outcome in geriatric patients, independent of time elapsed since successful treatment ($P=0.89$).
Conclusion
Cushing's syndrome affects muscle strength in the acute phase, but functional impairment remains also severely impaired in one fifths of patients in the long-term.
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OC7.4

Cortisol autonomy is associated with increased risk of cardiovascular events and mortality in patients with adrenal incidentalomas: beneficial effects of a selective use of adrenalectomy

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Introduction
Cortisol autonomy may be frequently demonstrated in patients with adrenal incidentaloma and this has been associated to increased cardiovascular (CV) risk. However, only few data are available on CV events and related mortality in such patients. Aims of the study were: 1) to stratify CV events and mortality by the degree of cortisol secretion; 2) to evaluate the effect of adrenalectomy on CV events and mortality.
Methods and Design
Data of 218 patients (89 M, 129 F, median age 62 years) followed for a median period of 60 (24–348) months were retrieved. All patients underwent a standard baseline hormonal evaluation. Patients with malignancy, aldosterone producing adenoma and pheochromocytoma were excluded; 30 patients underwent adrenalectomy.
Results
Patients who died during follow-up had higher post-DST cortisol at baseline than patients who survived ($P=0.04$). Death was mostly due to CV causes (41%). Among patients who were not operated on, more CV events ($P=0.04$) and more deaths ($P=0.07$) were observed in the group with post-DST cortisol ≥ 1.8 mcg/dl. Mortality was significantly increased in patients with post-DST cortisol ≥ 5 mcg/dl ($P=0.008$). Patients who were operated on had at baseline higher post-DST cortisol ($P<0.001$), lower ACTH ($P=0.02$) larger mass size ($P<0.01$) and younger age ($P=0.02$) than the remainders. At the last follow-up visit, the patients who were operated on had a lower frequency of hypertension ($P=0.01$). Non-operated patients had a higher frequency of new CV events during follow-up (23.5% vs 6.7%, $P=0.04$). One death was observed during follow-up in the surgical group (3.3%) versus 16 deaths among non-operated patients (8.5%).
Conclusions
In patients with adrenal incidentaloma cortisol autonomy is associated with increased risk of CV events and mortality. A selective use of adrenalectomy in younger patients with higher degree of cortisol autonomy may have a positive effect on CV outcomes.
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OC7.5

Hypothyroidism and levothyroxine treatment is associated with increased mortality in heart failure patients

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Introduction
Hypothyroidism has detrimental effects on the cardiovascular system but controversy remains over the benefit of levothyroxine substitution in heart failure (hf). The aim of this register based cohort study was to examine the effects of levothyroxine treatment on all-cause mortality in patients with hf.
Methods
The study cohort comprised all Danish citizens aged ≥ 18 years admitted with hf in 1997–2012 and still alive 30 days after discharge. Patients with a previous history of thyroid dysfunction, levothyroxine treatment, amiodarone treatment or related thyroid medication were excluded. Subsequent levothyroxine treatment was identified by individual-level linkage of nationwide registers of hospitalization and drug dispensing from pharmacies. Treated patients contributed with risk time in the untreated group and moved to the treated group when they initiated levothyroxine treatment. Patients left study at death, emigration, initiation of amiodarone treatment or end-of-study. Risk of death was analysed by calculating incidence rates per 1000 person years (PY) and incidence rate ratio (IRR) was analysed by Poisson regression models adjusted for age, gender and comorbidity.
Results
A total of 242,250 patients were admitted with hf in the study period (mean age 70.9 [s.d. $\pm$ 14.5] years, 53.5% male). 6,619 (2.7%) of these patients were prescribed levothyroxine after discharge. During a mean follow-up time of 7.4 years (s.d. $\pm$ 7.6), 167.874 (69.3%) patients died. Mortality rates were 93.4 and 139.6 deaths per 1000 PY among untreated and levothyroxine-treated patients, respectively. A 23% increased risk of all-cause mortality was found in patients substituted with levothyroxine (IRR: 1.23 [95% CI: 1.19–1.27]).
Conclusion
We found an increased risk of all-cause mortality in hf patients treated with levothyroxine compared with those without levothyroxine treatment. The impact of thyroid dysfunction on prognosis in hf and benefit or harm of thyroid hormone substitution warrants further investigation.
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Thyroid – Translational

OC8.1

Non-genomic effects of thyroid hormones on endothelial cell tube formation

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Wound healing and tumour stroma formation are associated with angiogenesis and require interactions of various different cell types. We and others have shown that mesenchymal stem cells (MSCs) differentiate into fibroblast-/pericyte-like cells and secrete proangiogenic factors. Thyroid hormones act as proangiogenic modulators mediated by non-genomic mechanisms via cell surface receptor integrin $\alpha v\beta 3$. The aim of this study is to evaluate the stimulatory activity of T3 and T4 on endothelial cell tube formation in concert with the assessment of angiogenic effects of MSCs.

Primary human umbilical vein endothelial cells (HUVECs) were seeded on Matrigel and tube formation was analysed microscopically. Treatment with T3 stimulated tube formation as evidenced by a larger number of junctions and meshes and an increased total tube length compared to untreated cells. Additional treatment with tetrac, a specific inhibitor of integrin αvβ3-mediated action of T3/T4, reduced tube formation to basal level. Similar, albeit weaker, effects were observed for T4. Further, primary human bone marrow-derived MSC-conditioned medium stimulated tube formation. After additional treatment with T3, an even more pronounced angiogenic effect was observed compared to untreated control cells and tetrac-treated cells. In a further set of experiments, co-cultures of HUVECs and MSCs were analysed in this assay. MSCs were found to be integrated into developing tubular networks adjacent to HUVECs - a system that we are now employing to elucidate effects of thyroid hormones on HUVEC-MSC interactions.

Our data suggest that thyroid hormones T3 and T4 stimulate angiogenesis in HUVECs in an integrin αvβ3-dependent manner, an effect that can be enhanced by additional treatment with MSC-conditioned medium. These studies improve our understanding of the critical role of thyroid hormone in the regulation of angiogenesis both in the context of wound healing and tumour stroma formation.

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OC8.2

Selenium modulates apoptosis in thyroid follicular cells: characterization of molecular mechanisms

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Inflammation and several oxidative processes are modulated by Selenium (Se) trough the selenoproteins. Se deficiency has been associated with thyroid autoimmune diseases and hypothyroidism, while Se-supplementation reduces antibodies titles and ameliorates ultrasound pattern of the gland.

Aim of the current study, is to study the molecular effects of Se-supplementation in thyroid follicular cells (FRTL5).

FRTL5 cells have been starved and treated with or without 100 nM Sodium-Selenite (Na-Se). In comparison to the untreated cells, the number of Se-supplemented cells is higher and mortality is reduced as demonstrated by Fluorescence-activated Cells Sorting (FACS) analysis. The maximum effect is present 48 h after the beginning of the treatment. Moreover, after 72 h of Na-Se treatment, cell proliferation improves, as demonstrated by DNA content measured by bisbenzimide fluorescent dye (Hoechst 33258).

Real-time qPCR performed from 12 to 96 h after Se-treatment demonstrate a reduced expression of pro-apoptotic genes (Casp8ap2, Bcl2l11) starting from 24 h and over-expression of anti-apoptotic genes (Bcl2, Bcl2l1, Dapk1 and NFKB1) starting from 48 h.

Next, the anti-apoptotic role of Se has been tested in FRTL5 cells pre-treated with tunicamycin, an inhibitor of N-linked glycosylation that induces apoptosis via ER-stress. In detail, FRTL5 were incubated for 24 hours with 2 μg/ml of tunicamycin (TN) with or without a 72–96 h 500 nM of Na-Se pre-treatment. Cell viability (measured by MTT) is higher ($P<0.05$) in Na-Se pre-treated cells compared to cells incubated with tunicamycin alone, and Western Blot confirmed a reduced Poly- (ADP-ribose) polymerase (PARP) cleavage at 96 hrs of combined treatment.

This is the first report directly demonstrating a specific effect of Se on apoptosis modulation in normal thyroid follicular cells. Our data provide a molecular explanation for clinical improvement observed after treatment with Se in patients with autoimmune thyroid disease.

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OC8.3

Identification of novel genetic loci associated with thyroid function

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Objective

Thyroid hormones have essential role in regulation of cellular growth, development and metabolism. Although genetic variants seem to be an important determinant of thyroid hormone levels the data about involved genes are still limited. Therefore, in order to determine genetic variants underlying thyroid-stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3) plasma level we performed a genome wide association study (GWAS) in Croatian subjects.

Methods

Immunoassay method was used to determine circulating plasma level of TSH, fT4 and fT3 in 1012 participants from Split, Croatia. Participants with a history of thyroid disease treatment (41 of them) were excluded from the study. The GWAS for TSH, fT4 and fT3 was performed using 1000 genomes imputed data and was accounted for genetic relatedness among individuals. Association was tested by linear regression adjusted for sex and age assuming an additive genetic model.

Results

We identified one new locus associated with fT3 level with genome-wide significance: rs118173732 located upstream of DIAPH3 gene on the 13q21.2 ($P=4.9059359\times10^{-8}$; $\beta=-1.2195316$; $SE=-0.2235750$).

Conclusion

The study found new locus associated with fT3 level in general population. The results should be checked in a replication study.

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OC8.4

Discovering the difference in the tear fluid proteome between Graves' patients with or without orbitopathy

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Background

Graves' orbitopathy (GO) is a severe organ-specific autoimmune inflammatory ocular complication most often associated with Graves' disease (GD). Besides the cosmetic problems these patients develop, GO may also cause severe eye complications threatening the vision of the patient. Additionally, GO complicates the treatment of patients with GD, making the identification of Graves patients at risk for eye disease before they develop symptoms a critical step for the clinical handling and quality of life of these patients. The high concentration of proteins in tear fluid makes it an important source for studying potential protein biomarkers for GO. The aim of the present study was to quantitatively compare tear fluid from GD patients with active GO and patients with GD without GO (controls) using untargeted quantitative proteomics based on dimethyl labeling in combination with 2D-LC-MS/MS.

Results

Among the 1212 proteins identified, 16 proteins showed significant alterations in abundance between the two groups. Thus, in the present study we reveal a number of novel dysregulated proteins in GO which may contribute to a better understanding of the disease. In particular, up-regulation of lacrimal gland proteins, suggest involvement of the lacrimal gland in the pathogenesis of GO. It remains to be elucidated whether some of these proteins can be used as markers for patients at risk for developing GO as well as useful indicators for disease activity.

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OC8.5

In vivo effects of repeated thyronamine (T_0AM) administration in mice

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Introduction
So far, only two representatives of thyronamines, namely 3-iodothyronamine (3-T_1AM) and the iodine–free thyronamine (T_0AM), have been detected *in vivo*. While intensive research is done on the (patho-) physiological function of 3-T_1AM, the physiological role of T_0AM is poorly studied. Conflicting data have been reported for the acute cardiac effects of T_0AM. This project therefore determined whether a repeated administration of T_0AM affects cardiovascular function, metabolism or thermoregulation.
Methods
C57BL/6J male mice were injected with a pharmacological dose of T_0AM (5 mg/kg/day, 7 days, i.p.). The mice were killed 24 h after the last injection, and organs were collected for subsequent gene expression analysis.
Results
Daily administration of T_0AM did not alter body weight, food or water intake, heart rate, blood pressure, brown adipose tissue thermogenesis or body temperature compared to sham-injected controls. There was no significant difference in hepatic glycogen content or mRNA expression of genes involved in cardiac, blood pressure or metabolic control between the treatment groups. While the thyroid hormone (TH) responsive genes *Spot14* and *selenoprotein S* were significantly up-regulated in liver after T_0AM treatment, hepatic *deiodinase 1 (Dio1)* was unaffected, which is in line with unaltered levels of serum total T_4 and T_3 concentrations. No significant effects were observed on hepatic or renal trace element concentrations like Se, Cu, and Zn.
Conclusions
Our data demonstrate that T_0AM displays only minor cardiovascular, metabolic and thermoregulatory activity in mice upon repeated administration. T_0AM does not interfere with TH metabolism, and does not affect *Dio1* as a most sensitive hepatic TH-target genes or TH serum levels. Hence, T_0AM may not constitute a physiologically active TH metabolite.

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Endocrine Tumours

OC9.1

Study of new tumor suppressor gene (ZNRF3) in adrenocortical carcinoma

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Introduction
Adrenocortical Carcinoma (ACC) is a rare and aggressive tumor with poor prognosis. Up to now, *CTNNB1* (*βcatenin*) and TP53 mutations were the most frequent alterations identified in ACC. By a combination of genomic approaches, we have recently analyzed a cohort of 122 ACC (European Network for the Study of Adrenal Tumors, ENSAT). This work confirmed recurrent alterations in *CTNNB1* and *TP53* and revealed new genes not previously reported in ACC. Strikingly, *ZNRF3* (zinc and ring finger 3) was the most frequently altered gene (21%). In a majority of cases, homozygous deletions of *ZNRF3* were observed. *ZNRF3* had never been associated with other tumor types. This original finding suggests that *ZNRF3* could be a novel tumor suppressor gene involved in ACC. Our objective is to demonstrate that *ZNRF3* acts as a tumor suppressor gene in the adrenocortical cell line (H295R) and to identify molecular pathways downstream of ZNRF3.
Methods
To investigate the potential function of ZNRF3 on apoptosis and cell proliferation, we performed measurement of Caspase3 activity and MTT assay in H295R cells, transfected with an interfering RNA targeting *ZNRF3* or a vector encoding ZNRF3. Then, to screen and identify new ZNRF3 binding partners we performed co-immunoprecipitation (IP)-coupled mass spectrometry (MS) experiments from H295R cells transfected with ZNRF3.
Results
In H295R cells, ZNRF3 overexpression decreases cell proliferation and increases apoptosis, while *ZNRF3* silencing confers protection against apoptosis induced by staurosporin. Different proteins partners of ZNRF3 were identified by coIP-MS, involved in various cellular processes. The interaction of ZNRF3 with these proteins is under investigation. Further experiments are required to identify the corresponding signaling pathways.
Conclusion
Our data show that ZNRF3 plays a role of tumor suppressor gene in adrenocortical cells. The results of this research will help to progress toward our understanding of adrenocortical tumorigenesis involving *ZNRF3* alterations.

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OC9.2

Role of luteinizing hormone receptor in the ontogeny and progression of adrenocortical tumors in transgenic mice expressing SV40Tag under the inhibin-α promoter

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We analyzed the occurrence of adrenocortical tumors in transgenic mice expressing Simian Virus 40 T antigen (SV40Tag) under the inhibin-α promoter (inhα/Tag) and searched for novel biomarker genes for the tumorigenesis. We studied 2-, 4-, 6-mo-old intact (never forming tumors) and prepubertally gonadectomized (GDX) inhα/Tag mice (developing tumors) and similar groups of wild-type mice as controls. Furthermore, the role of ectopic luteinizing hormone receptor (*Lhcgr*) expression in the tumors was explored by cross-breeding inhα/Tag mice with *Lhcgr* deficient mice (inhα/Tag/LuRKO) and by treating tumor-bearing GDX inhα/Tag mice with human chorionic gonadotropin (5 IU/week/for 3 weeks). In both sexes, the expression of *Grb10, Mmp24, Sgcd, Rerg, Gnas, Nfatc1, Gnrhr, Igf2* was significantly downregulated; whereas that of *Esr1, PrlR_L, Gata-4* and *Lhcgr* was upregulated in the tumorous vs. GDX wild-type adrenal gland. Sex steroid enzyme genes (*Srd5a1, Cyp19a1*) were also upregulated, but adrenal-specific steroidogenic enzymes (*Cyp21a1, Cyp11b1, Cyp11b2)* downregulated. Inhibin-α expression was scattered throughout the adrenal cortex of GDX inhα/Tag mice. SV40Tag expression was restricted to the upper layers of zona fasciculata in GDX inhα/Tag mice, but in intact mice to the subcapsular region, infiltrating cortex towards medulla along with aging/tumor progression. Adrenal tumors failed to form in GDX inhα/Tag/LuRKO double transgenic mice. *In vivo* hCG treatment increased plasma progesterone concentrations in GDX inhα/Tag, but did not affect the tumor progression.
Taken together, our results suggest that adrenal LH/LHCGR function was a prerequisite for tumor formation after GDX in Inhα/Tag, but not required for tumor progression. Downregulated genes found in the tumor tissues suggest their necessity in the normal adrenocortical phenotype development. Upregulated genes may serve as potential biomarker candidates for adrenocortical tumorigenesis. The steroidogenic enzyme gene expression pattern in inhα/Tag mice may suggest increased sex steroid hormone production (androgens, estrogens) at the expense of adrenal hormone steroidogenesis (corticosterone, aldosterone).

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OC9.3

Stressed to death – antioxidant pathway targeting as a novel therapeutic approach in adrenocortical carcinoma

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Context
Nicotinamide nucleotide transhydrogenase (NNT) is a NADPH-generating mitochondrial proton pump with a central role in mitochondrial antioxidant pathways. Recent studies revealed inactivating NNT mutations in patients with familial glucocorticoid deficiency, indicating a selective susceptibility of the adrenal cortex to NNT deficiency and oxidative stress. Here we explored the potential value of NNT as a therapeutic target in adrenocortical cancer.
Methods
We delineated the distinct effects of NNT loss on cellular proliferation and steroidogenesis employing two *in vitro* knockdown models: transient, siRNA-mediated and stable, shRNA-mediated NNT silencing, both utilising the adrenocortical carcinoma cell line NCI-H295R.
Results
Transient NNT knockdown impaired cellular redox balance, as indicated by a decline in the ratio of reduced to oxidised glutathione, and impeded cellular proliferation ($30 \pm 8\%$ decrease in proliferation compared to scrambled siRNA-transfected cells, $P < 0.01$). Importantly, NNT-deficient cells also became exceedingly sensitive to chemically induced oxidative stress ($55 \pm 10\%$ loss of cellular viability when co-treated with 20 μM Paraquat, $P < 0.01$). After long-term culture, H295R cells with stable NNT knockdown appeared to develop compensatory mechanisms, with evidence of improved redox balance and proliferative potential. This adaptation was associated with alterations in glycolytic and oxygen consumption rates, as demonstrated by extracellular flux analysis using Seahorse XF technology. Steroid profiling by liquid chromatography-tandem mass spectrometry revealed a distinct profile induced by transient NNT knockdown, surprisingly characterised by enhanced cortisol and androstenedione synthesis. This was underpinned by an increase in the activity of several key steroidogenic enzymes including CYP11B1, CYP17A1 and CYP21A2.
Conclusion
Our study suggests a potential role of NNT inhibition as a novel therapeutic approach in advanced adrenocortical carcinoma. Steroid profiling reveals a surprising increase in glucocorticoid and androgen synthesis in response to NNT loss, challenging our current understanding of the complex association between redox balance and adrenal function.

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OC9.4

The truncated somatostatin receptor sst5TMD4 is overexpressed in prostate cancer, where it increases aggressiveness features by regulating key tumor suppressors and oncogenes.

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Somatostatin is a pleiotropic neuropeptide that governs multiple biological targets, including tumor cell function, through a family of G protein-coupled receptors with 7-transmembrane domains (TMD), named sst1-5. However, we recently discovered sst5TMD4, an aberrantly spliced, truncated (only 4-TMDs) sst5-variant displaying unique molecular/functional features. sst5TM4 is over-expressed in various endocrine-related tumors exacerbating their malignant characteristics. Here, we present the first analysis of the presence, pathological relevance, functional role, and mechanisms of action of sst5TMD4 in human prostate cancer (PCa). Specifically, samples from human PCa, normal prostate (NP), and PCa cell lines (VCaP and PC3) were studied. Expression profiles were determined by qPCR and functional consequences of sst5TMD4 overexpression/inhibition were analyzed using different techniques. Intracellular mechanisms triggered by sst5TMD4 overexpression were determined using commercial arrays. Preclinical mouse models were used to study the in vivo consequences of sst5TMD4 overexpression on tumor growth. Our results revealed that sst5TMD4 was overexpressed in PCa samples, and its expression was higher in patients with metastatic PCa. In PCa cell lines, sst5TMD4 overexpression increased cell proliferation and migration, while its silencing reduced cell proliferation. sst5TMD4 overexpression stimulated key intracellular pathways involved in PCa function, including ERK/JNK, MYC/MAX, WNT and RB, and, consequently, altered the expression of tumor suppressors (APC, SFRP1, CDKN2A, ZNF185) and oncogenes (CAV1, IL-6, DAXX). Notably, sst5TMD4-transfected PC3 cells lost their usual response to somatostatin analogs in terms of calcium kinetics, evidencing the disruption of normal functioning of somatostatin system in PCa. Finally, nude mice injected with sst5TMD4 stably-transfected PC3 cells presented larger tumors with increased proportion of necrosis. In conclusion, sst5TMD4 is overexpressed in PCa, where it is associated to the presence of metastasis, and promotes aggressiveness features in *in vitro* and *in vivo* models, suggesting its potential value as biomarker and/or therapeutic target in PCa.

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OC9.5

Pituicytoma: a neuropathological analysis of 10 samples

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Introduction
Pituicytoma is a rare neoplasm of the sellar region, believed to originate from neurohypophyseal cells. Tumor resection is the primary treatment option, but may remain incomplete due to excessive bleeding of the well vascluarized tumor stroma. Therefore the search for alternative or additional treatment regimens is necessary. In a previous publication in 2012 the presence of VEGF-R was shown in one tumor sample, potentially opening the door for modern treatment options. However no series of pituicytomas was analyzed so far.
Material and methods
We analyzed pituicytoma samples collected from three institutions between 2006 and 2015. The tumor tissues were stained for VEGF, VEGFR, TTF1, SSTR 2, SSTR 3, SSTR 5; furthermore the Ki67 fraction was determined. The strength of the stainings were classified from 0=no staining to +++=strong staining. A complementary retrospective analysis of the patient charts regarding sex, age, and primary symptoms, pituitary function, and peri- or postoperative complications was performed.
Results
Ten samples were analyzed; mean patient age was 57.8 years +-16.3 years. Seven samples were acquired from male patients (one relapse) and three from female. All tumors stained strongly positive (+++) for VEGF-R. VEGF was unavailable in six samples, did not stain in 3 and was slightly positive (+) in one sample. Six samples stained positive for TTF1. As for somatostatin receptors, three samples were slightly positive for SSTR2; seven were negative. SSTR3 was + in 1, 3 were ++, 3 were +++ and 3 were 0. SSTR 5 stained +++ in 1, ++ in 5, + in 1 and 0 in three patients. Ki67 was unavailable for seven samples; it was 5% for two samples and 10% in one.
Conclusion
All pituicytomas stained strongly positive for the VEGF receptor presence thus indicating a possible treatment option through targeted therapies in cases where resection remains insufficient. Further research is necessary as to whether tumor growth can be inhibited using this pathway.

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Reproduction & Endocrine Disruption

OC10.1

Systemic enamel pathologies may be due to anti-androgenic effects of some endocrine disruptors

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There has been increasing concerns over the last 20 years about the potential adverse effects of endocrine disruptors (EDs). Anecdotally, molar incisor hypomineralization (MIH), a recently described enamel pathology, now affecting 15–18% of 6–9 years old children, is increasing concurrently with ED related pathologies. Our previous data show that bisphenol A (BPA) and vinclozolin, two anti-androgenic EDs, impact amelogenesis and enamel mineralization preferentially in male rats and generate similar enamel defects as those described for MIH. The resulting irreversible enamel defects may provide an easily accessible marker for reporting early ED exposure in humans. The aim of the present study was to decipher the mechanism of action of low-dose ED during amelogenesis.
Wistar rats were exposed to low-dose EDs from the first day of gestation to 30 days after birth. Global transcriptomic analysis showed BPA and vinclozolin modulated the expression of a small group of genes directly involved in enamel mineralization, among them the protease KLK4 and the ion-exchanger SLC5A8 which are crucial for amelogenesis. Analysis of the ED putative receptor expression pattern showed that in contrary to estrogen receptor α (ERα) which is mainly expressed by ameloblastic precursors, androgen receptor (AR) was three- to fivefold more expressed in full differentiated ameloblasts responsible of enamel mineralization. *In vivo* and *in vitro* analysis carried out on the rat ameloblastic cell line HAT-7 and human androgen-sensitive prostate cancer cells LNCaP showed AR nuclear translocation upon testosterone treatment, and testosterone up-regulation of two enamel specific gene expression (KLK4 and SLC5A8). This induction occurred at the transcriptional level and was inhibited by siRNAs directed against AR as well as by vinclozolin and BPA.
In conclusion, we report that i) dental epithelial cells are sensitive to estrogens and androgens, ii) amelogenesis is modulated by androgens and that iii) two anti-androgenic EDs, BPA and vinclozolin, irreversibly disrupt this process preferentially in male rats by modulating the transcription of enamel specific genes. We thus provide evidence of hormonal influence on amelogenesis and probably on sexual differences of enamel quality.

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OC10.2

Human luteinizing hormone (hLH) and chorionic gonadotropin (hCG) display biased agonism at the LH/CG receptor

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Human luteinizing hormone (LH) and human choriogonadotropin (hCG) were considered biologically equivalent for decades due to structural similarities and binding to the same receptor (LHCGR). However, LHCGR triggers differential, LH- and hCG-specific, cAMP production, steroidogenesis, ERK and AKT activation and gene expression in granulosa cells. Besides the Gs/cAMP/PKA pathway, hCG and LH bioactivity on β-arrestin- and Gq/PLC-dependent pathways are yet to be determined. We compared the abilities of recombinant hLH and hCG to elicit cAMP and inositol phosphate production, β-arrestin 2 activation and recruitment, as well as steroids production in two cell models: i) human embryonic kidney 293 (HEK293) cells transiently expressing LHCGR; ii) mouse Leydig tumour cells (mLTC-1), endogenously expressing the murine LH receptor. Bioluminescence/fluorescence resonance energy transfer (BRET/-FRET) technologies were used, allowing quantitative analysis of hCG/hLH activities in real-time in living cells treated by increasing doses of gonadotropins (1 pM-1 μM). Both hormones trigger identical maximal cAMP response, with the EC_{50} of hCG 30 times lower than that of hLH (12.91 ± 1.48 pM versus 378.6 ± 1.2 pM, respectively) (Mann-Whitney's *U*-test; $P < 0.05$; $n = 4$). hLH clearly led to weaker maximal response of progesterone production than hCG (hCG = $94.36 \pm 3.1\%$; LH = $41.46 \pm 4.1\%$; *t*-test; $P < 0.05$; $n = 3$), exhibiting partial agonism for steroids synthesis. IP1 production and β-arrestin responses confirmed the biased actions of the two hormones. EC_{50} values measured for IP1 production were higher compared to EC_{50}s obtained for cAMP, indicating that higher receptor occupancy must be reached to recruit Gαq than Gαs. Moreover, we found that hLH led to partial maximal β-arrestin 2 recruitment, with 5-fold lower potency compared to hCG (hLH = 0.14 ± 0.008 versus hCG = 0.2 ± 0.008; Mann-Whitney's *U*-test; $P < 0.05$; $n = 4$). These results challenge the traditional view that hLH and hCG are biologically equivalent, since they trigger clearly different intracellular responses and suggest that these pleiotropic gonadotropins could act as natural biased agonists in vivo, opening novel pathophysiological scenarios.

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OC10.3

LHCGR signaling promotes gonadal-like cell differentiation and proliferation in gonadectomy-induced adrenocortical tumorigenesis in mice

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Adrenocortical tumorigenesis in prepubertally gonadectomized (GDX) DBA/2J mice has been attributed to chronically elevated luteinizing hormone (LH) and ectopic expression of luteinizing hormone receptor (LHCGR) and GATA-4 transcription factor. We analyzed now the mechanistic role of LH-LHCGR activation in GDX-induced adrenocortical tumorigenesis in intact and ovariectomized (OVX) wild-type (WT) and *Lhcgr*$^{-/-}$ mice in the DBA/2J genetic background mice, or by treating OVX DBA/2J mice with gonadotropin-releasing hormone antagonist (GnRH-a, Cetrorelix; 2.3 mg/kg/24 h for 21 days). The adrenal glands of 6 mo-old OVX *Lhcgr*$^{-/-}$ mice were significantly smaller than their haploinsufficient (*Lhcgr*$^{+/-}$) or OVX WT control littermates. Histopathology of OVX *Lhcgr*$^{-/-}$ adrenals showed lack of gonadal-like sex-steroid producing large lipid-laden cells, termed B cells, whereas non-steroidogenic GATA-4-positive spindle-shaped cells, known as A cells, were observed in both intact and OVX *Lhcgr*$^{-/-}$ mice. Furthermore, OVX *Lhcgr*$^{-/-}$ mouse adrenals displayed down-regulated gonad-specific markers *Foxl2*, *Spinwl1, Cyp19* and *Ers2*. Lack of sex steroid producing B cells in *Lhcgr*$^{-/-}$ adrenals resulted in decreased plasma estradiol and progesterone levels and significantly smaller uterus vs. WT control. GnRH-a treatment of 12 mo-old OVX DBA/2J mice significantly reduced the weight of adrenal glands, followed by the downregulated expression of proliferation marker Mki67, gonad-specific genes *Lhcgr*, *Cyp19*, *Spinlw1* and GATA-4 co-regulator *Zfpm2*. Taken together, these data provides evidence for LHCGR signaling promoting the differentiation and proliferation of neoplastic sex steroidogenic B cells in GDX-induced adrenocortical tumorigenesis.

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OC10.4

Impaired adipose function in PCOS – evidence that the primary abnormalities are in subcutaneous rather than visceral fat

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Central obesity and increased visceral adipose tissue (VAT) are key factors contributing to metabolic dysfunction in PCOS. We therefore hypothesized that

there would be alterations in the morphology and function of adipocytes from visceral fat depots. The female offspring of pregnant sheep treated biweekly with either 100 mg of testosterone propionate (TP) or vehicle control (C) from day 62–102 of gestation develop a clinically realistic PCOS-like condition. They develop hyperinsulinaemia and early fatty liver changes in adolescence followed by increases in body weight and adiposity in adulthood.
We examined adipose tissue development and function in PCOS-like sheep during fetal life (D112: C = 9; TP = 4), before puberty (11 weeks: C = 8; TP = 8), at adolescence (11 months: C = 5; TP = 9) and in adulthood (30 months: C = 11; TP = 4).
Impaired adipocyte differentiation was not observed in fetal or early life. There were no differences in the expression of the master adipogenic regulators (*PPARG*, *CEBPA, CEBPB*) or markers of fully differentiated adipocytes (*LEP, ADIPOQ, PLIN1, LPL*) in VAT of adolescent sheep, however all were downregulated in the subcutaneous adipose tissue (SAT) ($P < 0.05$–0.01). This altered adipogenesis in SAT was accompanied by increased expression of *TNF* and *HIF1A* ($P < 0.05$) and correlated with increased fasting Free Fatty Acids (FFA) ($r = 0.55$; $P < 0.05$). As adults PCOS-like sheep had decreased total adipocyte numbers ($P < 0.05$) and increased mean adipocyte size in SAT ($P < 0.05$) but not in VAT. SAT hypertrophy was associated with increased expression of *CCL2, TNF* and *IL6* ($P < 0.05$–0.01) and correlated with increased fasting FFA ($r = 0.61$; $P < 0.05$).
Altered adipogenesis in SAT, rather than VAT, of PCOS-like sheep correlates with onset of puberty and hyperinsulinaemia. Impaired preadipocyte differentiation in SAT in adolescents results in hypertrophy and inflammation of adult SAT. This consequently lowers capacity of SAT to safely store fat and potentially explains metabolic perturbations observed in PCOS-like female sheep.

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OC10.5

Effect of clomiphene citrate and metformin on testosterone levels in hypogonadal obese men with impaired glucose tolerance (IGT) or type 2 diabetes (DM2)

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Low testosterone (T) levels are often found in obese men with metabolic abnormalities, however the mechanism underling this condition is unclear. This study aimed to evaluate the effectiveness of clomiphene citrate (CC) in increasing T levels and improving metabolic control in hypogonadal obese men with IGT or DM2. A randomized cross-over double blind controlled study was conducted in twenty obese hypogonadal caucasian men, mean age 47 ys, classified in IGT ($n = 11$) or DM2 ($n = 9$). Participants were assigned to receive either 25 mg/day of CC plus 2 g/day of metformin (MET) or placebo plus 2 g/day of MET for 3 months. After 6 weeks wash-out period, subjects were moved to the alternate arm for additional 3 months. Inclusion criteria were age (35–56 ys), BMI > 30 kg/m^2, T level < 3 ng/ml and glycemia compatible with IGT or DM2. At baseline and at the end of each phase, BMI, glycemia, T and E2 were evaluated. T and E2 were measured by LC/MS-MS. In the CC + MET treatment phase, T and E2 levels increased significantly compared to baseline ($T = 2.91 \pm 0.76$ ng/ml vs 5.86 ± 1.69 ng/ml, $P < 0.001$; $E2 = 24 \pm 8$ pg/ml vs 49 ± 21 pg/ml, $P < 0.001$) whereas glycemia and BMI decreased (glycemia = 105 ± 24 mg/dl vs 99 ± 26 mg/dl, $P < 0.019$; BMI = 36.0 ± 5.9 kg/m^2 vs 35.4 ± 5.7 kg/m^2; $P < 0.007$). Indeed, in the placebo + MET phase no significant changes in any of these parameters were observed. The sex-hormonal changes were similar in IGT and DM2 subjects. Only CC + MET therapy was able to significantly increase serum T levels in all participants independently of the metabolic state and to reduce BMI and glycemia.

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Bone & Calcium Homeostasis

OC11.1

An increase of bone mineral density in male-to-female and female-to-male transgender persons after one year cross-sex hormonal treatment

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Introduction
Estrogen has positive effects on bone mineral density (BMD), in particular in trabecular bone through inhibition of bone resorption. Testosterone increases bone size, but the effect on BMD is less clear. Cross-sex hormonal treatment (CSHT) in transgender individuals can affect BMD. Therefore, the aim of this study is to investigate effects of CSHT on BMD during the first year of treatment in male-to-female (MtFs) and female-to-male (FtMs) transgender persons.
Methods
This is a prospective observational study and part of ENIGI (European Network for Investigation of Gender Incongruence). 188 adults who completed one year of CSHT were included. In 99 FtMs and 89 MtFs a dual-energy X-ray absorptiometry was performed to measure lumbar spine (LS) and total hip (TH) BMD before and after one year CSHT. FtMs received intramuscular testosterone undecanoate (1000mg/12 weeks), testosterone gel (50mg/day) or testosterone esters intramuscular (250mg/2 weeks). MtFs were treated with cyproteronacetate (50mg/day) in combination with oral estradiol valerate (2-4mg/day) or an estradiol patch (200ug/week). Analyses were stratified for calcium with colecalciferol (CaD3) use.
Results
In FtMs the mean LS BMD increased with 1.00% (95%CI 0.15 – 1.85%) and the mean TH BMD with 0.91% (95%CI 0.29 – 1.53%). In MtFs, the mean LS and TH BMD increased with 3.72% (95%CI 2.85 - 4.59%) and 1.52% (95%CI 0.90 – 2.14%), respectively. In MtFs who used CaD3, BMD increased more than in patients who did not use this: 4.87% (95%CI 3.49 – 6.25%) vs. 2.86% (95%CI 1.76 – 3.95%) in LS, and 2.33% (95%CI 1.27 – 3.38%) vs. 0.92% (95%CI 0.18 – 1.66%) in TH. In FtMs, use of CaD3 did not influence the change of LS or TH BMD.
Conclusion
After one year CSHT BMD increases in MtFs more than in FtMs, particularly in lumbar spine. This confirms the role of estrogen on bone in biological males.

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OC11.2

Associations of insulin sensitivity with cortical bone geometry in healthy adult men

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Objective
In type 2 diabetes mellitus, fracture risk is increased despite preserved BMD. This might in part be due to insulin resistance affecting bone geometry; however, studies investigating the associations of insulin sensitivity with bone geometry are lacking. We aimed to explore this relationship in a cohort of healthy, young adult men.
Methods
In 1001 healthy men aged 25–45 years, cortical bone geometry was assessed using pQCT (radius and tibia, 66% from distal end point). Insulin and glucose were measured from fasting serum samples; insulin resistance was evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR).

Results
In age and BMI-adjusted analyses, HOMA-IR and insulin levels correlated inversely with periosteal circumference (PC), endosteal circumference (EC) and polar strength-strain index (SSIp) at both the radius (PC: both ß = −0.13, $P < 0.001$; EC: ß = −0.08, $P \leq 0.031$; SSIp: ß = −0.14 and ß = −0.16, $P < 0.001$) and tibia (PC: ß = −0.12, $P < 0.001$; EC: ß = −0.10 and ß = −0.09, $P \leq 0.007$; SSIp: ß = −0.10, $P \leq 0.003$). Moreover, insulin levels but not HOMA-IR correlated inversely with cortical thickness at the radius (ß = −0.07, $P = 0.048$). After adjustment for DXA-derived body composition (total fat and lean body mass) instead of BMI, the associations of HOMA-IR and insulin with PC and SSIp at both the radius and tibia and with EC at the tibia remained significant (ß ≥ −0.11, $P \leq 0.019$), whereas the associations of HOMA-IR and insulin with EC and the association of insulin with cortical thickness at the radius lost significance.
Conclusion
In this cohort of healthy young men, insulin sensitivity correlates with cortical bone size at least in part independently of body composition. Given the important contribution of bone geometry to overall bone strength, this might contribute to the paradoxically increased fracture risk in patients with type 2 diabetes mellitus. Whether this association is a direct consequence of impaired insulin signaling in bone tissue or reflects indirect effects through modulation of the muscle-bone relationship remains to be established.

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OC11.3

Ultra-trail marathon induces bone response in association with acute and established metabolic changes

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Introduction
Bone and energy metabolisms are deeply related determining a two-way street aimed in regulating the energy utilization [1]. Mountain ultra-marathons are peculiar aerobic performances hardly proving whole body homeostasis [2]. In this study we aimed at investigating and characterizing the metabolic profile (hormones involved in energy metabolism), the metabolic inflammation profile (adipokines), the bone metabolism (bone turnover markers), and their integration (mediated by osteocalcin [3]) both in experienced ultra-marathon runners and control subjects.
Methods
Serum concentrations of bone turnover markers (pro-collagen type I N-terminal propeptide, carboxylated/undercarboxylated osteocalcin), measured by ELISA, and metabolic hormones (C-peptide, insulin, glucagon, glucagon-like peptide, gastric-inhibitory peptide, ghrelin, leptin, resistin, and visfatin), measured by fluorescent-based multiplex assay, were compared before and after a 65-km mountain ultra-marathon in 17 trained runners and in 12 age-matched controls with a low physical activity profile.
Results
After the race, runners experienced a reduction in pro-collagen type I N-terminal propeptide ($P < 0.05$), although it remained higher than in controls ($P < 0.05$), while carboxylated osteocalcin remained unchanged. Among the metabolic hormones, only glucagon and leptin were different between runners at rest and controls. C-peptide and leptin decreased after the race in runners, while glucagon, glucagon-like peptide 1, resistin, and visfatin were increased ($P < 0.01$). Undercarboxylated osteocalcin was decreased (50%, $P < 0.05$) and highly correlated with insulin and C-peptide ($r = 0.65$, $P < 0.01$).
Conclusions
In order to keep homeostasis, the energy use is strikingly regulated at expenses of bone metabolism. Undercarboxylated osteocalcin changes clearly mark the global energy needs of the body.

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OC11.4

The prevalence of GNAS deficiency-related diseases in a large cohort of patients characterized by the EuroPHP network

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The clinical condition resulting from end-organ resistance to parathormone (rPTH), caused by (epi)genetic alterations of GNAS, was termed as Pseudohypoparathyroidism (PHP). The high phenotype heterogeneity, the existence of additional clinical features such as resistance to other hormones (TSH/GHRH/gonadotropins) and Albright's hereditary osteodystrophy (AHO), led to the distinction of specific PHP subtypes.
The purpose of the present work is to provide data about PHP-associated molecular defects prevalence. We collected in a specifically designed questionnaire the data from all the patients (pts) characterized by 3 laboratories members of the EuroPHP network, i.e. 407 pts.
Isolated rPTH (126/407, 31%) was caused only by epigenetic defects, as 70% of pts had a loss of imprinting (LoI) affecting all GNAS DMRs and 30% a loss of methylation (LoM) restricted to the A/B DMR. Multihormone resistance with no AHO signs (61/407, 15%) was essentially due to epigenetic defects, 64% to broad LoI and 26% to LoM A/B, although a 10% of pts had a point mutation.
In pts with rPTH and AHO (40/407, 10%), the percentage of point mutation grown up to 28% and methylation defects reduced (59% broad LoI and 13% LoM at A/B). In pts with multihormone resistance and AHO (155/407, 38%), we found all types of molecular defects; in particular, most pts were affected by *GNAS* point mutations (81%), while the remaining cases were due to either large deletions involving *GNAS* (6%), or broad LoI (10%) or isolated LoM at A/B (3%). Finally, isolated AHO (18/407, 4%) and POH (7/407, 2%) were caused by point mutations only.
To conclude, this work allowed us, for the first time, to quantify the prevalence of different (epi)genetic lesions in PHP pts. As outcome, we plan to derive objective criteria to guide a cost-efficient strategy of genetic testing and to examine the implications for management and prognosis.

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OC11.5

Effects of vitamin D supplementation on respiratory muscle strength and physical performance in patients with COPD: a pilot trial

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Introduction
Although vitamin D is well known for its function in calcium homeostasis and bone mineralisation, several studies have shown an effect on physical function and muscle strength. Also, vitamin D has been associated with pulmonary function and the incidence of airway infections. As vitamin D deficiency is highly prevalent in COPD-patients, supplementation might have a beneficial effect in these patients.
Objective
To assess the effect of vitamin D supplementation on respiratory muscle strength and physical performance in vitamin D-deficient COPD-patients. Secondary outcomes were exacerbation rate, pulmonary function and quality of life.
Methods
We performed a randomised, double-blind, placebo-controlled pilot trial. Participants were randomly allocated to receive 1200 IU vitamin D3 per day ($n = 24$) or a placebo ($n = 26$) during 6 months. Study visits were conducted at baseline, at 3 and at 6 months after randomisation. During the visits blood was

collected, respiratory muscle strength was measured (maximum inspiratory and expiratory pressure (kPa), MIP and MEP respectively), physical performance tests were performed (3-meter walking test, tandem test, chair-stands test and 6-minutes walking test) and pulmonary function was assessed. In addition, during the whole study period participants kept a diary card in which they registered respiratory symptoms.

Results

At baseline, both groups were deficient (mean serum 25-hydroxyvitamin D (25(OH)D) in nmol/L (S.D.): 42.3(15.2) and 40.6(17.0) in the vitamin D and placebo-group respectively). Participants with vitamin D supplementation had a significant increase in 25(OH)D compared to the placebo-group after 6 months (mean difference (S.D.): 52.8(29.8) vs. 12.3(25.1), $P<0.001$). Pulmonary muscle strength did not differ between the groups after 6 months (mean difference MIP(S.D.): −0.28(1.43) and 0.25(1.23), $P=0.215$; mean difference MEP(S.D.): 0.92(3.37) and 0.51(2.07), $P=0.649$). Also, no differences were found in physical performance, exacerbation rate, pulmonary function or quality of life.

Conclusion

Vitamin D supplementation did not affect respiratory muscle strength and physical performance in vitamin D-deficient COPD-patients.

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Obesity

OC12.1

Functional characterization of naturally occurring mutations in the melanocortin receptor accesory protein 2 (MRAP2)

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Introduction

The melanocortin 4 receptor (MC4R) is the most important hypothalamic expressed G protein coupled receptor in weight regulation. Mutations in the MC4R are the most frequent genetic cause of obesity. Recently an accessory protein of the MC4R (melanocortin receptor accessory protein 2, MRAP2) was discovered that was found to play a role in body weight regulation. MRAP2 deficient mice develop early-onset obesity. The mechanisms of disturbed weight regulation is potentially a role of MRAP2 at MC4R function. However, naturally occurring mutant MRAP2 were yet not been identified and the impact of MRAP variants for regulation of signaling properties of the MC4R were not characterized so far.

Methods

Mutational screening and determination of cAMP accumulation by AlphaScreen technology.

Results

By screening for *MRAP2* mutations in nearly 200 obese children and over 180 lean controls, we detected three non-synonymous MRAP2 variants which are all heterozygous in the patients. For functional characterization of the three non-synonymous MRAP2 variants, we established an experimental procedure to characterize MRAP2 mediated effects on MC4R signaling. Characterization of the three mutations revealed for only for one MRAP2 variant a significant decrease in MC4R signaling in comparison to MC4R signaling in presence of MRAP2 wild-type. We also tested different transfection ratios between MC4R/MRAP2 and determined MC4R signaling after alpha-MSH challenge. This experiment demonstrated that the impact of MRAP2 on MC4R function is dependent on the ratio between MC4R to MRAP2, which can be modified by mutations in *MRAP2* pointing to the fact that MRAP2 might act in a dimeric state.

Conclusion

For the first time we describe a mode of action for the MRAP2/MC4R complex and provide hints for a relevance of this complex for body weight regulation in humans.

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OC12.2

Female 5β-reductase knockout mice are protected from diet induced obesity, insulin resistance and glucose intolerance

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Steroid hormones and bile acids are potent regulators of metabolic phenotype. The enzyme 5β-Reductase (AKR1D1) has a crucial role in bile acid synthesis and also generates 5β-reduced dihydrosteroid metabolites, regulating intra-cellular steroid availability though the clearance of cortisol, testosterone, androstenedione and progesterone. As AKR1D1 sits at the interface of bile acid synthesis and steroid metabolism, we have hypothesised that it plays a key role in metabolic homeostasis and have generated and characterised an entirely novel, global AKR1D1 knockout (KO) mouse.

As expected AKR1D1KO mice had altered hepatic steroid (*in vitro* cortisone clearance: 100% [WT], 70% [KO]; *in vitro* 5α-cortisone/cortisol generation 100% [WT], 390% [KO]) and bile acid metabolism (hepatic bile concentration males: 1164±626 pmol/mg [WT], 122±42 pmol/mg [KO] $P<0.05$; females: 310±67 pmol/mg [WT], 113±23 pmol/mg [KO] $P<0.01$). At 10 weeks, KO animals were the same weight as wildtype (WT) littermates with no differences in glucose tolerance. Mice were challenged with a further 20-weeks of high fat diet feeding whereon female, but not male, AKR1D1KO mice were protected from diet induced weight gain (weight gain males: 21.8 g±0.9 g [WT], 21.4 g±0.7 g [KO] $P=$ns; females: 27.2 g±0.5 g [WT], 15.8 g±1.2 g [KO] $P<0.01$), with reduced adipose tissue mass across all depots (gonadal: 4.0 g±0.2 g [WT], 2.4 g±0.4 g [KO] $P<0.005$; subcutaneous: 3.9 g±0.3 g [WT], 2.4 g±0.5 g [KO] $P<0.05$; mesenteric: 1.9 g±0.2 g [WT], 1.2 g±0.3 g [KO] $P<0.05$), but with preserved lean mass. Female AKR1D1KO mice were also protected from the metabolic consequences of the high fat diet, with improved glucose tolerance (ipGTT AUC females: 3216 mMol×min [WT], 2601 mMol×min [KO] $P<0.05$) and enhanced insulin sensitivity (ipITT AUC females: 1171 mMol×min [WT], 947 mMol×min [KO]).

AKR1D1KO mice display a sexually dimorphic metabolic phenotype, where female mice are protected from the adverse metabolic effects of a high fat diet. Although the underpinning mechanisms remain to be fully defined, AKR1D1 may represent a future novel therapeutic target for the treatment of metabolic disease.

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OC12.3

Effects of weight loss and long-term weight maintenance with diets varying in protein and glycemic index on circulating pro-neurotensin in the Diet, Obesity, and Genes (DiOGenes) Study: a randomized, controlled trial

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Aims

Elevated levels of neurotensin (NT), a neurotransmitter and postprandial secreted intestinal hormone, are associated with an increased risk of diabetes, cardiovascular disease and breast cancer. Here we studied the regulation of

circulating pro-NT (a stable NT precursor fragment) by weight loss and dietary interventions.
Methods
DiOGenes is a pan-European controlled dietary intervention study in overweight adults who first lost body weight on an 8-week low-calorie diet (800 kcal/day) and were then randomized to 1 of 5 ad libitum diets for 26 weeks. The diets were either high (HPI) or low (LPI) protein or high (HGI) or low (LGI) glycemic index in 4 combinations or control.
Results
Weight loss (11.2 ± 3.5 kg; $P < 0.001$) reduced pro-NT (202.6 ± 117.8 pmol/l to 186.5 ± 96.1 pmol/l; $P = 0.007$) and was similar in both genders. During the weight maintenance period, pro-NT showed a trend to increase among both genders assigned to HGI diets (m/w; $P = 0.11$ and $P = 0.08$), and no changes of pro-NT in LGI diets. LPI increased pro-NT levels in male subjects ($P = 0.003$), and no changes in HPI. In women, both HPI and LPI had no effects on circulating pro-NT. Additionally we divided subjects in three groups depended on baseline pro-NT values. Subjects with "low-proNT" (values $< 25^{th}$ percentile) showed an increase of pro-NT after weight-loss followed by small decrease in the 26-week weight maintenance period. In contrast, the subjects with "high-proNT" (values $> 75^{th}$ percentile) showed an opposite response. No differences were observed in anthropometrical or biochemical parameters between three quartiles at baseline. "Low-proNT" stratum showed lower weight under both LGI-diets ($P = 0.046$).
Discussion
Our data suggest that a pro-NT reduction after weight loss is better maintained by LGI and HPI diets. Weight loss inversely regulates circulating pro-NT suggesting an intrinsic physiological phenomenon that possibly reflects the central regulation of the weight maintenance.

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OC12.4

GLP-1 directed delivery of dexamethasone ameliorates hypothalamic inflammation and reverses diet-induced obesity

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Abstract
Inflammation plays a contributing role in the pathogenesis of several metabolic disorders, including type 2 diabetes and obesity. Intriguingly, obesogenic diets induce markers of hypothalamic inflammation and neuronal injury in both rodents and humans, suggesting that targeting inflammatory pathways in the hypothalamus might represent a novel strategy to control energy metabolism. Unfortunately, the majority of steroid-based anti-inflammatory drugs are fraught with adverse off-target effects that restrict their use for the chronic treatment of metabolic diseases. We developed a new series of peptide/nuclear hormone conjugates with the aim to selectively deliver anti-inflammatory signals to tissues entwined in metabolic inflammation, including the hypothalamus. Our data show that GLP-1/dexamethasone conjugates allow selective delivery of dexamethasone to tissues expressing GLP-1 receptors. This pharmacological approach reduces markers of inflammation in the hypothalamus in a body weight-independent manner; it restores energy metabolic signalling and drives weight loss in diet-induced obese mice. Such positive metabolic effects are greater than those observed with equivalent GLP-1 or dexamethasone treatment alone. Intriguingly, mice bearing a genetic deletion of GLP-1R in the central nervous system, were only partially responsive to the compound-induced effects on energy metabolism, indicating that central delivery of anti-inflammatory signals is required for the positive metabolic effects of GLP-1/dexamethasone conjugates.
The GLP-1/dexamethasone conjugate does not induce glucocorticoid signalling in GLP-1R negative tissues and further, classical hallmark drawbacks associated with chronic dexamethasone treatment are circumvented with the peptide-medicated delivery approach, including: (i) muscle wasting, (ii) negative impact on bone turnover, and (iii) the diabetogenic liability of hepatic glucocorticoid action.
These preclinical studies imply that selective delivery of dexamethasone to GLP-1R expressing cells hold promise to safely treat metabolic inflammation and obesity, possibly by reversing inflammatory like processes in the hypothalamus.

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OC12.5

GNB3 overexpression causes obesity and metabolic syndrome

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Duplication of the guanine nucleotide-binding protein beta subunit 3 (*GNB3*) gene is associated with early-onset obesity in individuals with an unbalanced chromosome translocation. Additionally, a cytosine to thymine (C825T) polymorphism in *GNB3* is associated with hypertension, obesity and metabolic syndrome; however, the mechanism of *GNB3*-related obesity is unknown. We created BAC-transgenic mice that carry an extra copy of the human risk-allele (T) of GNB3.
Heterozygous mice express transgenic *GNB3* in whole brain, hypothalamus, olfactory bulb, and cerebellum at levels significantly greater than endogenous Gnb3.
These *GNB3*-T mice weigh significantly more than their wild-type littermates starting at age 6–7 weeks ($P = 0.002$). At 20 weeks, *GNB3*-T mice have increased adiposity, indicated by greater subcutaneous and visceral white adipose tissue (WAT) and brown adipose tissue (BAT) depots, larger white adipocytes, and larger livers compared to wild-types. Lean mass is approximately the same in *GNB3*-T and wild-type mice, suggesting that the difference in weight is strictly due to an increase in fat mass. *GNB3*-T mice have similar food intake and activity levels compared to wild-types. Fasting plasma ghrelin and PYY levels are similar to wild-types, while amylin is elevated in *GNB3*-T mice at 20 weeks, indicating proper satiety. *GNB3*-T mice have glucose intolerance and elevated fasting plasma glucose, insulin, C-peptide, consistent with type 2 diabetes. *GNB3*-T mice also have higher fasting plasma leptin, triglycerides, total cholesterol and phospholipids compared to wild-types. Volume oxygen consumed, heat produced and respiratory exchange ratio are not significantly different in *GNB3*-T mice and wild-types. *GNB3*-T mice have difficulty maintaining core body temperature during acute cold stress compared to wild-types. Citrate synthase activity in subcutaneous WAT and BAT depots is not different in *GNB3*-T and wild-types. *GNB3*-T mice have lower *Ucp1* expression in subcutaneous WAT. Taken together, these data support a role for *GNB3* overexpression in obesity and metabolic syndrome.

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Pituitary Clinical

OC13.1

Acromegaly is associated with increased cancer risk: a nationwide survey in Italy on behalf of the Italian study group of acromegaly

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Introduction
That acromegaly may cause cancer remains an unsolved issue. Aim of the present study was to assess the standardized incidence ratios (SIRs) of different types of cancer in a nationwide multicenter cohort study in Italy on acromegalic patients who have been treated in the somatostatin-receptor ligands era.
Methods and design
We have evaluated the prevalence of neoplasia from a series of 1512 patients who were proactively followed in 24 tertiary referral centers in Italy. They were 624 (41.2%) men (median age at diagnosis 42 years) and 888 (58.8%) women (median age at diagnosis 47 years). Cancer registrations were coded using the ICD-9, and data were compared to the general Italian population using the cancer registry AIRTUM.
Results
SIR for all cancers was increased compared to the general Italian population (1.41; 95%CI, 1.18–1.68, $P < 0.001$). In female patients, incidence of all malignancies was increased (SIR 1.51; 95% CI, 1.20–1.91, $P < 0.001$), as was incidence of thyroid cancer, colorectal cancer, and breast cancer. In male patients, incidence of all malignancies was increased (SIR 1.29; 95% CI, 0.99–1.7), as was incidence of thyroid cancer, kidney cancer, and colorectal cancer. In multivariable analysis, factors significantly associated with an increased risk of cancer were age and family history of cancer.
Conclusions
We found evidence that acromegaly is associated with a moderate increase in cancer risk. This may explain why previous underpowered studies failed to

demonstrate it. Much of the risk is attributable to thyroid and colon cancer in both genders, breast cancer in women, and kidney cancer in men.

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OC13.2

Growth hormone and insulin signalling after acute GH exposure in patients with controlled acromegaly: impact of surgery versus somatostatin analog treatment

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Background
Somatostatin analogue treatment (SA) is used in acromegaly to suppress GH secretion and tumour growth. In addition, SA also suppresses insulin secretion and may impact on GH signalling in peripheral tissues.
Objective
To compare GH and insulin signalling in skeletal muscle and adipose tissue in vivo before and after a single exogenous GH bolus in patients with acromegaly controlled by either surgery alone or by ongoing treatment with a slow-release SA.
Design
Eighteen patients considered controlled by either surgery alone ($n=9$) or SA treatment ($n=9$) were studied for 3 h after an overnight fast ($t=-60$ min to $t=120$ min) with frequent blood sampling. A GH bolus was administered at $t=0$ min and muscle and fat biopsies were obtained at $t=0$ min and at $t=30$ min (muscle) and at $t=120$ min (fat). Interstitial fluid was obtained from skin suction blisters at $t=0$ min.
Methods
GH and IGF-I measurements in serum and interstitial fluid. Insulin and FFA levels measured in serum. Targets of GH and insulin signalling measured in muscle and fat by quantitative RT-PCR and western blotting.
Results
The two groups were comparable as regards GH and IGF-I levels. However, SA treated patients exhibited higher circulating levels of free fatty acids ($P=0.04$) and glucose ($P=0.02$). The SA treated group exhibited increased basal SOCS1 mRNA expression in adipose tissue. A distinct activation of GH signalling (STAT5 phosphorylation) in skeletal muscle was detected after GH exposure in both groups ($P<0.01$), which was accompanied by increased expression of SOCS and CISH genes. A significant GH-induced phosphorylation of muscle AKT was only observed in SA treated patients. In both groups the gene expression of PTEN, a negative regulator of insulin signalling, increased significantly in fat after GH exposure.
Conclusion
1) Certain metabolic and biological signatures of GH and insulin signalling differ between acomegalic patients controlled by either surgery alone or SA treatment, 2) SA treatment unmasks an acute stimulatory effect of GH on AKT signalling in vivo, 3) These differences may be secondary to SA-induced insulin suppression of insulin.

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OC13.3

Increased glucocorticoid replacement doses are associated with excess mortality in patients with non-functioning pituitary adenoma

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Background
Patients with secondary adrenal insufficiency have an excess mortality. Data concerning the influence of the glucocorticoid replacement regime on mortality is sparse.
Objective
To investigate if the total daily dose of glucocorticoid replacement has an effect on mortality in patients with non-functioning pituitary adenoma (NFPA).
Method
Patients with NFPA treated for hypopituitarism in the western region of Sweden were retrospectively analysed. Patients were cross-referenced with the Swedish National Death Registry. Cox-regression analyses with 95% confidence intervals (CI) were used to identify predictors for mortality. Patients were sub-grouped depending on their total daily dose of hydrocortisone (HC) equivalents (156 patients with $\leq$20 mg HC; 50 patients with $>$20 mg HC). HC was used by 198 patients (96%) at last follow-up.
Results
A total of 405 patients (264 men, 141 women) with NFPA were identified. Mean ($\pm$SD) age at diagnosis was 58 ± 15 years and mean follow-up time was 11 ± 9 years. Treatment with radiotherapy was used in 75 patients (19%). Death occurred in 76 patients (51 patients with glucocorticoid replacement). Secondary adrenal insufficiency was found in 206 patients (151 men, 55 women), which received a mean daily HC equivalents dose of 21 ± 8 mg. A cox-regression of the glucocorticoid replacement patients showed that age (Hazard ratio (HR) 1.14; 95% CI 1.10–1.19), diabetes insipidus (3.18; 1.50–6.74) and a daily HC equivalents dose of $>$20 mg (2.07; 1.13–3.77) had a negative effect on mortality, whereas body weight (0.99; 0.97–1.01) and treatment with radiotherapy (1.00; 0.45–2.22) did not. The HR for male gender was 1.75 (95% CI 0.83–3.68).
Conclusion
Daily HC replacement doses of more than 20 mg per day and the presence of diabetes insipidus are associated with increased mortality risk in patients with NFPA and secondary adrenal insufficiency.

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OC13.4

Diagnosis and management of thyrotropin-secreting pituitary tumors: a single center experience with a long-term follow-up of 30 patients

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TSH secreting pituitary adenomas are rare tumours for which the treatment of choice is neurosurgery but in some cases medical treatment with somatostatin analogs (SSA) can lead to a good control of symptoms and shrinkage of the tumour.
The objective of this study was to review 30 patients diagnosed with TSH-omas between October 1981–July 2014, followed-up for a median of 43.93 months (1.12–192.11) in our University Hospital from Lyon, France.
The median age was 49 years, 73% of the patients were females. Fourteen patients presented signs and symptoms of hyperthyroidism, nine presented signs of a pituitary tumour. Before diagnosis, 2 patients undergone thyroidectomy and one received radioactive iodine. The median delay until positive diagnosis of TSH-oma was 18 months (2–264). Biochemical hyperthyroidism was found in 22 patients, alpha subunit was above upper normal limit in 77.7% of patients, nine patients presented hyperprolactinemia and 3 were also diagnosed with acromegaly. In 80% of cases, the tumours were macroadenomas with a median diameter of 13.2 mm. Fourteen adenomas had suprasellar extension, cavernous sinus invasion was present in 26.6% ($n=8$) of cases and 13.3% ($n=4$) of cases presented with sphenoid sinus invasion.
Ten patients were treated with SSA that lead to adequate control of the disease in 4 cases. In other six patients, SSA therapy was followed by surgery after achieving euthyroidism ($n=3$) or because of side effects ($n=3$). After a median follow-up of 45.63 months (2.3–190.82) after surgery of 26 patients, 78.9% ($n=15$) were in complete remission, 3 with macroadenomas had persistent disease controlled by medical treatment (SSA or SSA and GHRA) and one patient with a macroadenoma was controlled after pituitary radiotherapy and SSA while 7 patients were lost during follow-up.
In conclusion, neurosurgery should be first line therapy for microadenomas, while SSA treatment could be used for invasive macroadenomas.

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OC13.5

Unmet health and information needs of women with hypogonadotropic hypogonadism

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Background
Congenital hypogonadotropic hypogonadism (CHH) is a rare disorder (1:4′000-10′000) characterized by absent puberty and infertility. There is striking gender discordance (3–4 males for each female case) thus women with CHH are the "rarest of the rare". Unlike many orphan conditions, treatments are available and hormonal therapies are effective for inducing puberty and fertility. However, the presumable availability of treatment does not necessarily ensure quality of life. Therefore, we aimed to better understand the healthcare experiences and unmet needs of women with CHH to develop more patient-centered approaches to care.
Methods
We utilized a community-based participatory research approach to engage patient community leaders and develop an online survey. We then leveraged patient social media sites to reach these dispersed women. Demographics, medical history, and information on healthcare interactions were collected and patients completed three validated questionnaires to assess the relationship between illness perceptions, depressive symptoms and adherence to treatment. Descriptive statistics and comparisons to reference populations were conducted.
Results
In total, 55 women completed the survey (18–68 years, mean 35 ± 10, median 34). Women were more likely to have been in a relationship compared to their male ($n = 101$) counterparts ($P < 0.05$). Roughly 1/3 of CHH patients had received fertility treatment yet women were more likely to have biologic children (80% vs. 28%, $P < 0.01$). Notably, both sexes struggled with adherence to treatment and shared similar negative illness perceptions. Compared to community base rates, women with CHH have increased levels of moderate (9/55, 16%) and severe depressive symptoms (7/15, 13%).
Conclusions
Despite available treatment and successful fertility outcomes, patients with CHH report significant physical, psychological and social consequences as a result of their condition. They often struggle with adherence and exhibit increased depressive symptoms which negatively impact quality of life. These data underscore the importance of attending to the psychological needs of patients in addition to adequate hormonal therapy.

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Thyroid Cancer

OC14.1

Tumor and normal thyroid stem-like cells: from tissues to zebrafish

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Introduction
Cells with stem-like properties have been reported in benign and malignant thyroid diseases, and can be propagated by culturing them as non-adherent spheres.
Design
Aim of the present study was to widely characterize the stem-like cells in tumor and normal thyroid tissues and in the corresponding *in vitro*-cultured thyrospheres, and to investigate *in vivo* the proangiogenic potential of thyrospheres in a zebrafish model.
Result
Among the stemness markers tested, POU5F1/OCT4 has the highest expression in both tumor tissues and thyrospheres. POU5F1/OCT4 is expressed in the core of tumor thyrospheres, whereas TG and TTF1 differentiation markers are expressed at the periphery, indicating a progressive differentiative process from the center to the border of the spheres. Endothelial markers (CD34 and CD31) are co-expressed in both tumor and normal spheres, mimicking the formation of vascular structures, consistent with the pluripotency of the spheres cells which are able to directly contribute to their own vasculature. Finally, we show that the injection of either tumor or normal thyrospheres into the subepidermal space of zebrafish embryos stimulates the migration and growth of sprouting vessels toward the implant.
Conclusion
We widely characterized stem-like cells in thyroid tissues and in the corresponding thyrospheres, and established xenografts in zebrafish. These *in vitro* and *in vivo* models are expected to become a valuable platform to test the effects of novel compounds on stem-like cells.

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OC14.2

Complex immunometabolic pathways mediate the interaction between thyroid carcinoma cells and tumor-associated macrophages

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Background
Tumor-associated macrophages (TAMs) with dysregulated inflammatory phenotypes play a key role in carcinogenesis. In thyroid carcinoma (TC), excessive release of proinflammatory cytokines decreases the expression of sodium-iodine transporter and inflammation potentiates tumor progression.
Aim
To assess the impact of TC cells on the functional reprograming of TC-induced macrophages at the level of transcriptome and metabolic pathways, and assess their influence on the proinflammatory phenotype of TAMs.
Methods
TC cell lines TPC1, BC-PAP and FTC133 were co-incubated with human monocytes in a trans-well system. Release of cytokines and transcriptomics profiles of the immune cells and of the TC cell lines were investigated. The metabolic reprogramming was validated by metabolite assessment, perturbation experiments, and immunohistochemical (IHC) assessment of metabolic enzymes in TAMs in TC tissue samples.
Results
Co-incubation of TC cells with monocytes and stimulation of monocytes with TC-conditioned medium resulted in differentiation of TC-induced macrophages with a strong proinflammatory profile producing 3- to 5-fold more proinflammatory cytokines (TNF, IL–6) and chemokines (IL–8) than control macrophages. Metabolite assessment and perturbation experiments revealed a central role for lactate-mediated effects. Transcriptome profiling of TC-induced macrophages identified strongly upregulated metabolic pathways e.g. glycolysis. This was confirmed by IHC staining of glycolytic enzymes and receptors (PFKFB3, PKM2, lactate receptor) in TAMs in TC tissue and by an increased maximal extracellular acidification rate of TC-induced macrophages. Inhibition of mTOR reversed the upregulation of cytokine production which was partially dependent on epigenetic histone modifications (H3K4me3) at the promoter sites of IL6 and TNFα.To support the role of mTOR pathway we investigated SNPs in PI3K, Akt, and mTOR in two separate cohorts of TC patients. Akt1 SNP rs3803304, resulting in increased phosphorylation of Akt, was more prevalent in TC patients.
Conclusion
Transcriptional regulatory nodes involving metabolic pathways e.g. aerobic glycolysis regulate the interplay between TC cells and TAM, resulting in a microenvironment with a strong inflammatory profile. These pathways represent potential therapeutic targets in TC.

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OC14.3

Tert and the oxidative stress in papillary thyroid cancer

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Abstract
During hormonogenesis, thyroid cells are physiologically exposed to high levels of reactive oxygen species (ROS) which could either be involved in the pathogenesis of thyroid cancer or exert a cytotoxic effect. We analyzed the oxidative status of papillary thyroid cancer (PTC) either directly, by measuring H_2O_2 generation by NADPH oxidases (NOXs), and indirectly, by evaluating the antioxidant activity of glutathione peroxidase (GPX), which neutralizes H_2O_2 excess, and lipid peroxidation (LP). Moreover, since TERT exhibits a stress protection activity upon its translocation to the mitochondria, we investigated its subcellular localization in PTC.
A significantly higher calcium-dependent and independent H_2O_2 generation activity was found in tumors with respect to normal tissues. Interestingly, BRAF/RAS mutated tumors had a H_2O_2 production higher than wild-type tumors, and a trend towards a higher H_2O_2 generation activity was found in tumors from females compared to males. The GPX activity was found to be higher in PTCs with respect to normal tissues, and was significantly increased in tumors from young than from older patients, while no differences were found in lipid peroxidation. GPX activity. Moreover, we demonstrated for the first time the mitochondrial localization of TERT in PTC, suggesting that the elevated ROS levels associated with TC could be responsible for the shuttling of TERT from the nucleus to the mitochondria.
In conclusion, present data demonstrate that PTCs are exposed to elevated ROS, with a potential cytotoxic effect. Nevertheless, the increase of GPX activity and the mitochondrial localization of TERT seem to be able to compensate the damage derived from the excessive ROS exposure, supporting the neoplastic process.

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OC14.4

Prognostic value of microscopic extrathyroid extension in papillary thyroid carcinoma

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Introduction
Although recognized as a risk factor in most staging systems, including the UICC TNM classification, the significance of microscopic extrathyroid extension (ETE) in papillary thyroid carcinoma (PTC) remains controversial. Despite this fact, its diagnosis by a pathologist following surgery for tumours $\leq$ 4 cm without metastases means an upstaging to pT3 and stage III in patients over 45 years, implying a poorer survival. Our study aimed to evaluate the impact of microscopic ETE on outcome in patients with otherwise T1 and T2 PTC.
Methods/design
This was a retrospective study of 603 consecutive patients identified from our institutional database, who underwent surgery for PTC between 2000 and 2012. All patients had: tumours $\leq$ 4 cm, apparent complete tumor resection, without clinically apparent lymph node or distant metastasis at diagnosis and nonaggressive histologic variant. The association between variables was assessed using chi-square and Student's t-tests.
Results
All patients were followed for a minimum of 3 years postoperatively (76.7 ± 48.7 months). Ninety four (15.6%) patients were upstaged to T3 based on the finding of microscopic ETE. These patients were older (54.3 ± 12.4 versus 49.9 ± 14.2 years; $P=0.005$) and had larger tumours (15.9 ± 9.3 versus 13.5 ± 9.7 mm; $P=0.0025$). Radioiodine ablation therapy was administered more often to T3 patients (97.7% versus 40.2%; $P<0.001$), as well as prophylactic lymph node resection (37.6% versus 25.6%; $P=0.017$). There were no significant associations between microscopic ETE and extension of thyroid surgery (total thyroidectomy was performed in 94.9% of T1/T2 patients versus 97.9% of T3 patients; $P=0.288$), in recurrence rate (3.8% versus 6.7%; $P=0.245$) or persistence of disease at the end of the follow-up period (1.7% versus 4.4%; $P=0.106$). No disease-specific mortality occurred in either group.
Conclusion
Our results suggest that upstaging of T1/T2 PTC because of microscopic ETE may not have an impact on patients' outcomes, namely recurrence, persistence of disease and mortality.

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OC14.5

Clinical presentation, treatment and outcome of anaplastic thyroid carcinoma in Germany: a retrospective multi-center study

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Context
Anaplastic (ATC) thyroid carcinoma is an orphan disease accounting for about 2% of all malignant thyroid tumors. ATC confers a dismal prognosis and standard treatment is not established.
Objective
To describe the epidemiology, current treatment regimens and outcome of ATC, to identify clinical prognostic markers and treatment factors associated with improved prognosis. To establish a consensus treatment schedule.
Design
Retrospective multicenter study.
Setting
6 German tertiary referral centers.
Patients
100 ATC patients diagnosed 2000 -2015
Main outcome measure
Disease specific overall survival (OS).
Results
Tumor stage was IVA in 9, IVB in 32 and IVC in 54 patients (unknown: 5). The 1-month, 1-year, 3-year, and 5-year disease specific OS rates were 37%, 28%, 18%, and 5%, respectively. Stage dependent OS at 6 months was 78%, 54% and 18% for stage IVA, B and C respectively. 29 patients survived >1 year. Multivariate analysis of OS using Cox proportional hazard regression identified age ≥ 70 years, incomplete local resection status and the presence of distant metastasis as significant risk factors for shorter survival. Radical surgery (hazard ratio [HR] 2.201, 95% confidence interval 1.186–4.086, $P=0.012$), external beam radiation (EBRT) ≥ 40 Gy (HR 0.339, 95%–CI 0.152–0.759, $P=0.008$) and any kind of chemotherapy (CTX) (HR 11.636, 95%–CI 2.424–60.394, $P=0.003$) were associated with longer survival in multivariate analyses adjusted for age and tumor stage. A multimodal treatment regimen applied in 49/100 patients was associated with a marginal survival benefit (HR 1.040, 1.007–1.075, $P<0.0001$) only in IVC patients ($n=25$).
Conclusion
Disease specific OS is still poor in ATC. Treatment factors associated with longer survival were identified. These were taken into account to develop a consensus treatment schedule for multimodal management of ATC.

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Guided Posters

Adrenal

GP1

The role of primary cilia in the molecular pathogenesis of phaeochromocytoma

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Phaeochromocytomas are neuroendocrine tumours arising from adrenal medulla chromaffin cells. They are life threatening due to adrenaline and noradrenaline release and potential for metastatic spread. Understanding of phaeochromocytoma pathogenesis is incomplete with limited ability to predict malignant potential. Additionally, once metastatic, response to conventional therapies is disappointing.
Phaeochromocytomas are a common feature of the inherited cancer syndrome von Hippel-Lindau disease, which is caused by loss of function of the VHL protein. As well as its canonical function in degradation of the transcription factor hypoxia-inducible factor, VHL is implicated in formation and maintenance of primary cilia. These are microtubule-based organelles that protrude from the cells, functioning in transduction of extracellular signals. This is dependent on localisation of signalling components to cilia, including proteins linked to pathways that are dysregulated in tumorigenesis. Moreover, cilia are believed to act as a checkpoint for cell division, because they assemble from the basal body, which is a modified centriole and thus required for spindle pole formation at the end of interphase.
In this study we tested the hypothesis that primary cilia structure is disrupted in phaeochromocytomas, observing that incidence and length of primary cilia was reduced in sporadic and inherited phaeochromocytomas relative to normal adjacent tissue. This was also the case in primary cells cultured from phaeochromocytomas. Using the phaeochromocytoma derived PC12 cell line we showed that abrogation of cilia, through knockdown of the ciliary protein IFT88, correlated with an increased rate of cell division (quantified by Ki67 staining). We then investigated if features of the tumour microenvironment impact on ciliary function. These studies revealed that hypoxic conditions and succinate dehydrogenase inhibition result in disrupted cilia structure in the context of phaeochromocytoma.
Our data indicate primary cilia dysfunction is a feature of phaeochromocytomas, potentially contributing to pathogenesis and representing a target for therapeutic intervention.

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GP2

Screening for a ten-gene panel in a group of 90 phaeochromocytomas

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Background
Several new gene mutations have been reported in recent years to be associated with a risk of familial phaeochromocytomas (PHAEOs). However, it is unclear as to whether extensive genetic testing is required in all patients (pts).
Methods
Clinical data of consecutive patients operated for PHAEO over a decade in a tertiary referral centre were reviewed. Genetic screening was performed using a ten-gene panel: RET, VHL, SDHB, SDHD, SDHA, SDHC, SDHAF2, MAX, TMEM127, (NF1 when indicated; TMEM127 and SDHB if > 45 years and isolated PHAEO).
Results
A total of 157 patients (68 M: 43.3%, 89 F: 56.7%, age range 6–86 years, median 50.3 ± 17.4 years) underwent laparoscopic (85%), open (10.5%), or laparoscopic converted to open (4.5%) adrenalectomy for unilateral (92%) or bilateral (8%) adrenal PHAEOs: 90 pts underwent genetic screening, in particular 60/90 (66.7%) pts presented with apparently sporadic tumours and 30/90 (33.3%) pts had genetic mutations. These were more frequently seen with bilateral PHAEOs ($P = 0.02$). Mutations were seen in 12.2% pts for VHL, 10% NF1, 5.6% MEN2, 1.1% MEN3, 2.2% SDHD and 2.2% MAX. During a median follow-up of 50.4 months, 8% showed recurrent and 7% had metastatic disease. Younger pts showed a significant higher percentage of mutations compared to older pts (44% vs 17%). Twenty-seven percent of mutations were identified in pts with unilateral-non-recurrent PHAEOs within 5 years vs 62.5% in the recurrent-bilateral-metastatic group. Eighty-six of pts with bilateral disease had germline mutations (2 VHL, 2 RET, 1 NF1, 1 MAX).
Conclusions
The advent of rapid genetic screening for a ten-gene panel makes it feasible to screen large cohorts of pts, and allows for the prediction of bilateral and malignant disease and the screening of family members.

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GP3

Follow-up of adrenal incidentalomas – are we overdoing it? Follow-up of 145 patients from a single centre

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Background
Current practice of monitoring adrenal incidentalomas with biochemical follow-up and repeat imaging studies is under review by the ESE.
Following an audit presented in 2015, we proposed that this extensive follow-up was unnecessary in radiologically benign lesions, as neither functional nor malignant lesions were present in this subgroup.
Methods
A retrospective review of the same cohort of 145 patients with adrenal incidentalomas (January 2013 – January 2015), evaluated the outcome of repeat imaging and biochemistry.
Functionality was determined by overnight dexamethasone suppression test (cortisol > 140 defines autonomous cortisol secretion), renin: aldosterone, serum DHEAS and 24 h urinary metanephrines.
Results
Eighty-five percent were non-functional adenomas, 6% were benign lesions (e.g. angiomyolipomas). 0.7% had Conn's adenoma with raised renin:aldosterone. No patients had autonomous cortisol secretion. 4% were phaeochromocytomas – all were suspected on imaging and had raised urinary metanephrines; one had elevated DHEAS in addition. 4% were malignant lesions – 1.4% adrenocortical carcinomas (ACC), 2.1% metastases and 0.7% sarcoma.
Forty-eight percent of images were typical of benign adenomas, of which 70% had repeat imaging at an average time interval of 18 months – none changed. 45.5% of scans were indeterminate, however on further imaging 80% were considered benign adenomas with no change over an average time interval of 13 months. 3.5% of scans appeared malignant, of which 60% were phaeochromocytomas and 20% ACCs. The remainder were non-adrenal. 3% of scans were angiomyolipomas.
Mean duration from detection scan to most recent biochemical testing was 9 months, during which, 91% of incidentalomas remained non-functional. 23% of the cohort had repeat biochemistry; none progressed from non-functional to functional lesions.
Conclusion
We maintain that, follow-up is unnecessary for adrenal incidentalomas that are consistent with benign adenomas on initial imaging, and non-functional. Transformation to malignant or functional lesions is rare.

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GP4

The role of immunochemistry in the SDHx mutations in pheochromocytomas and paragangliomas

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Introduction
Early detection of succinate dehydrogenase complex (SDH) mutations in patients with pheochromocytoma and paragaglioma (PPC/PGL) has important implications as it is associated with increased risk for malignancy. The use of negative immunohistochemical (IHC) staining for SDH subunit B, D, A (SDHB/-D/-A) has been proposed as an indicator of SDHs mutation and as an effective substitute for the high-cost genetic screening of all of these genes.

Methods
We have performed SDHB/-D/-A immunohistochemical staining in a series of 27 paraffin embedded PPCs/PGLs specimens. Screening for point mutations by direct Sanger sequencing was performed in germline DNA from patients with potential aggressive (PASS > 6) or metastatic PPCs at the initial diagnosis or in cases of PGLs.
Results
Twenty-five cases with PPCs and two with PGLs were enrolled (16 females). Three cases were metastatic at diagnosis whereas one developed metastases during follow up. Ten cases (40%) had a PASS > 6. Genetic testing for germline analysis had previously been performed in 18 cases and positive results were found in six (one case was found posit if for SDHB mutation, one for familial SDHD, two for RET, one for NF1 and one for VHL mutation). The patient with the SDHB germinal mutation exhibited negative SDHB and positive SDHD/-A staining pattern. The patient with the SDHD germinal mutation exhibited negative SDHB/-D and positive SDHA staining pattern. Cases with RET, NF1 and VHL germline mutation as well as those wihout any mutations exhibited positive SDHB/-A and negative SDHD immunostaining.
Discussion
Our results are in agreement with previous series which have shown that SDHB/-D/-A immunohistochemical analysis could be a low cost technique to predict the presence of SDHx mutations.

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GP5

Improvement of bone turnover markers and bone mineral density following treatment of primary aldosteronism

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Context
Recent studies showed association between hyperaldosteronism and low bone density among patients with primary aldosteronism (PA) due to secondary hyperparathyroidism.
Objective
To assess bone turnover markers and bone mineral density (BMD) of PA patients compared to essential hypertension.
Design
This was an open label, prospective, case-controlled study, conducted over 12 months.
Setting
Eighteen consecutive out-patients with confirmed PA and seventeen age- and sex-matched controls were recruited.
Patients
All patients had confirmed PA based on Endocrine Society guideline. Controls were patients with essential hypertension.
Intervention
Bone turnover markers (CTX and P1NP), BMD, intact parathyroid hormone (iPTH), and bone profile were assessed at baseline and three months following treatment among 15 PA patients. Calcium intake was assessed using a validated questionnaire.
Main outcome measures
Primary outcomes were the changes of bone turnover markers and BMD following treatment of PA, and their relation to other parameters.
Results
PA patients had significantly lower serum calcium and higher iPTH despite comparable vitamin D levels with control group. Both bone turnover markers were significantly higher among the PA group. BMD of lumbar spine, neck of femur and distal radius did not differ between groups. Three months following treatment, there were significant i) increment of serum 25-OH vitamin D level, ii) reduction in iPTH level, iii) reduction in bone turnover markers and iv) improvement in the lumbar spine BMD.
Conclusion
PA is a state of high bone turnover in the presence of secondary hyperparathyroidism. Treatment of PA improves secondary hyperparathyroidism with reduction in bone turnover markers.

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GP6

Dissociation of subtype diagnosis by various criteria on adrenal venous samplings in primary aldosteronism

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Although the primary aldosteronism (PA) is the most common endocrinological hypertension accounted for approximately 10% of all hypertension population, the subtype classification criteria of adrenal venous samplings (AVS) have been still controversial. Thus, we demonstrated the several different criteria to diagnose the unilateral hyper-aldosteronism (UHA) suspected as adenomas in our series of patients with PA.
This study is included 213 AVS performed PA patients, diagnosed by at least one of the following conformational tests, upright furosemide test, saline infusion test and captopril challenge test, including both UHA and bilateral hyper-aldosteronism (BHA), and 184 AVS succeeded patients were analyzed. We employed as the success criteria of catheterization as selectivity index (SI), calculated by cortisol at each adrenal veins/inferior vena cava (IVC) > 2 for before ACTH stimulation and > 5 for after. We also employed the criteria for UHA; lateralized ratio (LR) > 2 for before stimulation and > 4 for the after, calculated by the dominant side of aldosterone/cortisol ratio (A/C) divided by the recessive side of A/C, the contralateral ratio (CR) < 1 for both before and after stimulation, calculated by recessive side of A/C divided by A/C at IVC, and the dominant side of aldosterone at adrenal vein (PAC) > 1400 ng/dl and ≤ 1400 ng/dl at the recessive side.
The patients background showed the average age was 56.0 ± 12.1 years old including 72 males and 112 females. Our result showed the prevalence diagnosed as UHA were 58.7, 12.0, 33.7, 15.2, 40.8% for LR > 2 without ACTH, LR > 4 with ACTH, CR < 1 without ACTH, CR < 1 with ACTH, and PAC > 1400 ng/dl, respectively.
These results clearly demonstrated that subtype diagnosis shows enormous dissociation depending on the decision criteria. The dissociated results of subtype cause profound impact in making decision for the type of therapy. The worldwide standardization of the decision criteria of AVS is required.

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GP7

New germline mutation in CACNA1H calcium channel causing primary aldosteronism

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Introduction
Primary aldosteronism (PA) occurs due to an excess production of aldosterone in the adrenal glands, resulting in low renin levels and hypertension. Familial hyperaldosteronism is considered to be a relatively rare disorder, with only a small number of genes having been implicated so far. The aim of the present study is to identify the molecular cause of disease in a PA family, as well as examining the mechanisms in an *in vitro* setting.
Patients and methods
Comprehensive biochemical and clinical phenotyping, as well as genome-level sequencing was performed in the PA family to identify the molecular cause. HEK293T cells then were transfected with wildtype and mutant expression plasmids to enable the production of electrophysiological recordings. To further investigate the potential physiologic effects of the mutation, we measured cytosolic Ca^{2+} dynamics by fluorescent live cell imaging in the HEK cells with wildtype and mutanted CACNA1H.
Results
We have identified the new heterozygous germline mutation in CACNA1H (p.G1064R) in the PA family. CACNA1H encodes a voltage-gated Ca^{2+} channel, which is expressed in the adrenal glomerulosa. The mutation lies in a conserved region in the II–III intracellular linker. Electrophysiological recordings showed no significant differences between the wildtype and mutant. However, the fluorescent live cell imaging experiments showed cell populations of HEK293T

cells transformed with the mutant variant with significant decrease in average periods of 10s ($P=0.02$), i.e. greater global spiking activity, compared to the wildtype variant.
Conclusions
Our analysis has identified a new mutation germline in CACNA1H that confers a decrease in average periods leading to greater spiking activity of the mutant. We postulate that these effects cause an increase in the influx of Ca^{2+} and that this is the stimulus for increased aldosterone production and cellular proliferation in the adrenal glands.

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GP8

Adequate salt intake attenuates mineralocorticoid receptor antagonist-induced hyperkalemia in patients with primary aldosteronism

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Introduction
Mild hyperkalemia is a common side-effect of mineralocorticoid receptor antagonists (MRA), which can be precipitated by minimizing dietary salt intake. Restoration of salt intake can overcome diminished kaliuresis and restore potassium levels. Aim of this study was the evaluation of the effect of adequate salt consumption on plasma potassium levels in relation to the mean, maximum and minimum blood pressure (BP) in MRA-treated sodium-depleted hyperkalemic patients with primary aldosteronism (PA).
Description of methods/design
Nine MRA-treated sodium-depleted PA patients (67.7 ± 9.7 years of age) were recruited. BP was documented by the patients and renin (plasma), aldosterone (plasma), potassium and sodium (plasma and 24 h urine) levels were measured while patients were following a sodium-restricted diet and after one month of adequate dietary salt supplementation (4 g of salt/day).
Results
Salt supplementation (24 h urine sodium: 199.39 ± 50.46 vs 101.06 ± 41.78 mmol/d) increased kaliuresis (68.9 ± 21.7 vs 54.21 ± 17.6 mmol/d, $P<0.001$) and resulted in a statistically significant decrease of potassium (4.64 ± 0.34 vs 5.28 ± 0.26 mmol/l, $P<0.001$), renin (43.2 ± 47 vs 53 ± 48.5 pg/ml, $P=0.004$) and aldosterone (1603 ± 1670 vs 2435 ± 1667 pmol/l, $P=0.015$) levels, without affecting plasma sodium levels (138.4 ± 2.65 vs 138 ± 2.69 mmol/l), mean diastolic or systolic BP (128.3 ± 10.6 vs 129.2 ± 10.2 and 71 ± 7.6 vs 71.1 ± 7.5 mmHg, respectively) or minimum and maximum BP values.
Conclusion
Adequate salt intake can attenuate MRA-induced hyperkalemia in sodium-depleted PA patients without short term effects on BP.

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GP9

Is steroid profiling using LC-MS/MS useful in the diagnostic work-up of primary aldosteronism?

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Introduction
Primary aldosteronism (PA) is mainly caused by unilateral aldosterone-producing adenomas (APA) or bilateral adrenal hyperplasia (BAH). Subtype differentiation relies on the invasive and technically challenging adrenal venous sampling (AVS). We recently demonstrated the potential utility of peripheral plasma steroid profiling by LC-MS/MS to distinguish APA and BAH. We tested the following hypotheses: first, if steroid profiling in combination with AVS, effectively identifies patients with unilateral disease who are candidates for surgery and second, if steroid profiling identifies those patients with a high likelihood for BAH in whom AVS may be avoided.
Methods
Two hundred and eight confirmed PA patients underwent computed tomography, AVS and steroid profiling of peripheral plasma by LC-MS/MS. Long-term outcome of adrenalectomy was assessed by clinical and biochemical re-evaluation in all subjects. The diagnostic accuracy for subtyping PA patients was calculated based on different strategies for PA subtype differentiation and compared to the gold standard of AVS.
Results
The diagnostic accuracy of AVS was 97%, with 6 out of 121 APA patients incorrectly classified on the basis of persistent PA following adrenalectomy. Steroid profiling correctly classified 79% of PA patients but this does not identify the adrenal source of aldosterone excess for the APA group. The most effective strategy in our model was steroid profiling followed by selective AVS in those patients designated by peripheral venous steroid profiling to have high likelihood of an APA. Here, 20 patients would have been falsely classified and treated as BAH while 6 patients with BAH falsely classified as APA by AVS would have been spared unnecessary adrenalectomy. Notably, the requirements for AVS would have been reduced by 43%.
Conclusion
Steroid profiling followed by AVS in the APA group could provide an alternative to AVS alone for subtype differentiation in PA patients, thereby significantly reducing the need for AVS.

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GP10

***PRKACA* somatic mutations are rare in aldosterone-producing adenomas.**

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Aldosterone-producing adenomas (APAs) are the most frequent cause of primary aldosteronism (PA). Somatic mutations of *KCNJ5*, *ATP1A1*, *CACNA1D* and *ATP2B3* are involved in APAs formation while *CTNNB1* and *GNAS* somatic mutations have been described in both APAs and in cortisol-producing adenomas (CPAs). In contrast, mutations of *PRKACA* coding for the catalytic subunit of protein kinase A have been yet only identified in CPAs.
We investigated a consecutive series of APAs from 122 Conn-patients after unilateral adrenalectomy. We performed exome or bidirectional Sanger sequencing of tumor-tissue and evaluated mutations in candidate genes as well as *PRKACA*. Exome sequencing revealed *PRKACA* somatic mutations in two APAs (1.6%). One APA carried a L206R mutation, previously described only in cortisol-producing adenoma with overt Cushing's syndrome, while in the second case a newly identified H88D mutation was found. Both affected patients were females with hypokalemic hypertension, aldosterone excess and lateralization during adrenal venous sampling. We functionally characterized the enzymatic activity of L206R and H88D mutated PKA catalytic subunit *in vitro* and characterized the immunoexpression of steroidogenic enzymes in affected tissues. Functional analysis showed that the newly found H88D mutation was not associated with gain of function of PKA. Interestingly, while CYP11B2 expression was found in the H88D-mutated APA, no co-expression of CYP11B1 was present. In contrast, in the L206R-mutated APA, CYP11B1 was expressed while CYP11B2 was weak or negative. Accordingly, biochemical Cushing's syndrome was present only in the patient with the L206R mutation. Following adrenalectomy, both patients improved with a reduced number of antihypertensive medications and normalized potassium levels. We describe here for the first time *PRKACA* mutations in APAs as rare findings associated with PA.

As cortisol co-secretion occurs in a sub-group of APAs other molecular mechanisms are likely to exist.

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GP11

Adrenal hormones as independent predictor factors of mortality during sepsis or septic shock

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Introduction
Activation of the hypothalamic–pituitary–adrenal axis is critical for adaptation to stress and serious illness. The imbalance between anti-inflammatory activity of cortisol and proinflammatory activity of the androgens, dehydroepiandrosterone (DHEA) and dihydroepiandrosterone sulfate (DHEAS) can be an important predictor factor of mortality in sepsis.
Material and methods
Patients diagnosed of severe sepsis or septic shock admitted to critical unit of Sierrallana Hospital in Torrelavega (Spain). Cortisol, DHEA and DHEAS were determined in the first 24 h of admission and mortality was recorded at 28 days. For each biomarker, area under curve (AUC) and its 95% CI were estimated by using ROC curves. Levels of biomarkers were ordinal categorized in tertiles (T1, T2 and T3), and as association measure odds ratios (OR) with their 95% CI adjusted for age, sex, SOFA and the presence of severe sepsis or septic shock were estimated.
Results
Data were obtained from 72 patients: median age 67.23 (IQR 17.9); 42/72 males (59.7%); 9/72 mortality at 28 days (12.7%). Predictive accuracy of biomarkers was: AUC total cortisol 0.74; 95% CI (0.55–0.93). AUC DHEA 0.55; 95% CI (0.34–0.76); AUC DHEAS 0,65 (0.50–0.79); AUC cortisol/DHEA 0.74 (0.55–0.92); AUC cortisol/DHEAS 0.79 (0.65–0.94). With regard to the risk of mortality for the patients at the higher tertil (T3) in comparison with the lower tertile (T1), the associations were: OR (total cortisol)=3.24 (0.56–18.76). OR (total cortisol/DHEA)=10.00 (1.10–90.59). OR (total cortisol/DHEAS)=4.17 (0.80–21.85). The results were not affected after adjusting for age, sex, SOFA scale or diagnosis of severe sepsis or septic shock.
Conclusion
Our results suggest that markers of adrenal function are independent predictors of mortality in patients with severe sepsis or septic shock. The predictive ability discriminated by the AUC of the ROC curve is higher for the ratios cortisol/DHEA and cortisol/DHEAs that for isolated values.

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GP12

Congenital adrenal hyperplasia (CAH) in adulthood

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Background and aim
Up to now, there is paucity of studies concerning health status in adults with congenital adrenal hyperplasia (CAH). We aimed to examine a group of adult CAH patients from different Czech centers.
Methods
Serum lipids, glucose, blood pressure and anhtropometrics were compared in 31 males and 71 females with CAH 21-hydroxylase deficiency and in healthy population from Czech post-MONICA study (1% random population sample).
Výsledky: CAH males were significantly smaller (161.4 (1.3) vs 178.5 (0.2) cm; $P=0.0001$), had lower total (4.6 (0.23) vs 5.2 (0.02) mmol/l; $P=0.009$) a and higher HDL-cholesterol (1.5 (0.07) vs. 1.30 (0.009) mmol/l; $P=0.004$) and lower triglycerides (1.16 (0.19) vs 1.6 (0.02) mmol/l, $P=0.02$) than healthy males. Dyslipidemia (total cholesterol $\geq$ 5 or LDL cholesterol $\geq$3 mmol/) was present in 24% of them.
Women with CAH were significantly smaller (154.9 (0.8) vs 165.7 (0.2) cm; $P=0.0001$), had higher BMI (28.5 (0.7) vs 26.5 (0.14) kg/m^2 $P=0.005$), higher total (5.49 (0.13) vs 5.16 (0.02) mmol/l; $P=0.02$) and higher HDL-cholesterol (1.8(0.06) vs 1.63 (0.009) mmol/l; $P=0.002$) than healthy females. Total cholesterol $\geq$5 mmol/l was present in 56% of them and LDL-cholesterol $\geq$3 mmol/l in 41%.
Osteopenia/osteoporosis was present in 35% (5/14) males and in 31% (8/26) females.
Conclusion
CAH males do not have impaired cardiovascular risk factors. In CAH women, dyslipidemia was present in 56 and obesity was more common than in healthy population.
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GP13

ACTH stimulation test (250 μg): is salivary cortisol an alternative to serum cortisol?

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Introduction
Most serum cortisol (SeC) is linked to *cortisol binding globulin* and albumin. When the synthesis of proteins is reduced or increased, SeC does not reflect the actual free cortisol (FC) (active fraction). Methods for FC analysis are very laborious and expensive, which makes difficult to use them as a routine laboratory tests. Salivary cortisol (SaC) mirrors the FC in serum, being its measurement easier and cheaper. The determination of SaC, instead of total cortisol after stimulation with ACTH, has been proposed as an alternative for adrenal insufficiency diagnosis, but this test has not been standardized yet. The goal of this study is to determinate the reference values for SaC after stimulation with 250 μg of ACTH i.v. and their correlation with those for SeC.
Methods and design
Forty-five healthy volunteers and 39 patients with known adrenal insufficiency (primary or secondary) were included. After at least 8 h fast, serum and saliva samples were collected before and after the administration of 250 μg of ACTH i.v. for the determination of cortisol in times: 0′, 30′, 60′ and 90′. Patients received their last dosage of hidrocortisone at 0900 h the day before.
Results
All healthy volunteers had a SeC peak at 30 min $\geq$18 μg/dl. Healthy volunteers SaC [mean$\pm$SD (range), μg/dl] was: 0′:0.56$\pm$0.31(0.08–1.37); 30′;1.58$\pm$0.45(0.83–2.72); 60′:2.35$\pm$0.63(1.43–4.24); 90′:2.91$\pm$0.82(1.63–5.42). Patients SaC [mean$\pm$SD (range), μg/dl] was: 0′:0.33$\pm$0.30(0.05–1.53); 30′:0.32$\pm$0.24(0.05–1.17) 60′:0.32$\pm$0.24(0.05–0.90); 90′:0.37$\pm$0.50(0.05–3.13). The SaC correlated with SeC at all times, except in time 0′ for the group of patients. Healthy volunteers lower limit value SaC at 60′ was 1.43 μg/dl. This cut-off classified all patients correctly.
Conclusion
Measurement of SaC offers an alternative to SeC ACTH stimulation test (250 μg). We suggest that adrenal insufficiency can be excluded when SaC at 60′ is $\geq$1.43 μg/dl.

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GP14

A Phase 3b, open-label, extension study to evaluate the long-term safety of once-daily, dual-release hydrocortisone (DR-HC) in patients with adrenal insufficiency (AI)

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Introduction
Glucocorticoid replacement for adrenal insufficiency (AI) remains inadequate, resulting in high morbidity, premature mortality and quality-of-life (QoL) impairment. This study investigated the long-term safety of dual-release hydrocortisone (DR-HC) in patients with primary AI.
Methods
AI patients who completed a randomized, 3-month crossover study of once-daily DR-HC versus thrice-daily conventional immediate-release hydrocortisone plus a 6-month extension of DR-HC (Study 1; $n=55$) or who were newly recruited ($n=16$) were included in an open-label, 5-year study of DR-HC (Study 2). Outcomes included safety, intercurrent illness episodes and QoL. Study 2 results are presented for baseline (start of Study 2) to 5 years.
Results
In Study 1, DR-HC was well tolerated and improved metabolic factors, blood pressure and QoL [Johannsson et al. J Clin Endocrin Metab 2012;97:473−81]. In Study 2, 88.7% of patients completed the 5-year visit. Seventy patients (98.6%) reported 1060 adverse events (AEs), of which 84.8% were unrelated to DR-HC. Of 65 serious AEs reported by 32 patients (45.1%), four were possibly related to DR-HC: acute AI ($n=2$), gastritis ($n=1$), syncope ($n=1$). Two deaths were reported (fall from height, subarachnoid haemorrhage), both unrelated to DR-HC. For each 12-month period of the 5-year study, mean number of intercurrent illness episodes per patient varied from 2.64 to 5.42 and mean hydrocortisone dose per episode varied from 18.7 to 23.5 mg. Mean fasting plasma glucose (0.7 mmol/l; $P<0.0001$) and HDL-cholesterol (0.2 mmol/l; $P<0.0001$) increased. Patient-assessed DR-HC tolerability was better in 29.5% of patients, equal in 60.7% and worse in 9.8% at 5 years versus baseline ($P=0.02$). There were no significant changes in Fatigue Impact Scale (FIS) or Psychological General Well Being total scores, but FIS physical functioning worsened ($P=0.008$).
Conclusions
Long-term DR-HC therapy for AI patients was well tolerated with no safety concerns. Intercurrent illness episodes were stable, and fasting glucose and HDL-cholesterol increased during 5 years' treatment.

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GP15

Reduced temperature and the chemical chaperone 4-phenylbutyrate enhance stability of CYP21A2 mutations

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Background
Mutations of 21-hydroxylase (CYP21A2) cause congenital adrenal hyperplasia. Its severe (classic) form constitutes a life-threatening disease. Patients suffer a significant disease burden due to co-morbidities that are often treatment-related. The current therapeutic situation is unsatisfying and demands novel treatment approaches. *In silico* modelling suggests protein misfolding and intracellular retention to play a significant role in the pathogenesis of CAH.
Objective
To investigate protein misfolding and intracellular retention due to CYP21A2 mutations and explore pharmacological chaperones as potential therapeutic tools.
Methods
Clinically relevant CYP21A2 mutations where *in silico* modelling suggested protein misfolding to play a role in the pathogenesis of CAH were selected and subcloned into pcDNA6-V5/His expressing vectors. Residual activity of variant CYP21A2 proteins was determined in living COS-7 cells using an enzyme activity assay with LC/MSMS based analysis of steroids. The effect of mutations on protein half-life (susceptibility to proteinase K) was measured comparing wild-type and variant CYP21A2. The influence of 4-PBA and temperature on protein half-life was investigated.
Results
Our preliminary results show that with decreased temperature, susceptibility of selected mutations to proteolysis was significantly attenuated (protein half-life increased from 0.9 min ± 0.4 to 5.9 min ± 0.8 for G90V; from 1.4 min ± 0.1 to 5.5 min ± 0.9 for P30L; from 1.0 min ± 0.1 to 8.0 min ± 1.3 for P30Q; from 0.6 min ± 0.1 to 9.8 min ± 1.0 for R356W). The use of the chemical chaperone 4-PBA enhanced CYP21A2 half-life (3.8 min ± 0.5 to 11.0 min ± 1.6 for G375S). The same applied when the temperature was reduced to 30 °C resulting in partial rescue of the CYP21A2 loss-of-function phenotype.
Conclusions
Our preliminary data substantiate the hypothesis of protein misfolding with loss-of-function as a relevant molecular mechanism in CAH that can be addressed by structural stabilisation of CYP21A2.

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GP16

Increased morbidity and hospital admissions in patients with adrenal insufficiency

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Introduction
Patients with adrenal insufficiency (AI) (primary (PAI), secondary to pituitary disease (PIT) and congenital adrenal hyperplasia (CAH)) have reduced life expectancy with reported standardized mortality ratios of ∼2:1 but given the rarity of AI, the underlying explanation remains largely unknown.
Objective
To evaluate patient characteristics, prevalence of concomitant conditions and hospitalization incidence in patients with AI compared to a general population sample.
Methods
Using a US-based national payer database comprising > 108 million patients, we used strict inclusion criteria with robust diagnostic codes and pharmacy fill records of steroid prescriptions to identify 10 383 patients with AI; 1014 with PAI, 8818 with PIT and 551 with CAH were followed for > 12 months. Patients were matched 1:1 to controls, based on age (±5 years), gender, insurance type and region.

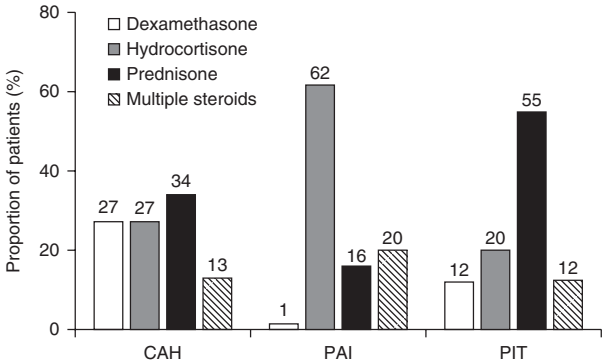

Figure 1 Steroid usage in the 6–12-month period after diagnosis of AI.

Results
Figure 1 shows steroids used according to AI cohort. Compared with controls, patients with AI had higher odds of diabetes mellitus, hypertension, hyperlipidaemia and depression and anxiety ranging from an OR of 1.51 for hyperlipidaemia in PAI and CAH to 3.85 for diabetes in CAH. The odds of having diabetes (OR = 3.85, 95% CI = 2.52–5.90) or anxiety (OR = 2.99, 95% CI = 2.02–4.42) were highest in CAH, while depression was highest in the PAI and PIT cohorts (OR = 2.40 and 2.55). Hyperlipidaemia and hypertension (OR = 1.98 and 2.24) were more common in the PIT cohort versus controls. Inpatient admissions were more frequent in PAI and PIT versus controls; for every 1 control inpatient admission, there were an estimated 4.64 admissions for the PAI cohort ($P < 0.0001$) and 4.00 admissions for the PIT cohort ($P < 0.0001$). Infection was the most common cause for admission.
Conclusion
Using data from > 10 000 adults with AI, our study suggests that all types of AI carry a significant metabolic and psychiatric burden, with higher risk of comorbidities and hospital admissions compared to the general population sample.

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GP17

Improved evening and nocturnal cortisol exposure time profile in patients with adrenal insufficiency treated with dual release hydrocortisone: correlation with improvement in metabolic profile

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Conventional glucocorticoids (GCs) are unable to mimic physiological cortisol rhythm in adrenal insufficiency (AI), with a significant impact on morbidity and mortality. Possible explanations are supra-physiological doses and impaired cortisol profile. In particular, elevated evening cortisol levels were related to glucose tolerance and insulin sensitivity alterations and visceral obesity. Once-daily-dual-release-hydrocortisone (OD-DR-HC), better reproducing the physiological cortisol profile, reported metabolic improvements in primary AI (PAI) patients switched from immediate release HC, thrice daily, to OD-DR-HC. The aim of this study was to evaluate the cortisol profile and its impact on metabolic outcome in PAI and secondary AI (SAI) patients treated with cortisone acetate twice daily (CA-BID). Eight AI patients on CA-BID underwent full sampling for serum cortisol during 24 h, at 3 h intervals, at baseline and 6 months after the switch to OD-DR-HC. Mean (0700–1300 h) AUC was 5.76% ($P = 1$) higher, whereas mean (1300–1900 h), (1900–0100 h), (1300–0700 h), and (1900–0700 h) AUC were 5.92% ($P = 0.6$), 48.69% ($P = 0.008$), 25.08% ($P = 0.031$) and 40.12% ($P = 0.008$) lower with OD-DR-HC than with CA-BID, respectively. Mean total cortisol (1900–0700 h) AUC was 14.4% lower ($P = 0.148$) with OD-DR-HC than with CA-BID. The afternoon peak with CA-BID was not observed with OD-DR-HC. Moreover, the decrease in (1900–0100 h) and (0100–1900 h) AUC was significantly correlated with glucose level decrease ($r = 0.99$; $P < 0.001$) and insulin sensitivity index (ISI) increase 120′ after glucose load ($r = -0.99$; $P < 0.001$), as well as with waist circumference ($r = 0.98$; $P < 0.001$) and triglycerides level reduction ($r = 0.95$; $P < 0.001$). In conclusion, total 24 h cortisol profile was reduced by 14.4%, providing a higher exposure during the first 6 h in the morning and then significant reductions throughout day and night. OD-DR-HC reduces late afternoon, evening and nocturnal GC overexposure, avoiding the second afternoon peak, suggesting a significant improvement in glucose tolerance, visceral adiposity and lipid profile. Further studies are needed to confirm and extend these preliminary data.

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GP18

Restoration of HPA axis is rapid in subclinical Cushing's syndrome after adrenalectomy

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Objective
In subclinical Cushing's syndrome (SC), it is assumed that glucocorticoid production is insufficient to cause a clinically recognizable syndrome. Differences in hormonal levels or recovery time of the hypothalamic–pituitary–adrenocortical (HPA) axis after adrenalectomy between patients with overt Cushing's syndrome (OC) and SC remain unknown.
Design and patients
Thirty seven patients (ten were OC and 27 were SC) with adrenal Cushing's syndrome who underwent adrenalectomy from 2004 to 2014 were reviewed retrospectively. Patients were treated with glucocorticoid after adrenalectomy, and adrenal function was evaluated every 1–6 months with a rapid ACTH stimulation test.
Results
Patients with SC were older than patients with OC. Levels of basal 24-h urine free cortisol (24hUFC), serum cortisol after an overnight dexamethasone suppression test (DST), and serum cortisol and 24hUFC after low- and high-dose DST were all significantly lower in patients with SC compared with OC ($P < 0.01$). The probability of recovering adrenal function differed significantly between patients with OC and SC ($P = 0.001$), with significant correlations with the degree of preoperative cortisol excess. Patients with OC required a longer duration of glucocorticoid replacement to recover a normal ACTH stimulation test compared with patients with SC (median 13.5 vs 4 months, $P < 0.001$), and seven patients with SC (26%) did not receive steroid replacement after adrenalectomy.
Conclusions
The HPA axis recovery time after adrenalectomy in patients with SC is rapid (within several months) and is dependent on the degree of cortisol excess. Routine postoperative glucocorticoid replacement is not necessary in some patients with SC.

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GP19

MUC-1: update on a newly established tumor model for adrenocortical carcinoma

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In an attempt, to overcome the lack of preclinical models for adrenocortical carcinoma (ACC), we recently aimed at the development of patient-individual tumor models for ACC. During these studies one xenograft (MUC-1), derived from a neck metastasis of an ACC, showed extraordinary engraftment properties and sustained tumor growth over several passages in the murine host. During ongoing studies we investigated and compared all currently available xenograft models for ACC (NCI-H295R, SW-13 and SJ-ACC3) regarding Ki67, SF-1 and EGF-receptor status among others with the newly established MUC-1 xenografts. *In vitro*, we established a primary culture based on explanted MUC-1 xenograft pieces. A first try of cell culture establishment failed after several passages due to a massive contamination by murine fibroblasts. Thus, we initiated a second round of culturing involving continuous and highly specific murine and human fibroblast removal. The resulting multi-clonal cell suspension is now viable in passage 15. In these cultures, cross-contamination by murine fibroblasts could be excluded on the basis of a Universal-Primer Probe-Assay. Representative pictures of passages 4, 7, 10 and 13 demonstrate furthermore specific Ki67 as well as nuclear SF-1 and cytoplasmic 3ßHSD immunopositivity. Moreover, genetic characteristics of MUC-1 cells were investigated by PCR-Single-Locus Technology ensuring a distinct marker profile different from that of NCI-H295R and SW-13 cells. Thereby, MUC-1 cells were recently authentified as a novel adrenocortical cell line of human origin.

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GP20

Responsiveness to hCG in postmenopausal women with adrenal adenomas

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Introduction
Luteinizning hormone (LH/hCG) responsiveness has been documented in both normal and pathological adrenal glands, but it is unclear whether chronic

exposure to LH could affect adrenal function by increasing LH receptor (LHR) expression.
Subjects and methods
We studied 12 postmenopausal women with previously documented adrenal tumor. All patients underwent standard hormonal testing for assessment of tumor functionality. Then hCG test was performed with measurement of adrenal androgens and estradiol levels from the blood. A 50% or more change of plasma level from baseline was considered as positive response. Statistical analysis was done by SPSS Software.
Results
Our patients were 60.4±5.8 years old (54–71), and were 12.4±7.9 years postmenopausal (1–23). Five patients (41.7%) had Cushing's syndrome, three of which had bilateral adrenal tumors, and the remaining seven had unilateral, clinically nonfunctional adrenal adenoma. By adequate rise in levels of estradiol, testosterone, DHEA-S and 17-OH progesterone we identified six patients (50%) that could be categorized as responders to hCG. Three out of five patients with Cushing's syndrome were responders, and three out of seven patients with nonfunctional tumors. There was no significant correlation between LH level and years after menopause with percent of change in any hormone tested ($P>(0.05)$. Responders and non-responders were not significantly different in any of the basal hormonal levels ($P>(0.05)$, but were significantly different in percents of hormone level change of all tested hormones ($P=0.019$ for estradiol, $P=0.002$ for 17-OH progesterone, $P=0.013$ for testosterone, and $P=0.029$ for DHEA-S). Among responders, there was no difference in hormonal responses to hCG regarding presence of Cushing's syndrome ($P>(0.05$ for all).
Conclusion
Responsiveness to hCG was more prevalent in our group of postmenopausal women than previously reported in patients with adrenal adenomas, suggesting a possible role of long term LH exposure.

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GP21

Clinical characteristics and tumour size evolution in patients with bilateral adrenal tumours

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10% of patients with adrenal tumours have bilateral lesion.
Objective
To evaluate clinical, imagistic and hormonal characteristics of bilateral adrenal tumours.
Design and mehods
Retrospective series of 150 consecutive patients (104F, 46M) with bilateral adrenal tumours with maximal diameter of at least 1 cm, evaluated from 2001 to 2015 in a tertiary endocrinology clinic with clinical, hormonal and imagistic methods.
Results
Age at diagnostic was 57.26±10.32 years (27–85). In 122 patients, adrenal tumours were diagnosed simultaneously, and 28 patients had metachronous tumours. Mean tumor size was 2.4±2.3 cm (right) and 2.5±2.4 cm (left). 22% patients had functioning tumours (22 patients with cortisol hypersecretion, including subclinical Cushing's syndrome, eight patients with pheocromocitoma, three patients with aldosterone hypersecretion). Four patients had adrenal carcinoma and ten patients adrenal bilateral metastasis. Clinical evaluation revealed younger age (44.90±12.98 years) in patients with pheocromocitoma and higher blood glucose (123.75±52.26 mg/dl vs 103.34±26.62 mg/dl, $P=0.03$) and tumor diameters (3.48±2.22 cm vs 2.23±2.42 cm, $P=0.02$ – right side and 3.86±2.23 cm vs 2.31±2.43 cm, $P=0.007$ – left side) in patients with cortisol secreting tumours as compared to patients with nonfunctioning tumours. Mean follow-up was 1.84±0.89 years in patients with synchronous tumours; in patients with metachronous tumours, second tumour was diagnosed after 5.44±9.37 years (maximum 49 years). In nonoperated nonfunctioning tumours, nonsignificant tumour size evolution was observed.
Conclusion
Our study suggests cortisol hypersecretion is the most frequent hormonal abnormality in patients with bilateral adrenal tumours. Although most nonfunctioning tumours are nonevolutive, as 9.3% of patients have primary or secondary adrenal cancer, conservative long-term follow up is needed.

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GP22

Clinical and polysomnographical evaluation of sleep in patients with Cushing's syndrome

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Introduction
Patients with Cushing's Syndrome (CS) frequently have sleep complaints. The aim of the study was to evaluate the prevalance sleep disturbances and sleep structure of patients with CS.
Materials and methods
33 patients with CS were evaluated both clinically and with polysomnograhy (PSG) findings in terms of sleep disorders and data were compared with 20 healthy controls.
Results
Seventeen (51.1%) patients with CS demonstrated sleep apnea (Apnea Hypopnea Index (AHI)≥5), with seven (21%) of 17 had severe sleep apnea (AHI≥30). Five (15%) patients had periodic limb movements (PLM) of sleep (PLM Index ≥15), 20 (60%) patients had clinical insomnia, and two (6.1%) patients had restless legs syndrome. None of the CS patients complained of hypersomnia (Epworth sleepiness scale ≥10). PSG parameters were compared only if participants had an AHI<5 and PLMI<15. The percentage of stage N2 sleep was significantly increased in CS patients (65.3±11.4%) compared to control subjects (54.4±13.3%). Although total sleep time (297.9±104.0 min in CS, vs 354.8±52.8 min in controls) and percentage of time spent in stage N3 sleep (12.9±1.9% in CS, vs 23.3±16.2% in controls) was reduced in CS patients, the difference was not statistically significant. Average heart rate (73.7±6.9/min in CS, vs 65.6±7.5/min in controls) and minimum heart rates (58.8±6.1/min in CS, vs 51.8±7.6/min in controls) were significantly higher in CS patients. There was a significant positive correlation between post-dexamethasone cortisol levels and AHI, and midnight cortisol levels and AHI in REM sleep. Minimum O_2 saturation was found to be negatively correlated with midnight cortisol and basal cortisol levels.
Conclusion
Insomnia and sleep apnea are frequent sleep disorders in CS patients. Absence of hypersomnia, alterations in sleep structure and higher heart rate during sleep support a hyperarousal state in CS. These alterations may potentially influence metabolic comorbidities associated with CS.

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GP23

Deterioration of indices of insulin resistance in patients with non-functioning and cortisol secreting adrenal incidentalomas during a long term follow-up

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Introduction
Adrenal incidentalomas (AI) with or without concomitant autonomous cortisol secretion can be associated with several metabolic alterations that may lead to increased cardiovascular risk. However, data regarding insulin resistance (IR) during long term follow-up of AI are scarce. The aim was to prospectively investigate the presence and evolution of IR in patients with AI between 2003 and 2014.
Methods
Seventy three patients with AI for at least a 3-year follow-up underwent a diagnostic protocol, which included clinical examination, anthropometric assessment, basal and dynamic adrenal testing for autonomous cortisol secretion (low dose dexamethasone suppression test). IR was define at HOMA >2.16 and QUICKI <0.34. Pheochromocytomas, aldosterone secreting adenomas and adrenocortical carcinomas were excluded.
Results
During the follow-up (5.60 ± 1.74 years) AI max diameter was increased ($P<0.001$) but this increase measured <0.5 cm; BMI ($P=0.02$) and waist circumference ($P=0.001$) increased, while more patients developed hypertension (11%), dyslipidemia (22%) and diabetes mellitus (T2DM). At baseline 2 (2.7%) patients were found to have T2DM that increased to 9 (12.3%) at the last follow-up ($P<0.001$). Hence, T2DM developed in 9.4% of patients with non-functioning AI (NFAI) and 20% with subtle autonomous cortisol secretion (CSAI). Moreover, 49.3% of patients had IR that increased to 68.5% at the last follow-up ($P<0.001$). At baseline, 41.5% of NFAI and 70% of CSAI patients exhibited IR compared to 58.5% of NFAI and 95% of CSAI at the last follow-up ($P<0.001$ and 0.3 respectively). At baseline, 20 AI patients had CSAI that increased to 31 at last follow-up ($P<0.001$). There was a positive correlation between post-dexamethasone cortisol levels (F-post-LDDST) and indices of IR in the whole group of patients both at baseline and at the last follow-up
Conclusions
Apparently non-functioning and/or autonomous cortisol secreting AI exhibit deterioration of carbohydrates metabolism and IR over a >3years follow-up that correlates with the F-post-LDDST levels.

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GP24

Does measurement of serum dexamethasone increase diagnostic accuracy of the overnight dexamethasone-suppression test?

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Background
1-mg overnight dexamethasone-suppression test (DST) is commonly used to screen for hypercortisolism. Sensitivity is high (95%), but specificity is low (80%), leading to false positive results. Identifying individuals with abnormal dexamethasone absorption or metabolism could enhance diagnostic accuracy.
Aim
Use serum dexamethasone (s-DXT) to increase diagnostic accuracy of DST.
Methods
Prospective study of DST for clinical suspicion of Cushing's syndrome (CS) ($n=49$), incidentaloma ($n=152$), and healthy controls ($n=101$). S-cortisol and s-DXT were assayed by liquid chromatography tandem mass spectrometry (LCMSMS). DST results were correlated to the final diagnosis based on current clinical guidelines.
Results
83/302 did not suppress s-cortisol (<50 nmol/l). Of these 11 had overt CS, and 27 subclinical CS (16% of the incidentalomas). A s-DXT cut-off level at 3.3 nmol/l was chosen based on the 2.5% quantile of DXT in those suppressing s-cortisol <50 nmol/l. Applying this cut-off, 10/302 (3.3%) DSTs were false positive with both inadequate s-DXT-levels and elevated s-cortisol. Of these, three were misdiagnosed as subclinical-CS. 12% of the positive DSTs could be explained by low levels of s- DXT. Among non-CS samples, s-cortisol values were higher in the incidentaloma-group (median 42.5 nmol/l, range 13–576) than in those with clinically suspected but not confirmed CS (22.7 nmol/l, 9.9–289) ($P<0.01$) and healthy controls (22.2 nmol/l, 8.4–102) ($P<0.01$). These findings were similar after eliminating patients with the lowest levels of DXT and estrogen users ($n=16$). Repeating DST in 30 healthy individuals shows excellent reproducibility of the test (interclass coefficient, ICC = 0,936).
Conclusions
Abnormal absorption or metabolism of dexamethasone is a common reason for false positive 1-mg DSTs. Simultaneous measurement of s-DXT increases the accuracy of the test, and reduces the risk of falsely diagnosing subclinical CS. A minimum s-DXT level of 3.3 nmol/l is needed to suppress S- cortisol <50 nmol/l.

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GP25

Novel genetic changes in Autosomal dominant, ACTH independent nacronodular adrenal hyperplasia associated with hypercortisolism and giant adrenals

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ACTH independent macronodular adrenal hyperplasia (AIMAH) is a rare cause of Cushing's syndrome. Both Phosphodiesterase 11A4 (PDE11A4) mutations and inactivating mutations of armadillo repeat containing 5(ARMC5) have been associated with familial AIMAH. A family with autosomal dominant AIMAH was studied trying to elucidate the involved genetic basis.
Methods and results
Adrenal hypercortisolism with giant bilateral AH was diagnosed in three adult members of the family, a mother and two sons. Further evaluation excluded the presence of aberrant receptors. Bilateral adrenalectomy of the index case was performed showing huge adrenal glands (460 g). DNA were extracted from peripheral blood lymphocytes. Sequencing of ARMC5 coding region in the proband revealed a novel heterozygote mutation, S767X. Interestingly, sequencing of PDE11A4 coding region revealed a heterozygote rare variant R867G, that has frequency of 2–3% in the general population. PDE11A4 gene defects have been associated with Carney complex and AIMAH, including R867G, probably acting as a phenotype modifier. Inmunohistochemical studies of the excised adrenal tissue showed a very low expression of PDE11A4 and ARMC5 compared to normal adrenals. The family was screened for hypercortisolism, adrenal hyperplasia (MRI) and genetic testing. All the patients with AIMAH carried both variants. Other siblings carrying either one mutation or none were healthy, with normal adrenal size. A 15 years old daughter of the index case harbored both variants, but her HPA axis evaluation was normal and the adrenals showed a normal size.
Conclusions
A family with ADAIMAH causing giant adrenal hyperplasia associated with a novel mutation in ARMC5 in conjunction with PDE11A4 mutation, causing low protein expression is reported. Coexistence of PDE11A4 variant in all three affected individuals may indicate a phenotype modifier role. Because clinical and biochemical abnormalities appear during adulthood, young phenotypically normal mutation carriers may be at risk of developing clinical disease in the future.

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GP26

LCI699 is a potent inhibitor of cortisol production *in vitro*

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Introduction
The steroidogenesis inhibitors ketoconazole and metyrapone are frequently used for treatment of Cushing's syndrome, but can cause side effects. LCI699 is a known 11β-hydroxylase inhibitor, but effects on other steroidogenic enzymes are unknown. We aimed to compare effects of LCI699, ketoconazole, and metyrapone *in vitro*.
Methods
HAC-15 cells, with or without 10 nM ACTH, and three primary human adrenocortical adenoma cultures were incubated with LCI699, ketoconazole, or metyrapone (3 days; 0.01–5 μM). Cortisol was measured in the supernatant using a chemiluminescence immunoassay system (Immulite 2000Xi), corrected for cell amount. Steroid profiling was carried out in HAC-15 control and 5 μM treated cells by liquid chromatography/mass spectrometry (LC-MS/MS).
Results
LCI699 inhibited cortisol production at significantly lower concentrations (EC_{50}: 0.038 μM; 95% CI 0.031–0.048) than ketoconazole (0.764 μM; 0.535–1.092, $P<0.0001$), and metyrapone (0.084 μM; 0.0602–0.117, $P<0.0001$). Under ACTH stimulation (mean cortisol increase 37.4±1.98%, $P<0.0001$), sensitivity only changed for LCI699 (0.056 μM; 0.046–0.070, $P<0.05$ vs basal EC_{50}). Treatment did not affect cell number. For three primary cultures, the cortisol EC_{50} of LCI699 (mean 0.050 μM) was significantly lower compared to that of ketoconazole (mean 0.984 μM; $P<0.05$). LCI699 strongly suppressed corticosterone and cortisol (91%, 87%, resp.; both $P<0.001$), and modestly suppressed androstenedione (38%), DHEA (38%), DHEAS (33%), testosterone (21%), and 17-hydroxyprogesterone (9.0%) production by HAC-15 cells ($P<0.05$). Progesterone increased by 70% under LCI699 treatment, while 11-deoxycortisol remained unchanged. The same trend was seen for metyrapone. Ketoconazole strongly inhibited concentrations of all steroids (mean 90%, $P<0.001$), except progesterone, which increased (644%, $P<0.001$).
Conclusion
LCI699 is a potent inhibitor of basal- and ACTH-stimulated cortisol production in adrenocortical tumor cells, and in these conditions seems to block 11β-hydroxylase (CYP11B1), and to a lesser extent 17,20-lyase activity. Besides, the absence of strong accumulation of steroid precursors might indicate an inhibition proximal of 3β-HSD.

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GP27

Evening not morning plasma cortisol level is higher in women with polycystic ovary syndrome

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Introduction
The aim of our study was to assess the morning and evening cortisol plasma levels in women with polycystic ovary syndrome (PCOS).
Material and method
95 patients gave their informed consent to participate in the study and were divided into two groups. Group A consisted of 40 PCOS patients and group B consisted of 55 women without features of PCOS. Between day 5 and 8 of the menstrual cycle, morning (0700 h), fasting blood samples were taken for the assessment of LH, FSH, estradiol (E_2), cortisol, prolactin, TSH, testosterone and DHEAS. Evening (1700 h) blood samples were also taken for the evaluation of plasma cortisol level.
Results
There were no differences in mean age, BMI, FSH, SHBG, PRL, E_2 and TSH levels between group A and group B. Mean plasma LH level was higher in group A compared to group B (10.7±6.8 IU/l vs 6.6±4.5 IU/l, $P<0.02$). Mean plasma testosterone and DHEAS levels were also higher in PCOS patients (3.8± 0.6 nmol/l vs 1.63±0.6 nmol/l; 427.7±162.9 vs 236.6±97.8 resp, $P<0.001$). Mean evening plasma cortisol level was higher in PCOS patients (11.8±4.1 μg/dl vs 7.4±5.0 μg/dl, $P<0.02$). Mean morning plasma cortisol levels did not differ between groups.
Conclusion
PCOS women showed the increased plasma cortisol level with impacted diurnal secretion rate.

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GP28

Restoring the circadian cortisol rhythm with metyrapone in patients with adrenal incidentalomas and subclinical hypercortisolism reduces IL6 levels

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Introduction
Patients with adrenal incidentalomas and sub-clinical Cushing's (SCH) have increased cardiovascular events and mortality. We hypothesised that these patients have a disturbed cortisol rhythm amenable to being restored to normal by using timed short-acting cortisol synthesis blockade, and that this may have a positive effect on IL6 levels.
Methods
In a phase 1, prospective study (Eudract No. 2012-002586-35) we recruited eight patients with adrenal incidentalomas and SCH and two control groups of six sex, age and BMI-matched individuals: i) patients with adrenal incidentalomas and no SCH ii) healthy volunteers with no adrenal incidentaloma. 24-h circadian cortisol analysis was performed using LC-MS/MS to measure serum cortisol hourly and salivary cortisol/cortisone when awake, before and after metyrapone. IL6 was measured.
Results
Patients with SCH had significantly higher nocturnal mean (S.D.) serum cortisol exposure than both control groups:$\ln AUC_{18:00–22:00}$(6.6(0.4)vs(i)6.1(0.6) and (ii) 6.0(0.3)nmol/l.hr; $P=0.035$) and $\ln AUC_{22:00–02:00}$(6.3(0.5)vs(i)5.8(0.4) and (ii) 5.7(0.5)nmol/l.hr; $P=0.040$). Similarly, SCH had significantly higher nocturnal mean (S.D.) salivary cortisone exposure than both control groups:$\ln AUC_{20:00–23:00}$ (3.6(0.5)vs(i)3.0(0.7) and (ii)2.8(0.3)nmol/L.hr; $P=0.02$). In light of these findings six patients with SCH were administered metyrapone 500 mg at 18:00 and 250 mg at 22:00 with a significant reduction in nocturnal serum cortisol and salivary cortisone, achieving analogous cortisol exposure to both control groups. IL6 levels were higher in these six patients with SCH compared to both other groups combined ($\ln AUC_{18:00–22:00}$ 3.2(0.6) vs 2.3(0.7) and $\ln AUC_{22:00–02:00}$ 3.3(0.5) vs 2.4(0.8) pg/ml.hr). This intervention was associated with a significant reduction in IL6 AUC.
Conclusion
We have shown for the first time that patients with SCH have an abnormal cortisol rhythm with higher cortisol exposure starting from the early evening period and which was associated with increased circulating IL6 levels. After metyrapone 500 mg at 18:00 and 250 mg at 22:00 nocturnal cortisol levels were 're-set' to normal; this was associated with a significant reduction in IL6. We hypothesise that this intervention is likely associated with patient benefit.

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GP29

Plasma metabolomics profile in patients with Cushing's syndrome

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Background
Cushing's syndrome (CS) is a chronic disorder characterized by endogenous cortisol excess resulting in long-term metabolic and cardiovascular consequences. The identification of metabolic alterations related to hypercortisolism could be beneficial in tailoring treatments of co-morbidities. Our aim was to characterize the metabolic alterations of patients with hypercortisolism by targeted plasma metabolomic profiling.
Methods
Subjects ($n=149$) were recruited from three German centers (Munich, Berlin, and Würzburg) belonging to the German Cushing registry (CUSTODES) and the European Network for the Study of Adrenal Tumors (ENSAT). According to clinical and hormonal characteristics, four groups were identified: non-secreting adrenocortical adenomas (NS) ($n=27$), subclinical hypercortisolism (SH)

($n=34$), CS ($n=46$), and patients in whom CS has been excluded (EC) ($n=42$). Plasma targeted metabolomics profiling was performed using the mass spectrometry-based kit Absolute*IDQ*-p180 (BIOCRATES AG, Austria).
Results
Metabolic profile of patients with CS was characterized by reduced carnitine and acetyl-carnitine levels, with respect to EC. Polyamine levels were increased in CS patients, whereas several glucogenic amino acids were decreased, when compared to EC. Similar alterations were also identified in SH patients. Spermidine was progressively increased among NS, SH, and CS patients, and showed positive correlation with post-DST cortisol (Coefficient = 0.341, $P<0.001$). Serotonin levels were increased in adrenal-dependent hypercortisolism (SH and CS), when compared to EC, NS, and ACTH-dependent CS. Logistic regression analysis showed that the panel of significant metabolites among groups was able to correctly classify 83.8% of the patients. Three scores were identified from logistic regression that showed good accuracy in discriminating CS vs. EC, CS vs SH, and SH vs NS (sensitivity/specificity of 87%/83%, 89%/88%, and 78%/74%, respectively).
Conclusion
Metabolomic profiling revealed the presence of several disturbances in patients with hypercortisolism, mainly involving polyamine and amino acids metabolism, and β-oxidation. Metabolomic analysis showed also good accuracy in classifying patients with hypercortisolism according to their specific metabolic profile. Further studies are currently ongoing to analyze a large cohort of matched normal control subjects.

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GP30

Hair Cortisol Measurements in the Evaluation of Cushing's Syndrome

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Context
Hair cortisol has been recently studied to determine evidence of hypercortisolemia in humans. This test may be valuable in estimating cortisol levels, particularly in patients with cyclical Cushing's syndrome (CS).
Objective
To determine correlations with biochemical evidence of CS, and to compare hair cortisol measurements in patients with CS to normative data.
Methods
Hair samples from 49 study subjects were collected (30 with CS (mean age: 25.9 ± 18.2 years) and 19 without CS (mean age: 39.0 ± 19.4 years)). Three hair samples from each patient were processed and analyzed for cortisol according to the methods described by Meyer et al 2014. Diurnal serum cortisol and ACTH measurements, 24-h-urinary free cortisol corrected by body surface area (UFC/BSA) and 17-hydroxysteroids, corrected for creatinine (17OHS/Cr), were pre-operatively assessed. Average hair cortisol data were log-transformed for normality and compared to normal data of healthy adults as measured in the same laboratory.
Results
Average hair cortisol values in the groups with CS and without CS were 46.2 ± 64.9 pg cortisol/mg hair (median: 24.6 pg/mg; range: 3.1–406.3 pg/mg) and 125.7 ± 455.2 pg cortisol/mg hair (median: 18.0 pg/mg; range: 1.9–2745.6 pg/mg), respectively. In the CS group, hair cortisol was positively and moderately correlated with UFC/BSA ($r=0.31$, $P<0.001$). Mean hair cortisol levels in CS patients were significantly different from patients without CS ($P=0.02$) but not statistically significantly different from the mean level of 22.0 ± 59.0 pg/mg in a cohort of healthy individuals ($P=0.07$ and $P=0.12$, respectively).
Discussion
We found that hair cortisol levels correlated with some biochemical tests for CS; in addition, there was a difference in hair cortisol levels between those with and those without CS among our cohort at the NIH, yet not among a separate normal control cohort. We speculate that hair cortisol can assist in the diagnostic workup for CS. More research is needed on the use of hair cortisol in patients with CS.

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Bone & Calcium Homeostasis

GP31

Bone-specific circulating miRNA profile changes over an 8-week repeated sprint training protocol

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Introduction
Although underlying mechanisms are largely unknown, bone metabolism is regulated by specific microRNAs and changes in their expression are associated with metabolic bone disorders. Exercise is a determinant of bone metabolism; however, different training protocols differently affect bone. Little is known about the effects of exercise on bone-specific miRNA expression.
We studied the effect of a 8-week high-intensity training protocol on circulating levels of selected miRNA regulating bone metabolism.
Methods
18 male adults were assigned to one of two groups. One group ($n=9$) performed repeated sprint training (3 times/week, 18 maximal all-out 15 m sprints with 17 s of passive recovery); the other served as a control group ($n=9$). Blood samples were taken before the start of the protocol (T0) and after 4 (T1) and 8 weeks (T2). Plasma circulating miRNAs (miR21 5P, miR125b 5P, miR23a 3P, miR93 5P, miR100 5P) were evaluated by real-time PCR (normalized on miR425 5P); relative expression levels were calculated by the $2^{-\Delta\Delta CT}$ method. Changes over time where tested by repeated measure one-way ANOVA, while inter-group differences at each time-point were tested throughout t test.
Results
While in the control group the miRNA expression remained stable, in the trained group miR23a 3P was 1.4-fold downregulated, between T0 and T2 ($P<0.05$). miR100 5P was 3-fold downregulated between T0 and T1 ($P<0.05$) and twofold downregulated between T0 and T2 ($P<0.05$). miR125b 5P expression was twofold downregulated at T1 compared to both T0 ($P<0.01$) and T2 ($P<0.05$).
Conclusions
An 8-week long high-intensity training protocol downregulates the expression of circulating miRNA associated with fracture risk.

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GP32

Hormone replacement therapy has favorable effects on bone microarchitecture, bone mineral density and body fat mass, without affecting lean mass: the OsteoLaus Cohort

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Introduction
Hormonal replacement therapy (HRT) increases bone mineral density (BMD). Controversy exists regarding residual effect after withdrawal. We aimed to explore the effect of HRT and HRT withdrawal on: i) BMD and bone microarchitecture assessed by trabecular bone score (TBS); ii) fat (FMI), lean (LMI) and appendicular lean (ALMI) mass indexes.
Methods
The OsteoLaus Cohort assessed 1500 women (50–80 years) for BMD, TBS, total energy expenditure (TEE), alternative health eating index (AHEI) and depression prevalence. 1094 women had body composition analysis by dual X-ray absorptiometry. According to HRT status, women were classified as: Never (NU = 504), Current (CU = 205) and Past (PU = 262) users.
Results
The three groups differed in age (67.4 ± 6.8, 64.0 ± 6.8, 62.1 ± 8.0 for PU, CU and NU respectively, $P<0.001$), AHEI and TEE but not in BMI or depression

prevalence. HRT users presented higher age- and BMI-adjusted TBS (CU and PU versus NU, $P<0.001$ and $P=0.066$ respectively) and BMD at lumbar spine (LS) and total hip (TH) (CU and PU versus NU, $P<0.05$). TBS was negatively associated with age and BMI-adjusted slopes for 10-year increment were −0.051 (−0.060; −0.041), −0.032 (−0.048; −0.017) and −0.022 (−0.038; −0.005) (NU, PU and CU respectively, $P<0.05$). Slopes of LS and TH BMD showed similar pattern (NU<PU<CU, $P<0.015$). After multiple adjustments, no difference existed between the 3 groups for LMI and ALMI. Slopes for 10-year increment of FMI were 0.887 (0.566; 1.208), 0.084 (−0.463; 0.631) and 0.225 (−0.350; 0.800) for NU, PU and CU respectively (CU or PU versus NU, $P<0.05$).

Conclusion

Current HRT use is associated with higher BMD values and better preservation of TBS. The benefits of HRT seem to persist in PU. HRT has no effect on lean mass. However, the age-associated gain of FMI is reduced in HRT users. Further analysis is ongoing to assess whether it concerns subcutaneous or visceral fat.

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GP33

Relationships between lower-limb muscle strength and tibial outcomes in ageing UK men

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Ageing is associated with sarcopenia, osteoporosis and an increased risk of falling, which together contribute to increased fracture risk. There are few data describing the associations between functional measures of muscle and bone during ageing. Therefore, the aim of this study was to examine in ageing men associations between measures of lower-limb muscle strength and age and then to investigate the relationships with tibial bone outcomes.

Men ($n=301$) aged 40–85 years were recruited in the UK (201-White, 43-Black, 57-South-Asian). pQCT outcomes from the 38% tibia were: cortical bone mineral content (Ct.BMC), cross-sectional area (CSA), and cross-sectional moment of inertia (CSMI). Jumping mechanography assessed muscle force (kN) and power (kW) from a single 2-leg counter-jump. Linear regression was used to describe the relationships between: power/force and age with an ethnicity*age interaction; and force and bone outcomes; all were adjusted for weight and height. Results are expressed as β-coefficients (95%CI) of percentage unit change in age/force.

There were significant negative relationships between muscle power and age in all groups ($P<0.001$): White (−1.9% (−2.1, −1.7)), Black (−1.3% (−1.8, −0.8)) and South-Asian (−1.8% (−2.3, −1.3)), with a significant difference between the slopes of White and Black men ($P=0.03$). There was a significant negative relationship between force and age in White (−3.9% (−0.6, −0.20); $P<0.0001$) and South-Asian (−4.2% (−0.8, −0.08); $P=0.017$) but not Black men (−3.0% (−0.7, 0.8); $P=0.121$). Muscle force and bone outcomes were positively associated: Ct.BMC 8.5% (3.6, 13.4); CSA 9.3% (5.4, 13.2) and CSMI 18.6% (11.1, 26.2), all $P<0.001$; there were no ethnic differences in these relationships (with an additional age-adjustment).

The relationship between power and age was different between ethnicities which may lead to differences in fall risk. Muscle force positively predicted bone outcomes in ageing men. Together, these findings may contribute to the understanding of fracture incidence in different ethnic groups.

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GP34

Impact of Laboratory assays on the diagnosis of hyperparathyroidism

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Abstract withdrawn

GP35

Retrospective analysis of bone metabolism in patients waiting for simultaneous pancreas kidney transplantation

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Objective

Osteoporosis is a typical long-term complication after solid organ transplantation. Patients after simultaneous pancreas kidney transplantation (SPK) are at a very high risk due to preceding renal osteopathy and diabetic status. To determine the best preventive strategy we analysed the bone metabolism at the point of the pretransplant examination.

Design and methods

In years 2011–2014 the number of 112 patients with type 1 diabetes (69 men, 43 women) entered the waiting list for the SPK for the first time. The mean age was 40.71 ± 10.44 years, duration of diabetes 24.69 ± 7.98 years. The hemodialysis or peritoneal dialysis was alredy established in 40 patients, 72 patients had renal impairement in stage CKD 3-4. We analysed biochemical results and the bone densitometry from their pretransplant investigation.

Results

The mean serum total calcium level was 2.23 ± 0.16 mmol/l, phosphorus 1.67 ± 0.36 mmol/l and intact parathormone 19.05 ± 13.32 pmol/l. The mean 25-hydroxycholecalciferol level was 15.39 ± 7.67 μg/l; 24% patients had vitamine D deficiency. The average lumbal spine T score was −0.94 ± 1.38 with significantly worse results in men than women (−1.19 ± 1.23 vs −0.54 ± 1.46; $P=0.015$). The average proximal femur T score was −1.39 ± 1.12; comparable between men and women but significantly worse than lumbal spine ($P<0.001$). Osteoporosis was diagnosed in 22.5% and osteopenia in 50.5% patients, only 27% had normal bone density. The incidence of osteoporosis and osteopenia was similar between men and women.

Conclusions

Patients with type 1 diabetes in CKD 3-5 suffer from serious bone mineral density impairment despite their young age. On contrast to population data the incidence of low bone density is the same among men and women. Bone metabolism should be monitored since early stages of diabetic nephropathy and adequate preventive measures should be introduced.

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GP36

Fontan palliation in children is associated with bone deficits

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Background

Survivors with Fontan circulation suffer from chronic systemic hypoperfusion resulting in end-organ injury. Little is known about the effects of these

hemodynamic perturbations on bone. We hypothesized that chronic Fontan circulation (>5 years after surgery) would be associated with bone deficits.
Methods
Peripheral quantitative computed tomography (pQCT) was performed on 10 Fontan patients (seven males, 11.8±1.7 years) and 11 healthy controls (nine males, 12.0±1.5 years) with Tanner stage ≤3. Height-adjusted Bone Mineral Density Z-scores for lumbar spine (LBMD) and total body less head (TBLH) were also measured in Fontan patients by dual energy x-ray absorptiometry (DXA). Linear regression was used to compare radius pQCT measures of bone strength index (BSI), trabecular (3% site) and cortical (33% site) volumetric BMD (vBMD) and thickness between Fontan patients and controls (with adjustment for radius length, age, and sex), and to correlate pQCT outcomes with DXA Z-scores.
Results
The adjusted differences in means (95% CI) for Fontan patients vs. controls were: −28.1 mg/cm^3 (−54.8, −1.34; $P=0.040$) for trabecular vBMD, −10.9 mg/cm^3 (−49.8, 28.0; $P=0.584$) for cortical vBMD, −0.35 mm (−0.64, −0.06, $P=0.017$) for cortical thickness, and −7.2 mg^2/mm^4 (−13.7, −0.8; $P=0.028$) for BSI. Mean height-adjusted LBMD Z-score was −0.46±1.1 and TBLH Z-score was −0.63±1.1. LBMD Z-scores were trending higher by 0.39 (−0.006, 0.78; $P=0.054$) per 20 mg/cm^3 of trabecular vBMD among Fontan subjects.
Conclusions
Children with Fontan palliation have lower trabecular vBMD, cortical thickness, and bone strength. This suggests that bone is another target organ sensitive to the Fontan physiology. Among pQCT outcomes, trabecular vBMD showed a similar trend as LBMD, underscoring a potential utility of DXA as a monitoring tool. Further studies should evaluate the etiology and impact on fracture risk of these deficits.

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GP37

Trabecular bone score in patients with inflammatory bowel diseases

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Introduction
Osteoporosis is known chronic complication of inflammatory bowel diseases (IBD). It is known that areal bone mineral density (aBMD) does not sufficiently reflect bone strength and quality. The trabecular bone score (TBS) provides an indirect measurement of bone microarchitecture, independent of aBMD.
Aims and methods
The aim was to assess TBS in IBD patients with regard to disease behavior using in comparison with lumbar spine (LS) BMD. The cohort consisted of 84 IBD patients, 53 with Crohn's disease (CD) and 31 with ulcerative colitis (UC). Clinical characteristics i.e. age, gender, anthropometry, clinical behaviour, medication were recorded. The BMD was determined by dual-energy X-ray absorptiometry (DXA, Hologic Discovery) at the lumbar spine. TBS was determined by TBS Insight software (Medimaps, France).
Results
Cohort mean age was 42±14.2 years with the average disease duration of 11±7 years. 12/84 (14%) of the cohort were postmenopausal women. 39.6% (21/53) of CD patients had prior resection of the ileum. At the time of assessment 8/84 (9.5%) of the IBD patients (3CD vs 5 UC patients) were on glucocorticoid therapy with >5 mg equivalent to prednisolone daily. The percentage of patients with substitution of vitamin D (800IU) and calcium (0.5–1 g) was similar between CD and UC (24.5% vs 29%), none of the patients were on antiporothic treatment. The average LS BMD was 0.964±0.113 g/cm^2 and TBS 1.36±0.14. Significantly lower TBS although not LS BMD was found in patients with fistulising CD as compared to those with luminal disease ($P=0.0039$). We did not observe any difference in TBS or BMD in UC patients according to the disease behaviour.
Conclusion
We observed that spine TBS can identify quality of bone mineral density in patients with Crohn's disease better than BMD itself. CD patients with severe disease are at higher risk of low bone mineral density.

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GP38

Influence of prematurity and low birth weight on peak bone mass

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Introduction
Intrauterine weeks 36–38 with rapid transplacental mineral transfer are crucial for skeletal development. Prematurity and low birthweight may therefore lead to a subnormal peak bone mass. We evaluated the influence of gestational age and low birthweight on bone mineral density (BMD) and content (BMC) in young adults born preterm with very low birthweight (VLBW) and small for gestational age (SGA) at term.
Description of methods/design
Altogether, 186 subjects (females=95) 26–28 years of age were included. Of these, 52 were born preterm with VLBW (<1500 g), 56 born SGA at term (<10th percentile) and 75 controls born at term with normal birthweight (>10th percentile). Weight, height, previous fractures, smoking, physical activity, calcium and vitamin D intake were recorded. BMC and BMD at spine, femoral neck, hip and whole body and spine trabecular bone score (TBS) were measured by DXA. Serum bone markers were analyzed.
Results
The VLBW and SGA groups were significantly shorter compared to controls. The VLBW group was more physically inactive and reported higher calcium intake. Previous fractures, smoking and vitamin D were similar between the groups. The VLBW group exhibited significantly lower BMC and BMD at most sites measured, also controlled for known confounders. Femoral neck BMD was 6.7% lower in VLBW. BMD was apparently dependent on gestational age, as each additional week of gestation resulted in 0.037 units increase in femoral neck Z-score. The SGA group displayed lower BMC at spine and lower whole body Z-score. No differences were observed in TBS or bone markers, except for higher Dkk1 in the VLBW groups.
Conclusion
Adults born premature with VLBW and SGA at term displayed significantly shorter height, and lower BMC and BMD compared to controls. The lower peak bone mass may imply an increased fracture risk in the future.

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GP39

Drug holiday in osteoporosis. reducing side effects of long lasting treatments

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Introduction
Osteoporosis is a chronic and dangerous disease, as it may be silent and may express itself with a sudden catastrophic event, such as a fracture. Treatment of osteoporosis demands the use of potent pharmaceutical agents with long lasting effects. In particular, bisphosphonates, such as ibandronate, may be used. It has become evident that chronic treatment with anti-osteoporotic agents may reverse the course of the disease, patients having normal bone mineral density or only osteopenia following treatment. In such a group of patients treatment may be interrupted and patients followed up.
Aim
The aim was to describe drug holiday in a group of patients with osteoporosis, having received treatment with ibandronate.
Methods
Within a group of 120 patients (108 female, 12 male) with osteoporosis, 20 patients (female) were receiving ibandronate 150 mg once monthly and calcium with cholecalciferol for a period of 1.8–3 years. These patients had osteoporosis on ibandronate initiation, T score ranging from −2.5 to −3.4.

Results
On reevaluation after treatment with ibandronate 150 mg once monthly and calcium with cholecalciferol, bone mineral density was measured. Osteopenia was observed in 12 female patients and normal bone mineral density in 8. Ibandronate was stopped, while treatment with calcium and cholecalciferol was continued. Patients were reevaluated after 1 and 2 years. Within this group 11 patients continued to have osteopenia, while one patient was found to have osteoporosis and he required the addition of another antiosteoporotic medication. Within the group of eight patients with normal bone mineral density 6 continued to have normal bone mineral density and two were had osteopenia.
Conclusions
Treatment with antiosteoporotic agents, especially bisphosphonates appears to have beneficial and long-lasting effects in some patients, enabling treatment interruption and absence of recurrence. Drug holiday seems to be possible in a significant group of osteoporosis patients, being associated with absence of recurrence. It appears that osteoporosis treatment should be individualized, as genetic factors may be associated with very good response in some of our osteoporosis patients.

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GP40

Severe osteomalacia caused by a phosphaturic mesenchymal tumor secreting fibroblast growth factor 23: a case report

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Tumor-induced osteomalacia (TIO) is a rare acquired paraneoplastic syndrome clinically presenting with recurring fractures, muscular weakness and pain. Laboratory values of affected patients are characterized by renal phosphate wasting and hypophosphatemia caused by an overexpression of fibroblast growth factor 23 (FGF- 23), a hormone belonging to the group of phosphatonins regulating phosphate and vitamin D homeostasis. Pathologically, it is secreted especially by small (and thus difficult to locate) mesenchymal tumors, leading to a significant delay from onset of (often debilitating) symptoms to diagnosis. TIO was first described in 1947 and so far only approximately 300 cases have been reported in the literature.
We present the case of a 41-year old female patient with a 4-year history of recurring fractures of the metatarsal bones and growing muscle pain of the extremities leading to a markedly decreased physical activity. The detailed workup showed reproducible low levels of serum phosphate and 1,25-OH Vitamin D and an increased fractional excretion of urine phosphate. FGF-23 was increased 20-fold (Ref.: 110 kRU/l, measured value 2100 kRU/l). In the subsequently performed imaging diagnostics (ultrasound, DOTATATE-PET-CT) a $2\times2\times1$ cm tumor was located on the left pubic bone. The patient underwent surgery and in the histopathological work-up a benign mesenchymal tumor was confirmed. After complete excision, the serum and urine phosphate normalized rapidly, FGF-23 levels were tested 2 weeks after surgery and had decreased to normal (35 kRU/l). Accordingly, the patient's symptoms greatly improved shortly after surgery and completely resolved over the course of 6 months. So far, there is no sign of tumor recurrence during a 6-month period of follow-up.
Our aim of presenting this case report is to increase awareness that any patient with hypophosphatemia, unexplained recurrent fractures and muscle weakness should undergo workup for TIO as this remains an extremely rare but potentially curable disease.

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GP41

A serum 25 hydroxy-vitamin D concentration in search of a bone disease

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Introduction
Vitamin D insufficiency and deficiency are defined as a serum 25-hydroxy-vitamin D (25(OH)D) below 50 and 30 nmol/l respectively. We aimed to determine whether there is a serum 25(OH)D that signals a low serum calcium and phosphate, secondary hyperparathyroidism, high bone remodelling, low area bone mineral density (aBMD), and so, an increased risk for microstructural deterioration and bone fragility.
Method
Concentrations of 25(OH)D, calcium, phosphate, creatinine and parathyroid hormone (PTH) were measured by Melbourne Pathology in serum from 11,855 subjects (8777 women, 3078 men). We measured serum C-terminal telopeptide of type 1 collagen (CTX), Procollagen type 1 N-terminal propeptide (P1NP) and aBMD at the spine and hip in 182 subjects from Austin Health. We excluded persons <20 years, patients with hypercalcaemia, chronic kidney disease and a serum 25(OH)D ≥ 180 nmol/l.
Results
Serum calcium and phosphate correlated positively with serum 25(OH)D. Serum PTH and alkaline phosphatase, but not CTX and P1NP, correlated negatively with serum 25(OH)D. There was no detectable association between serum 25(OH)D and aBMD and no level of 25(OH)D that identified persons with low serum calcium or phosphate, or high PTH or remodelling markers. Among 1439 subjects with 25(OH)D <30 nmol/l, 6.1% had a low serum calcium, 3.4% had a low serum phosphate, 6.1% had a high alkaline phosphatase, and 34.2% had an elevated PTH.
Conclusion
The sample size of subjects with 25(OH)D below 30 nmol/l may have limited the power to detect associations, but within this constraint and the cross sectional nature of this study, we infer that diagnosing persons as having vitamin D 'deficiency' or 'insufficiency' based on the current criteria is not evidence based. A diagnostic threshold level of serum 25(OH)D predisposing to bone disease, and the duration of exposure at this level, remain uncertain.

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GP42

Hypercalcemia in patients with lymphoma

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Introduction
Calcitriol-mediated hypercalcemia is one of the most common paraneoplastic syndromes associated with lymphoma.
Aim
Evaluate clinical and biochemical manifestations as well on the management of hypercalcemia in patients with lymphoma.
Materials and methods
Prospective analysis of patients with lymphoma who developed hypercalcemia during September-2011 and January-2016.
Results
Two hundred and six patients with high-grade lymphoma were reported, 189 with diffuse large B-cell lymphoma (DLBCL) and 17 with adult Tcell leukemia/lymphoma (ATLL). Hypercalcemia was documented in 15 patients (incidence of 7.28%) of whom 13 were DLBCL and two ATLL, mostly with stage IV disease. Median age was 60 years (range 36–85); 53.3% women. Up to one-third of the cases, symptoms of hypercalcemia were reported, predominantly those involving neurological manifestations (somnolence, delirium) and polyuria. Mean calcium was 3.1 mmol/l $\pm$0.4 (range 2.6–4.2) and phosphatemia 1.1 mmol/l $\pm$0.4 (range 0.7–1.5). Median concentration of serum calcidiol and calcitriol was 51.1 nmol/l $\pm$24.6 (range 14–95, reference value above 50) and 160 pmol/l $\pm$ 99 (range 6–342, reference value 39–193), respectively. Calcitriol was determined in 86.6% patients, only a quarter presented levels above de limit range. Serum PTH was suppressed in 13/15 patients. PTH-rp was determined in 13/15 cases; elevated serum levels were found only in one patient with supressed PTH. Eighty percent patients were treated with chemotherapy; the rest of them could not begin treatment due to impaired performance status. Slightly more than half of them received specific treatment for hypercalcemia previous to chemotherapy (66.6% hydration, 40% furosemide, 40% corticosteroids, 20% bisphosphonates). Calcium was normalized in 93.3% of patients, in relation to response to chemotherapy, with a mean value of 2.3 mmol/l $\pm$0.18, 18 $\pm$15 days after starting treatment.

Conclusion
Hypercalcemia associated with lymphoma is a relatively common disorder. In our series, the classic pattern mediated by calcitriol was observed only in 25% of the patients; most of them had multifactorial pathogenesis.

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GP43

Evaluation of preoperative ultrasonographic and biochemical features of patients with aggressive parathyroid disease: Is there any reliable predictive marker?

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Introduction
Parathyroid cancer (PC) is rare accounting for $<1\%$ of all presentations. Tumors that demonstrate these atypical features and do not fulfill criteria for carcinoma can be classified as atypical adenomas (APA). Herein we aimed to evaluate the clinical and biochemical features of the patients with an atypical parathyroid adenoma or carcinoma and compare it with benign parathyroid adenomas.
Method
Twenty-eight patients who were operated for primary hyperparathyroidism and diagnosed with APA or PC were enrolled. Another 102 patients with classical PA were included as the control group. Classic adenomas, APAs and PCs were compared according to preoperative biochemical and ultrasonographic parameters.
Results
Serum Calcium (Ca) was significantly higher in the carcinoma group compared to APA and classical PA groups in *post hoc* analysis, ($P<0.001$ and $P=0.010$, respectively). Serum median parathormone (PTH) was significantly higher in the APA and the carcinoma groups compared to classical PA group ($P<0.05$). Serum (alkaline phosphatase) ALP and 24-h urinary Ca excretion were significantly higher in the APA and PC groups compared to classical adenomas ($P<0.001$). Areas under ROC curve for Ca, PTH, ALP, 24 h Ca excretion and the adenoma diameter were significant for discrimination of aggressive (APA and PC) from benign disease. Best cut off for Ca, PTH, ALP, 24 h Ca excretion and the adenoma diameter were 12.45 mg/dl, 265.05 pg/ml, 154.5 IU/l, 348.5 mg/day and 21.5 mm, respectively. Multivariate analysis showed that Ca, ALP and isoechoic/cystic appearance were independent predictors for aggressive disease
Conclusion
Preoperatively high PTH, ALP and urinary Ca levels and large lesions with isoechoic or cystic appearance may be predictive for atypical adenoma or carcinoma that may requiring more extensive surgery and closer follow up to prevent any lifelong complications.

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GP44

Diabetes mellitus and carbohydrate metabolism in primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism (PHPT) results in alterations in carbohydrate metabolism, characterized by insulin resistance, hyperinsulinemia, and glucose intolerance.
Objective
The aim of our study was to evaluate carbohydrate metabolism status in patients with PHPT.
Methods
One hundred and nine patients with PHPT were investigated, healthy controls included 36 individuals matched by sex age and BMI ($BMI=27\pm5$ kg/m^2). Blood tests, and 75 g oral glucose tolerance test results were evaluated, HOMA index was adjusted as immunoreactive insulin*glucose/22.
Results
Eight percent patients had type 2 diabetes mellitus (DM), impaired fasting glycemia was observed in 3% and glucose intolerance in 12% of patients with PHPT. Basal glucose level, plasma immunoreactive insulin (IRI) and HOMA index did not differ between groups with mild and severe forms of the disease ($P=0.43$). Postprandial glucose increased in patients with severe compared to mild form ($P<0.06$). Thus glucose level was significantly raising in accordance with the PTH level elevation ($H=8.2$; $P=0.04$). Postprandial insulin was significantly increased in patients with severe form ($P<0.01$), we did not find any correlations with PTH level but with ionized serum calcium ($r=0.3$; $P=0.006$). The relative risk of type 2 DM in patients with severe PHPT (8.5%) raised by 2.3 times (CI 95% 0.3; 1.8) and is higher than in patients with the mild form (3.7%), which are comparable with control group.
Conclusions
Our work shows that patients with PHPT feature disturbances in carbohydrate metabolism. The incidence and prevalence of type 2 DM is significantly increased in group with severe form PHPT. These results argue for improved screening to identify carbohydrate metabolism status in patients with PHPT.

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GP45

Differencial diagnosis of increased serum parathyroid hormone: the importance of vitamin D deficiency/insufficiency

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Introduction
Vitamin D insufficiency is very common among Spanish adults. It is well established there is an inverse relationship between vitamin D and PTH levels. The diagnostic approach of an increased serum PTH concentration in a normocalcemic normophosphatemic patient is frequent in routine practice and the deficiency of vitamin D is the major cause of secondary hyperparathyroidism (SHPT). The aims of this study were to evaluate the prevalence of SHPT in a cohort of normocalcemic patients with elevated serum PTH levels and deficiency/insufficiency of vitamin D and to analyze the correlation between PTH and vitamin D levels.
Methods
Fifty-one patients with elevated PTH levels and a 25OHD <30 ng/ml were included. All patients were treated with vitamin D for 3–6 months and all parameters were re-evaluated. Patients with diabetes and chronic kidney disease were excluded.
Results
Fifty-one patients were included (60.8% female; 62.24 ± 14.28 median age). Baseline characteristics were: Serum calcium: 9.766 ± 0.84 mg/dl, serum phosphate: 2.81 ± 0.79 mg/dl, calciuria: 84.59 ± 110 mg/dl per 24 h, PTH: 112.28 ± 35 and 25(OH) vitamin D: 16.21 ± 5.3 ng/dl. After treatment with vitamin D there was a significant increase of 25(OH) vitamin D levels (38.47 ± 24, $P<0.0001$) and a significant decrease of PTH levels (88.02 ± 36.09 $P<0.001$), serum calcium (9.8 ± 0.6 $P<0.037$), serum phosphorus (3.11 ± 0.598 $P<0.018$) and calciuria (119.37 ± 110.12 mg/24 h; $P<0.032$). Five patients were diagnosed of primary hyperparathyroidism (9.8%) and two patients (3.92%) of normocalcemic primary hyperparathyroidism. Plasma 25(OH)D3 levels correlated negatively with PTH levels ($r=-0.465$ ($P<0.01$).
Conclusions
Vitamin D deficiency/insufficiency is the major cause of SHPT. To adequately assess this condition is critical to replenish levels of vitamin D. PTH levels correlate negatively with levels of vitamin D.

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GP46

Denosumab increases bone mineral density in primary hyperparathyroidism treated with cinacalcet

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Cinacalcet decreases and normalizes serum calcium levels across a broad severity range of primary hyperparathyroidism (PHPT), slightly reduces parathyroid hormone levels which generally remains elevated, whereas it has no effect on bone mineral density (BMD). Therefore, when administering cinacalcet to a patient with PHPT, concomitant treatment with an anti-catabolic drug should be considered.
An open-labeled, prospective trial was conducted in 32 patients with PHPT with cinacalcet treatment (contraindications to surgery, negative parathyroid imaging, persistent or relapsing PHPT after PTx- and refusal of PTx), to determine whether denosumab, maintains or improves BMD in patients with PHPT after 24 months of treatment.
PHPT patients with low BMD were treated with cinacalcet (Mimpara, Amgen; titrated dose), 25-OH vitamin D (Hidroferol, Faes) and denosumab (Prolia, Amgen) 60 mg sc injections given every 6 months. Serum calcium, phosphorous PTH and bone turnover markers were evaluates every 3 and 6 months. BMD was measured at the lumbar spine (LS) and total femur (TF) by dual-energy X-ray absorptiometry baseline and after 24 months of treatment.
The treatment normalized calcium decreasing 1.7 ± 0.1 mg/dl ($P < 0{,}0001$) and paratohormone 33.36 ± 21.6 ($P < 0{,}05$) pg/dl. Bone turnover markers remained suppressed for the duration of the trial. The treatment was also associated with a significant increase after 24 months in vs baseline in LS BMD: 8% (P: 0.037) and in TF BMD: 7% (P: 0.0001), improving to normal BMD in the 45.5%.
Denosumab associated to cinacalcet is an excellent therapeutic option to normalize serum calcium and paratohormone to treat the metabolic bone-disease in patients with PHPT who do not meet criteria for surgical treatment.

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GP47

Determination of 25-hydroxy-vitamin D status, serum CrossLaps, and calcium intake in individuals with primary adult-type lactose malabsorption

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Introduction
Primary adult-type lactose malabsorption (PALM) is a widespread inherited autosomal recessive condition. It is considered to be associated with osteoporosis. The purpose of the present study was to assess the 25-hydroxy-vitamin D (25[OH]D) status, serum CrossLaps and dairy calcium intake in individuals with PALM (i.e., *LCT* C/C$_{-13910}$ genotype) and normal controls (i.e., LCT C/T$_{-13910}$ and T/T$_{-13910}$ genotypes). In addition, the height, weight and body mass index (BMI) were determined.
Methods
In total, 210 adult individuals, who were referred to our outpatient clinic for PALM testing, were included in this prospective cross-sectional study. All participants underwent genotyping for the *LCT* C/T$_{-13910}$ polymorphism, 25(OH)D and CrossLaps measurements and clinical examinations. Blood sampling was performed after a 12 h overnight fasting in the morning between 8:00 and 10:00 h. A self-developed questionnaire was used to estimate daily calcium intake from dairy products.
Results
Fifty-five individuals with PALM (i.e., *LCT* C/C$_{-13910}$ homozygotes) showed significantly lower 25(OH)D (mean: 24.95 ± 10.04 vs 28.59 ± 9.56 ng/ml, $P = 0.018$) and higher CrossLaps serum levels (mean: 0.46 ± 0.31 vs 0.43 ± 0.49 ng/ml, $P = 0.251$) compared to 155 normal controls (i.e., *LCT* C/T$_{-13910}$ hetero- or T/T$_{-13910}$ homozygotes). Moreover, 26/55 (47.27%) *LCT* C/C$_{-13910}$ homozygotes reported to be lactose intolerant compared to 31/155 (20.0%) normal controls ($P < 0.001$). Total dairy calcium intake (mean: 303 ± 162 vs 330 ± 194 mg/day, $P = 0.463$) and anthropometric data were similar between PALM probands and controls.
Conclusion
In conclusion, individuals with PALM were found to have significantly lower 25(OH)D and higher CrossLaps serum levels compared to individuals with lactase-persistence. Based on these findings, we suggest to perform routine 25(OH)D and CrossLaps serum measurements in individuals with PALM. The determination of these biomarkers may contribute to the preservation of life-long bone health.

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GP48

Serum sclerostin levels are significantly higher in type 2 diabetes compared to latent autoimmune diabetes in adults regardeless the presence of metabolic syndrome

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Objective
Sclerostin, a circulating Wnt antagonist and a main negative regulator of bone formation, is increased in type 2 diabetes (T2DM). No data are available on latent autoimmune diabetes in adults (LADA) and whether sclerostin is affected by metabolic syndrome (MS) associated with T2DM or LADA. We evaluated serum sclerostin and bone turnover markers in LADA and T2DM in relation with MS.
Research design and methods
This cross-sectional study included 98 T2DM and 89 LADA recruited by the ACTION LADA and NIRAD cohorts, and further divided according to diagnosis of MS (NCEP criteria). Serum sclerostin, bone formation (P1NP) and bone resorption (serum beta-CTx) markers were analyzed by ELISA.
Results
Sclerostin was unrelated with age, but increased significantly with BMI ($\rho = 0.29$; $P < 0.0001$) and diabetes duration ($r = 0.32$, $P < 0.0001$), this parameter ($\beta = 1.77$; $P = 0.008$) and to a lesser extent triglycerides ($\beta = 0.03$; $P = 0.022$) were independent predictor of sclerostin levels in the overall population. T2DM subjects had higher serum sclerostin than LADA overall (median with range 30.7, 1.98–98.8, vs 21.9, 1–74.54 pmol/l, $P < 0.0001$) and also when further subdivided according to the presence of MS (31.6, 1.98–98.8, vs 22.2, 1–74.5 pmol/l, $P = 0.02$). In both T2DM and LADA groups, the presence of MS did not influence significantly serum sclerostin ($P > 0.15$). Patients with T2DM had lower P1NP compared to LADA (57.3 ± 16.6 vs 64.2 ± 59.2 pg/ml; $P = 0.038$) but similar beta-CTx.
Conclusion
T2DM patients present higher levels of sclerostin than LADA, this could result in low bone formation. MS or BMI may not play a crucial role.

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GP49

Longitudinal changes in maternal 25(OH)D_3 and free 25(OH)D, vitamin D binding protein and the relationship with cord vitamin D metabolites

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Low maternal vitamin D (VD) status is associated with adverse fetal development. However gestational changes in VD metabolites and their relationship with cord concentrations are unclear.
The plasma concentration of 25-hydroxyvitamin D_3 (25(OH)D_3) was measured using UPLC-MS/MS, and free 25(OH)D and vitamin D binding protein (DBP) concentrations were measured by ELISA. Plasma samples were collected longitudinally from women resident in rural Gambia with abundant exposure to UVB ($n = 21$), before pregnancy, at gestational week 13, 20, 30 and in cord blood. Data were analysed in Stata/SE 14.0 using mixed effects models and linear regression.
Concentrations (mean $\pm$ S.D.) of 25(OH)D_3 (64 ± 13, 71 ± 14, 81 ± 22, 100 ± 23 nmol/l) and DBP (356 ± 47, 488 ± 104, 570 ± 100 and 625 ± 105 mg/l) increased across gestation ($P < 0.0001$), before pregnancy, at week 13, 20 and 30, respectively. Free 25(OH)D concentration remained unchanged (13.2 ± 3.0, 12.2 ± 2.0, 12.5 ± 2.0, 12.7 ± 3.0 pmol/l) ($P = 0.2$), measured at the same time-points. Cord plasma concentrations of 25(OH)D_3 (58 ± 15 nmol/l) and DBP (270 ± 48 mg/l) were lower than maternal plasma at week 30 ($P < 0.0001$), and free 25(OH)D (15.5 ± 5.0 pmol/l) was higher ($P = 0.03$).
Maternal (week 30) and cord concentrations were highly correlated for free 25(OH)D (β (95% CI)) (1.38 (0.94, 1.82)) ($P < 0.0001$), but not 25(OH)D_3 (0.2

(−0.09, 0.52)) ($P=0.2$), suggesting efficient placental transfer of free 25(OH)D. The slope of the regression of free 25(OH)D on 25(OH)D_3 differed between cord, (0.09 (0.06, 0.11)) and maternal plasma (0.04 (0.02, 0.06)) ($P<0.05$), suggesting that free 25(OH)D contributes a higher proportion of total 25(OH)D in cord than maternal plasma, possibly reflecting relative DBP concentration.
Gestational changes in VD metabolism were apparent; the increasing 25(OH)D_3 and DBP concentration was in keeping with the unchanging free 25(OH)D. These data suggest that mechanisms exist to regulate placental VD transfer and the availability of free 25(OH)D to the fetal circulation and contribute to our understanding of maternal and neonatal VD requirements.

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GP50

Renal concentration capacity in primary hyperparathyroidism and changes after surgery and during medical management and monitoring

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Introduction
Patients with primary hyperparathyroidism (pHPT) run an increased risk of death, and in some studies cardiovascular diseases were inversely related to urine osmolality.
Aim
Evaluate the renal concentration capacity in patients with mild and severe pHPT, and its changes after surgery for pHPT and during medical management and monitoring.
Materials and methods
The study included 77 patients (median age 57 (52;61)) with pHPT, group contained patients with mild form ($n=23$).
Osmolality index was calculated as urine osmolality to blood osmolality ratio. Renal concentration capacity impairment was diagnosed with osmolality index <2. Changes in osmolality index were evaluated in 13 patients after surgery for pHPT and in 13 patients during medical management and monitoring. Follow-up period was up to 24 months.
Results
Osmolality index in patients with pHPT was low with median 1.64 (1.36; 2.08). We found a high prevalence of renal concentration capacity impairment in patients with pHPT, that was 72%. Both patients with mild and severe pHPT had similar prevalence. Urine osmolality was Me 0.475 (0.39; 0.588) osm/kg. In patients with renal concentration capacity impairment PTH level was significantly higher, than in patients with normal urine osmolality ($P=0.039$).
Changes in renal concentration capacity in long-term period after surgery for pHPT were characterized by increase of osmolality index, also in patients with mild form, (initially 1.75 (1.4; 2.14), after surgery 2.38 (1.84; 2.54)), changing Me was +12.4% in 6–24 months ($P=0.012$).
No significant changes in osmolality index were observed during medical management and monitoring, the same data found for patients with mild form pHPT.
Conclusions
Renal concentration capacity impairment is common in mild and severe pHPT. Renal concentration capacity is restorated after surgery for pHPT. The findings of this study add cause for measurement of urine osmolality or osmolality index in all patients with pHPT.

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Cardiovascular endocrinology

GP51

Pericardial rather than intramyocardial fat is independently associated with systolic and diastolic left ventricular heart function in metabolically healthy humans

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Background
Obesity is a major risk factor to develop heart failure, in part due to possible lipotoxic effects of increased intramyocardial (MYCL) and/or pericardial (PERI) lipid accumulation. Recent evidence suggests that MYCL is highly dynamic and might rather be a surrogate marker for disturbed energy metabolism than the underlying cause of cardiac dysfunction. On the other hand, PERI might contribute directly by mechanic and paracrine effects. Therefore, we hypothesized that PERI rather than MYCL is associated with myocardial function.
Methods
To avoid potential confounding of metabolic disease 38 metabolically healthy, but slightly overweight subjects (age: 33 ± 15 years; BMI: 25 ± 4 kg/m^2) were investigated using ^{1}H-magnetic resonance spectroscopy and imaging. MYCL and PERI, as well as systolic and diastolic left ventricular heart function were assessed.
Results
Correlation analysis with parameters of systolic heart function revealed significant associations for PERI (Ejection fraction: $R=0.404$ $P=0.016$; Cardiac index: $R=-0.482$ $P=0.003$), but not for MYCL. With regard to diastolic heart function MYCL ($R=-0.349$ $P=0.034$) and PERI ($R=-0.472$ $P=0.004$) were negatively correlated with the E/A ratio. In multiple regression analysis CI and E/A ratio were negatively predicted by PERI, whereas no impact of MYCL could be found in direct comparison.
Discussion
Cardiac fat depots impact heart function in slightly overweight subjects. Moreover, direct comparison of different lipid stores revealed that PERI is a more important predictor than MYCL for altered systolic and diastolic function in a metabolically healthy population.

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GP52

Sex specific effects of alterations in macronutrient composition on fat accumulation, lipid-synthesis, -transport and –storage

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Recent data suggest that not only caloric density but also macronutrient composition of diets can influence metabolism, body composition and the development of metabolic disorders. A limitation of previous studies was that effects were studied predominantly in males. To better understand potential differences in the response of males and females to manipulations of dietary macronutrients, our studies were undertaken in both sexes. As a dietary model, we used regular chow diet (CH), low carbohydrate-high fat diets of normal (LCHF-1) and low (LCHF-2) protein content as well as a high carbohydrate-high fat diet (HCHF). Purified diets (% of metabolizable energy, fat/protein/carbohydrate: Chow (CH, 16.7/19.0/64.3), protein matched LCHF-1 (78.7/19.1/2.2), ketogenic LCHF-2 (92.8/5.5/1.7) and HCHF (61.9/18.7/19.4)) were pair-fed isoenergetically for 4 weeks to male and female Wistar rats (12 weeks at start, $n=7$/group). At study end (6 h fasting, dark phase), blood samples and organs were collected. Compared to CH, all isoenergetically fed diets high in fat led to reduced body weight (BW) gain. This effect was seen in both sexes and was independent of carbohydrate content. However, despite lower BW, animals fed LCHF-1 and LCHF-2 but not HCFC exhibited a significant ($*P<0.05$; $***P<0.001$) increase in visceral fat (%; g/g BW) in both sexes (male CH: 0.93 ± 0.07, LCHF-1: $1.22\pm0.07***$, LCHF-2: $1.26\pm0.07***$, HCHF: 1.08 ± 0.06, female CH: 0.65 ± 0.05, LCHF-1: 0.93 ± 0.08, LCHF-2: $1.03\pm0.09***$, HCHF: 0.64 ± 0.05). Notably, subcutaneous fat mass increased significantly only in males. Higher serum leptin was seen in all animals fed HF-diets (male CH: 2837 ± 374, LCHF-1: 4094 ± 366, LCHF-2: $4646\pm617*$, HCHF: $4599\pm411*$, female CH: 904 ± 193, LCHF-1: $2433\pm434*$, LCHF-2: $2355\pm446*$, HCHF: 2157 ± 311). In white adipose tissues (WAT) a pronounced increase in adipokine mRNA expression (leptin, adiponectin) was seen only in males. Furthermore, surrogate markers of lipid synthesis (FASN), transport (LPL) and storage (ATGL) in subcutaneous WAT were also increased only in male individuals on HF. These data strongly suggest that macronutrients affect lipid metabolism differently in males and females. If macronutrients also affect transformation of subcutaneous WAT into beige fat in a sex specific manner is currently under investigation.

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GP53

Different repletion of intramyocellular lipid (IMCL) in patients with growth hormone deficiency (GHD) compared to control subjects (CS) 24 h after a 2-h aerobic exercise

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Background
We and others have shown that ectopic lipids are flexible fuel stores in healthy subjects, in patients with type 1 diabetes or with GHD. IMCL are depleted by exercise and repleted by diet, whereas intrahepatocellular lipids (IHCL) are increased immediately after exercise. It is unclear whether the exercise-induced flexibility of IMCL and IHCL persists until 24 h and whether healthy subjects and patients with GHD behave differently.
Methods
Male patients with GHD and sedentary CS were included. VO_{2max} was assessed by spiroergometry, visceral and subcutaneous fat by whole body MRI. ^{1}H-MR-spectroscopy was performed in the M. vastus intermedius (IMCL) and the liver (IHCL) before and after 2 h of exercise at 50–60% VO_{2max} and 24 h thereafter, while diet and physical activity were standardized.
Results
14 men (seven GHD and seven CS) were recruited. Mean ($\pm$S.D.) age was 46.9 $\pm$ 11.7 and 39 $\pm$ 12.6 years in GHD and CS, respectively (p = NS). BMI was 26.7 $\pm$ 3.8 and 27 $\pm$ 4.1 kg/m^2 (p = NS), waist circumference 93.3 $\pm$ 12.8 cm and 91.3 $\pm$ 13.8 cm (p = NS), VO_{2max} 30.5 $\pm$ 6.2 and 42.8 $\pm$ 10.9 ml/kg per min in GHD and CS, respectively (P = 0.03). Visceral fat content (of total body mass) was 4.2 $\pm$ 1.4% and 2.4 $\pm$ 1.5% (P = 0.04) and subcutaneous fat content was 16.7 $\pm$ 3.0% and 15.8 $\pm$ 4.0% (p = NS) in GHD and CS.
IMCL were decreased during aerobic exercise in both groups ($-$11.5 $\pm$ 21.9% in CS and $-$8.9% $\pm$ 19.1% in GHD) and repleted after 24 h in CS ($-$5.5 $\pm$ 26.6% compared to baseline) but not in GHD ($-$17.9 $\pm$ 15.3%), (P = 0.048 for interaction). IHCL increased immediately after exercise and decreased to baseline after 24 h (p = NS for interaction).
Conclusion
These findings suggest that IMCL's flexibility differs in patients with GHD 24 h after exercise whereas the kinetics of IHCL are similar. Apart from lower VO_{2max} and higher visceral fat in GHD, the lack of lipolytic action of GH could explain the findings: the reduced fat availability following exercise may have led to a decreased repletion of IMCL at 24 h.

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GP54

Oxytocin signalling involved in cardiac protection against ischemia reperfusion

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The oxytocin (OT) treatment protects heart against ischemia. Here we investigated heart-derived H9c2 cells in simulated ischemia-reperfusion (I-R) experiments in order to examine the mechanism of OT-induced cardioprotection.
Results
I-R was induced in an anoxic chamber for 2 h and followed by 2 h of reperfusion. In comparison to normoxia, I-R resulted in decrease of formazan production by H9c2 cells to 63.5 $\pm$ 1.7% (MTT assay) and enhanced apoptosis from 1.7 $\pm$ 0.3% to 2.8 $\pm$ 0.4% (Tunel test). Using these assays we found that treatment with OT (1–500 nM) exerted dose-dependent protection during I-R, especially when OT was added at the time of reperfusion. This involved OT receptor (OTR) because the cells exposed to I-R and treated with specific OTR siRNA responded to OT by enhanced apoptosis. The OT stimulation causes intracellular signaling involving Pi3K, Akt and eNOS, known as the canonical factors of signalosomes. Confocal microscopy demonstrated in OT-treated cells, the phosphorylated Akt co-localized with the mitochondrial marker Cox IV. In addition, the NOS dissociation from caveolin-3 and eNOS phosphorylation was accompanied by increased production of NO. The increased cell viability induced by OT was abolished by the co-treatment of the cells with a PKG inhibitor, KT-5823. Furthermore, stimulation with OT resulted in enhanced release of atrial natriuretic peptide. Using the CM-H_2DCFDA probe we have also observed the paradox that OT treatment stimulates moderate levels of reactive oxygen species (ROS) production in cells whereas inhibits excess of ROS produced as a consequence of ischemia evoked by I-R.
Conclusion
The OTR protected H9c2 cells against I-R, especially if activated at the onset of reperfusion. The OTR-transduced signals include Akt and PKG. These kinases translocate to the mitochondria, where they act in a localized signalosome involving activation of ROS in a positive feedback loop.

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GP55

IGF-1: A marker of cardio-metabolic risk in obstructive sleep apnea (OSA) syndrome?

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Introduction
Insulin-like growth factor-1 (IGF-I), the main growth factor associated with GH secretion, directly opposes endothelial dysfunction and limit early atherosclerosis by favoring nitric oxide production, promoting insulin sensitivity and preventing postprandial dyslipidemia. A low serum IGF-I level has been reported in patients with OSA syndrome and might be one of the mechanisms underlying cardio-metabolic risks in OSA patients. IGF-1 levels were evaluated in a large prospective cohort of patients referred for suspicion of OSA syndrome.
Patients and Methods
In a multicenter national study, 817 patients consulting for suspicion of OSA had serum IGF-1 measurements and OSA syndrome was confirmed in 567 patients by polysomnography or respiratory polygraphy. We analyzed the association between serum IGF-1 below the median value of the population with variables related to cardio-metabolic risks, like body mass index (BMI), apnea hypopnea index (AHI), cholesterol and triglycerides levels (expressed in quartile, median or continuous variables).
Results
Median IGF-1 median was 138 ng/ml. For the whole population (n = 817) and after adjustment for age and gender, an IGF-1 below the median was associated with increased BMI (OR = 2.83; P < 0.0001), AHI (OR = 3.03, P < 0.0001 for Quartile 4 vs 1), cholesterol (OR = 1.36, P = 0.0444), and triglycerides (OR = 1.36; P = 0.0008) levels, respectively. In patients with OSA syndrome (n = 567), IGF-1 level below the median value was also associated with increased BMI (OR = 2.03, P < 0.0069), AHI (OR = 3.03, P < 0.0001 for Quartile 4 vs 1), and elevated triglyceride levels (OR = 1.29; P = 0.0152).
Conclusion
In patients with OSA syndrome low IGF-1 levels are associated with recognized predictors of cardio-metabolic risks. So, IGF-1 has potentially a role as a prognosis biomarker in OSA patients and our results also provide insights regarding possible mechanisms of co-morbidities in such patients.

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GP56

The dual FXR/TGR5 agonist INT-767 reduces visceral fat mass, promoting preadipocyte brown differentiation, mitochondrial function and insulin sensitivity in a rabbit model of high fat diet-induced metabolic syndrome

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Expanding brown adipose tissue is a potential therapeutic strategy to counteract insulin resistance and metabolic syndrome (MetS). Farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5) activation enhances insulin

sensitivity, suggesting the capacity of FXR/TGR5 agonists to promote brown differentiation in adipose tissue. Treatment with increasing doses of the dual FXR/TGR5 agonist INT-767 (3, 10, 30 mg/Kg bw, daily for 5 days a week, by oral gavage, for 12 weeks) in a rabbit model of high fat diet (HFD)-induced MetS, characterized by insulin resistance, hypertension, dyslipidemia,visceral adipose tissue (VAT) accumulation, dose-dependently reduced VAT mass, as well as glycemia, insulin resistance, cholesterol levels while significantly increasing HDL levels. INT-767 also reduced HFD-induced hepatomegaly and ALT increase. Treatment with INT-767 decreased HFD-induced adipocyte hypertrophy and reduced GLUT4 translocation to the plasma membrane, both considered hallmarks of insulin resistance in VAT. Treatment with INT-767 also induced VAT expression of genes related to nitric oxide (NO)/cGMP/protein kinase G (PKG) signaling, mediating both mitochondriogenesis and brown adipocyte differentiation. Rabbit preadipocytes (rPADs), isolated from the different groups, were then investigated for their spontaneous adipogenic potential. The expression of genes specific for: i) brown fat ii) mitochondrial biogenesis, iii) membrane respiratory chain, iv) pro-fusion and pro-fission proteins of mitochondria, were all significantly increased in rPADs from INT-767-treated compared to HFD rabbits. Transmission electron microscopy demonstrated that INT-767 treatment normalized HFD-induced reduction of mitochondrial cristae. INT-767 treatment was also able to: i) improve mitochondrial architecture and dynamic, with the majority of mitochondria continuously moving and changing shape, as assessed by time lapse imaging with mitochondria-targeted fluorescent probe MitoTracker, ii) reduce superoxide production, assessed by measuring the time-dependent accumulation of dihydroethidium-derived fluorescence, iii) improve insulin sensitivity. In conclusion, the dual FXR/TGR5 agonist INT-767 ameliorates the metabolic profile and reduces visceral adiposity by improving insulin sensitivity and promoting brown differentiation in visceral adipose tissue.

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GP57

Prioritizing drug targets for non-alcoholic fatty liver disease based on comorbidity network analysis

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Background and aims
Non alcoholic fatty liver disease (NAFLD) is highly associated with other components of the metabolic syndrome, in particular obesity and diabetes. However, systematic network medicine approach of the complex phenotypic dependencies and comorbidities has yet to be performed. Our aim now is to identify novel drug targets for NAFLD treatment by a systematic in silico network analysis.
Methods
We constructed an interaction network of curated genes relevant to NAFLD and its comorbid diseases of interest. Network mining was applied to characterize the NAFLD comorbidity network, and identify the key genes based on centrality ranking. Large-scale shortest path analyses showed NAFLD connectivity to other comorbid diseases and allowed inferring the molecular mechanisms underlying comorbidities.
Results
Overall, we identified 594 disease genes, most of which (38.7%) were related to glucose metabolism disorders ($n=230$). Lipid metabolism disorders were represented by 116 genes, and obesity by 114 genes; 19 genes were associated with metabolic syndrome, and 30 genes with non-alcoholic fatty liver disease (NAFLD). Network construction on the 594 disease genes resulted in a network of 2175 proteins and 4605 interactions from the human protein reference database. Among the most central genes in the network, two genes were directly related to NAFLD (TGBF1 and F2) and eight new candidate genes were inferred. We identified ten key genes that were related to at least two diseases and then consecutively regulated the comorbidities between the diseases. Of note, most of the ten genes were related to lipid and glucose metabolism, and two (INS, IRS1) were involved in aldosterone-regulated sodium absorption and diabetes. Furthermore, we found a large number of paths linking the NAFLD-related genes to glucose and lipid metabolism disorders and obesity (46 143, 22 000 and 21 516 paths, respectively), in particular genes related to adipocytokine and PPAR signaling and cytokine-cytokine receptor interaction.
Conclusions
The comorbidity network analysis of NAFLD allowed the identification of genes that could represent the most promising molecular targets for prioritization of drug therapy in NAFLD.

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GP58

Cardiac status after long-term growth hormone replacement therapy in adult growth hormone deficient patients. A single centre audit based on echocardiographic investigations before and during GH replacement therapy

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Objective
To determine the effects of long-term growth hormone (GH) treatment on heart anatomy and function among adult GH deficient patients.
Design
A retrospective observational study at Copenhagen University Hospital, Rigshospitalet, Denmark between 1999 and 2015.
Patients
All patients with available echocardiography data at treatment baseline, 3–5 years and 8–10 years follow up. We included 25 naïve GH deficient patients, i.e. patients who had never received GH therapy before, and 16 semi-naive patients, i.e. patients previously on GH substitution therapy, but who had not received GH within 6 months before baseline evaluation.
Main outcome measures
Measurements of interventricular septum thickness (IVSD), left ventricular internal diameter end systole (LVISD), left ventricular internal diameter end diastole (LVIDD), left ventricular posterior wall diameter (LVPWD), mitral valve E/A ratio, mitral valve deceleration time and ejection fraction were assessed. Left ventricular mass (LVM), left ventricular mass index (LVMI) and fractional shortening were calculated based on data from the echocardiographic investigations. Biochemical data including cholesterol, triglycerides, IGF-1 and testosterone (in men), blood pressure, height and weight were assessed at baseline, 3–5 years and 8–10 years after commencement of GH substitution.
Results
No significant difference was observed in cardiac structure, nor in cardiac systolic or diastolic function during GH therapy. A non-significant positive correlation was observed between change in IGF-1 SDS versus change in LVMI, at 3–5 years and 8–10 years follow-up. In subgroups, a significant decrease was observed in both systolic function among semi-naïve patients and in diastolic function among adulthood-onset and naïve patients at follow-up.
Conclusion
Results from this study indicate that treatment duration of 8–10 years with GH replacement therapy in physiological doses on GH deficient patients appears not to be harmful, considering cardiac status. Verification of a positive effect of GH replacement on LVMI will require a larger cohort of GHD patients.

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GP59

Familial partial lipodystrophy type 3 due to PPARgamma mutation: presentation with diabetes and severe hypertriglyceridemia

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Introduction
Familial partial lipodystrophy (FPL) is an autosomal dominant disease characterized by selective loss of subcutaneous fat from the extremities and gluteal region, with lipohypertrophy of the face, neck and trunk. It is usually

tightly linked with severe metabolic complications. FPL type 3 results from peroxisome proliferator-activated receptor gamma (PPARG) mutations.
Case presentations
Fifty three-year-old woman, referred to endocrinology department for severe dyslipidemia with hypercholesterolemia and hypertriglyceridemia (11 729 mg/dl), and 'type 2' diabetes (T2D). She was treated with insulin totalling 128 UI/d, simvastatin (20 mg/d) and fenofibrate (267 mg/d). She presented with hypertension, and there was no history of pancreatitis. She had a family history of T2D, dyslipidemia and premature cardiovascular disease (CVD). Physical examination revealed: weight 50.3 kg; BMI 23.3 kg/m^2; lipoatrophy of the extremities with preserved subcutaneous fat in face and trunk. There was no xanthomas, xanthelasmas or lipemia retinalis. A_1c 10.3%; total cholesterol 921 mg/dl; HDL cholesterol 56 mg/dl; LDL cholesterol 195mg/dl; triglycerides 4679 mg/dl. Lipemic serum, with milky appearance. Genetic study detected the variant c.581G>A (p.Arg194Trp) in exon 4 of the gene *PPARG*. A patient's sister, a 40-year-old woman, was also admitted to endocrinology department, with the same metabolic disorders. Physical examination showed: weight 52.7 kg; BMI 24.4 kgm^2; lipoatrophic extremities with muscular hypertrophy and vascular prominence; abdominal prominence and hepatomegaly. A_1c 12.7%; total cholesterol 642 mg/dl; HDL cholesterol 90 mg/dl; LDL cholesterol 121mg/dl; triglycerides 2404 mg/dl. Hepatomegaly with steatosis (22 cm). There was an improvement of metabolic parameters after therapeutic optimization, but the patient was readmitted 10 months later, presenting A1c 12.2% and severe hypertriglyceridemia (14 845 mg/dl), with eruptive xanthomas. Genetic testing confirmed the same *PPARG* gene mutation.
Conclusion
The clinical features and biochemical profile suggested the diagnosis of genetic lipodystrophy, confirmed as FPL type 3. We underline the importance of clinical suspicion and early intervention of metabolic complications, in order to prevent early onset of CVD and the occurrence of pancreatitis.

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Clinical Case Reports

GP60

Endoscopic ultrasound-guided ethanol ablation therapy for pancreatic insulinoma: an unusual strategy

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Introduction
Insulinomas are the most frequent cause of endogenous hypoglycaemia. 90 to 95% of these are benign. Surgical enucleation or resection is the standard treatment. Medical therapy focuses mainly on the use of diazoxide with few alternatives in patients with high surgical risk.
Case-report
Female patient, 89 years-old, non-diabetic, with previous history of acute myocardial infarction, stroke with motor sequelae, pacemaker carrier and severe aortic valve disease was admitted to the emergency department due to recurrent hypoglycaemia, especially in fasting, with 3 weeks of evolution; without associated weight gain or access to hypoglycaemic drugs.
During hospitalization, the patient maintained multiple daily episodes of hypoglycaemia unrelated to food intake that conditioned need to maintain continuous hypertonic dextrose infusion during nighttime and frequent oral feedings during daytime.
Laboratory workout revealed a glycaemia value of 38 mg/dl (<55 mg/dl), serum insulin of 10 UUI/ml (>3 UUI/ml) and C-peptide of 1.9 ng/ml (>0.6 ng/ml); no other abnormalities were detected. Abdominal CT identified a 12 mm hypervascular nodular lesion of the pancreatic body suggestive of insulinoma. Attending to the comorbidities and age, the patient was not approved for surgery and therapy with diazoxide was initiated to a maximum dose of 75 mg/day. The lack of success of medical therapy was related to the difficulty in drug dose titration by the risk of congestive heart failure.
Endoscopic ultrasound-guided ethanol ablation therapy was a viable solution and 0.6 ml of ethanol was injected by transgastric approach; no complications were registered.
No symptomatic episodes of hypoglycaemia were noted during 5 months-follow-up.
Conclusion
Ethanol ablation therapy of insulinomas is a minimally invasive alternative treatment with low complication rates although with little experience. In high risk patients, this may be one of the only feasible options with satisfactory clinical results and significant impact on quality of life and survival.

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GP61

An unusual presentation of an ovarian teratoma

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Introduction
Hormone-secreting teratomas are well described. However teratomas secreting pancreatic hormones are rare, with even fewer cases producing clinically significant effects. We describe possibly the first documented case of hyperinsulinaemic hypoglycaemia due to an insulin-secreting ovarian teratoma.
Case report
A 23-year-old woman presented with transient symptoms of lethargy and weakness. She had used her father's capillary glucose meter to measure her own blood glucose, recording values of 2.1 and 2.8 mmol/l. Further investigation confirmed a fasting glucose of 2.7 mmol/l, elevated insulin (40.4 mIU/l) and C-peptide (5.6 ng/ml), with a normal cortisol (624 nmol/l) and IGF-2/IGF-1 ratio (<10). Abdominal ultrasound and CT scans revealed a 10 cm cystic teratoma arising from the right ovary, with normal appearance of the adrenal glands and pancreas.
The ovarian mass was removed laparoscopically. Histopathology findings were of a mature cystic teratoma containing teeth, hair, skin, sebaceous material, cartilage and a large, mature, pancreatic tissue component. Within this, immunohistochemistry showed differential expression of insulin, glucagon and somatostatin in islet cells. Hypoglycaemia did not recur post-operatively. The resolution of symptoms following surgical excision suggests that the patient's hyperinsulinaemic hypoglycaemia was due to ectopic insulin secretion from apparently mature pancreatic tissue within the teratoma.
Conclusions
Ectopic hormone release from teratomas is well described, including AFP from yolk sac-containing teratomas, hCG from pineal teratomas, and, most notably, thyroid hormones from cystic struma ovarii, which may rarely cause thyrotoxicosis. Nevertheless there are few cases of pancreatic hormone-secreting teratomas in the literature, with only a handful causing clinically significant effects. We could not find any other cases of hypoglycaemia secondary to an insulin-secreting ovarian teratoma. In summary, this unusual case demonstrates failure of normal glucose homeostasis secondary to ectopic insulin secretion from an ovarian teratoma, resulting in recurrent hypoglycaemia.

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GP62

Extreme enlargement of lower extremities mimicking elephantiasis in patients with severe insulin resistance syndrome; a novel phenotype

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Introduction
Severe insulin resistance syndromes are rare syndromes characterized by clinical features like: acanthosis nigricans, ovarian hyper androgenism in post pubertal females: hirsuitism, oligomenorrhea and infertility.
Major causes of severe insulin resistance are: i) genetic defects in insulin receptor like type A syndrome, or ii) autoimmune like antibodies to insulin receptor like in type B syndrome or antibodies to insulin itself, iii) congenital or acquired partial or generalized lipodystrophy.
Case report
Here, we report three females (17, 21, and 18 years) who had been diagnosed as severe insulin resistance based on the following shared features:
- Severe acanthosis nigricans;
- Hyperandrogeniticty (hirsutism and oligomenorrhea);
- Pseudoacromegaly;
- Very high fasting insulin levels ranging from 500 to 1700 pmol/l (reference range 17.8–173) pmol/l.
Interestingly, all three patients were noted to have extreme lower leg swelling of non-pitting edema that was present before starting the treatment. All of them were subjected to skin biopsy. Results of skin biopsy of lower leg showed normal subcutaneous tissue in one patient with perivascular lymphocytic infiltrate and occasional eosinophils in the other two patients.
All of the three patients were positive for the same insulin receptor mutation.
Conclusion
Awareness of this extreme lower extremity swelling in patient with severe insulin resistance syndrome would help to avoid unnecessary work up for other causes of lower limb swelling.

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GP63

Triple X and premature ovarian insufficiency – case report

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Introduction
Premature ovarian insufficiency is characterized by precocious depletion of ovarian follicles, associated with amenorrhea, hypoestrogenism and high gonadotropin levels. It afflicts 1% of the female population and in 5% cases it is due to X chromosome abnormalities.
Case report
A 22 year old previously healthy female, presented to the Endocrinology Clinic due to amenorrhea. She had no family history of amenorrhea, her menarche was at age 11 and she had normal pubertal development. She complained of transitory amenorrhea that lasted 6 months and spontaneously resumed to irregular cycles. She denied any other complaints and mentioned the desire to become pregnant. The analytical evaluation revealed: FSH 67.6 mUI/ml, LH 35.9 mUI/ml, E_2 13.5 pg/ml; TSH, Testosterone, Δ-4AE, DHEA-SO4, 17-HO-progesterone and PRL within the reference range. β-HCG <1 U/l. Transvaginal pelvic ultrasound showed a normal sized uterus with regular endometrium, the left ovary with normal dimensions and three microfollicles, the left ovary atrophic and without follicular activity. In a second visit, hypergonadotropic hypogonadism was confirmed (FSH 86.0 mUI/ml, LH 73.8 mUI/ml, E_2 12.9 pg/ml) and at this point she complained of progressively worsening hot flushes, that ameliorated with hormonal therapy institution. Bone densitometry studies showed osteopenia at the lumbar vertebra and femoral neck. Anti-ovary auto-antibodies were negative. Anti-mullerian hormone studies were normal. Genetic studies towards CGG sequence repetitions were negative for fragile X chromosome. The karyotype analyses revealed mosaic 47, XXX (90%)/46, XX (10%). The patient was sent to a clinic specialyzed in fertility for oocyte retrieval, but at this point there was none with viability.
Conclusion
Some women with triple X do not show any manifestations other than menstrual irregularity. In this backgrownd, premature ovarian insufficiency presents with accelerated loss of follicles. Genetic testing is part of the differential diagnosis and unexpected karyotype findings have important implications in fertility.

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GP64

Pseudohypoparathyroidism masquerading as seizures since childhood

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Introduction
Pseudohypoparathyroidism (PHP) refers to a group of rare sporadic or inherited disorders characterized by parathyroid hormone (PTH) resistance. We report a case of PHP with phenotypical expression and multiple hormonal resistance.
Case description
We report a 26-year-old lady who presented to us after a fall, with history of recurrent seizures since 12 years of age. There was a history of oligomennorhoea. Physical examination revealed round faced, short-statured, obese (BMI 31) dysmorphic lady with subnormal intelligence and brachymetacarpia. Laboratory work up revealed hypocalcemia with a corrected calcium of 1.4 mmol/l, phosphate 1.98 mmol/l, iPTH 366 pg/ml. CT brain revealed intracranial calcification. Hand radiograph showed shortened 4th metacarpals. She was managed symptomatically with intravenous calcium initially and commenced on calcium and vitamin D replacement. Further work up revealed hypothyroidism (FT_4 10.4 pmol/l TSH 20.73 mIU/l). On follow up she reported no seizures and was eucalcaemic. The elevated PTH in our patient with chronic hypocalcaemia, hyperphosphatemia, normal renal function and phenotypic features suggested pseudohypoparathyroidism type Ia (PHP-Ia).
Discussion
PHP is a complex disorder and diagnosis is often delayed. This was the case in our patient whose initial manifestation was seizures occurring during pubertal growth spurt corresponding to the higher calcium demand. The estimated prevalence in Japan (of PHP type 1a and 1b) is 1/295 000. PHP-1a is characterized by resistance to PTH and other hormones that stimulate adenyl cyclase in their target tissues, such as TSH, gonadotropins and GHRH. Primary hypothyroidism and reproductive dysfunction are commonly seen in these patients. Our patient did in fact have hypothyroidism. Heterozygous mutations in the GNAS1 gene, that encodes Gsα, when inherited from the maternal allele are associated with the clinical loss of function and hormonal resistance. Patient with inactive or decreased amounts of Gsα showing phenotypic and biochemical features are diagnosed as PHP type 1, similar to our case.
Conclusion
Our patient thus presents as a rare case of PHP-1a with multiple hormone resistance with typical phenotypic expression.

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GP65

Turner syndrome and liver involvement: is there a place for treatment with ursodeoxycholic acid?

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Introduction
Abnormalities in liver biochemistry are frequent in Turner's syndrome (TS) with a reported prevalence between 20 and 80%. While their aetiology remains unclear, metabolic factors and intrahepatic biliary disease have been postulated. Moreover, some TS patients have a predominantly cholestatic biochemical abnormality and others a hepatitic picture. Ursodeoxycholic acid (UDCA) has been shown to be a useful treatment of cholestatic disease.
Case report
A 28-year-old patient with TS (45X/46XrX) was noted to have abnormal liver function tests (LFTs) in 2006 (ALT 171 IU/l (10–45), ALP 693 IU/l (75–250), GGT 232 IU/l (15–40)). At yearly follow-up, for the last 10 years persistently elevated LFTs were found, mostly 2–3 times the upper limit of normal. The bilirubin was normal and hepatic autoimmunity and serology screening were negative. BMI has been stable (25 kg/m^2). There was no history of diabetes, hypertension, dyslipidaemia, cardiac, renal or autoimmune disease, excess alcohol intake or family history of liver disease. Treatment with HRT (started age 13 years) was reduced, stopped and changed without any improvement in her LFTs.
Persistence of abnormal LFTs led to liver ultrasound and liver biopsy in 2008, both of which were normal. In 2009 she underwent cholecystectomy due to biliary colic. MRCP in 2014 revealed normal intra and extra-hepatic bile ducts. She was started on UDCA (13 mg/kg per day) from 2014 and after 12 months her LFTs had improved considerably to near normal ranges (ALT 46 UI/l, ALP 144 IU/l (30–130), GGT 89 UI/l).
Conclusions
This case illustrates that oestrogen therapy does not lead to deterioration in LFTs in TS patients, and importantly shows for the first time that UDCA treatment may be of benefit to TS patients with abnormal LFTs. Due to the high prevalence of LFT abnormalities in this population, the use of UDCA warrants further study.

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GP66

Secondary adrenal insufficiency and hypogonadotropic hypogonadism in a patient with advanced medullary thyroid carcinoma on treatment with vandetanib. May it have a pathogenic role?

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Clinical case
We report the case of a 40-year-old woman, diagnosed with sporadic medullary thyroid carcinoma (MTC) treated with total thyroidectomy, cervical lymph node dissection and chemotherapy. During follow-up, cervical lymph node, lung, breast, bone and subcentimeter cerebellous affectation was observed. She started on Sunitinib, but withdrawal at 6 months due to severe inguinal inverse psoriasis. Then, treatment with vandetanib was started with good response. Tumor markers levels decreased with treatment with tyrosine kinase inhibitors (TKIs) from calcitonin 19 504 pg/ml and carcinoembryonic antigen (CEA) 202.1 ng/ml, to 273 pg/ml and 23.4 ng/ml respectively. While lung, cerebellous and bone lesions remained stables, breast metastasis dissappeared. Secondary adrenal insufficiency

(AI) and hypogonadotropic hypogonadism developed, with other hypophyseal function preserved. Pituitary MRI and anti-hypophysis antibodies were normal.
Discussion
AI has been reported as consequence of hypophysitis secondary to anti-tumor agents as Ipilimumab. In our case, there were not data of hypophysitis. We suggest that this effect of vandetanib may be due to its anti-angiogenic effect probably by inhibiting epidermal growth factor receptor (EGFR). EGF is expressed in a lower form in nontumoral cells, as hypophysis cells, where EGFR has been detected in 5–10% of them, mainly in gonadotrope and thyrotrpe cells. Likewise, EGFR sobreexpression has been described in metastatic MTC, associated with RET mutation M819T with a specific well response to vandetanib. In the same way, ACTH-producing pituitary macroadenomas has been identified as good responders to TKIs, as gefitinib, due to the sobreexpression of EGF in tumoral corticotrope cells that could be present in nontumoral corticotrope cells.
Conclusions
In patients on treatment with TKIs, especially those with effect of EGFR, may be interesting to rule out the presence of pituitary abnormalities if it is clinically suspected.

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GP67

Nivolumab associated thyroiditis in a patient with squamous non small cell lung cancer

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Nivolumab is the first programmed death 1 (PD-1) immune checkpoint inhibitor. It is approved for use in advanced melanoma and squamous non small cell lung cancer (NSCLC). PD-1 immune checkpoint inhibitors can cause autoimmune disease of endocrine glands, including the thyroid. Here, we present a case of thyroiditis after nivolumab therapy.
A 61 year-old female patient with NSCLC was consulted to endocrinology department for abnormal thyroid function test results. Thyroid hormone results are consistent with hyperthyroidism (TSH: 0.01 μIU/ml, fT_4: 45.4 pmol/l, fT_3: 10.8 pmol/l). Thyroid gland was smooth, non tender and minimally enlarged. She did not have history of prior thyroid dysfunction. In 2006, she was diagnosed with stage III ovarian carcinoma and she received paclitaxel-carboplatin therapy. Relapse occured after seven years in remission and she was given six courses of paclitaxel-carboplatin and four courses of ipilimumab. In March 2015, she was diagnosed with NSCLC and received thirteen weeks of paclitaxel-carboplatin. Then six courses of nivolumab (3 mg/kg) was given fortnightly. Thyroid hormone levels were normal after two courses of nivolumab. Serum TgAb, TPOAb, and TRAb were undetectable. Thyroglobulin levels were >500 ng/ml (0–85) and thyroid ultrasonography showed paranchymal heterogenity and small multiple nodules. Thyroid scintigraphy result was consistent with diffusely reduced uptake but the patient did not give consent to iodine uptake test. Propranolol treatment was given. She was euthyroid approximately 8 weeks later. On follow up one month later, she was found to have an elevated TSH of 81 μIU/ml, low fT_4 of 3.7 pmol/l (12–22), and fT_3 of 1.1 pmol/l (3.1–6.8). L-thyroxine therapy was initiated.
This case demonstrates painless thyroiditis which initially presented as hyperthyroidism and progressed to hypothyroidism under nivolumab therapy. We recommend that all patients on anti-PD1 therapy should be screened for the clinical and laboratory manifestations of thyroid dysfunction.

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GP68

Autoimmune polyglandular syndrome type 1 in children: a clinical case in siblings

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Introduction
Autoimmune polyglandular syndrome type 1 (APS1) – severe disease that is rare in pediatric practice. Clinical sings of APS1 are quite diverse, new components may manifest at any age. Their timely diagnosis is critically important, some symptoms can threaten patient's life. We present our own clinical observation of the APS1 course in siblings.
Case report
A 10-year-old previously healthy boy presented with severe weakness, drowsiness, weight loss, craving salty foods. Physical exam showed skin hyperpigmentation and low blood pressure. Patient had candidiasis of his oral mucosa and nails. Investigations showed the low serum calcium, sodium and high serum phosphorous and potassium levels. Cortisol level was 57.4 nmol/l (171–720) and ACTH level was 2006 pmol/l (7.2–63.3). Values of other indicators were in norm (TSH–4,1 mIU/l, GADA–0,38). Treatment of primary adrenal insufficiency with hydrocortisone and fludrocortisone was started. For hypoparathyroidism correction boy was commenced on calcitriol, calcium and vitamin D3 supplements. The patient responded well to treatment with normalization of the overall health and positive dynamics at laboratory inspection.
The patient's 8-year-old sister was diagnosed with the primary hypoparathyroidism at the age of 6 years on the basis of low serum ionized calcium (0.7 mmol/l) and PTH levels (5.5 pg/ml). A treatment with calcitriol, calcium and vitamin D3 supplementation was started. She was noted to have candida infection of her mouth requiring frequent antifungal treatment. Considering existence of APS1 in a family the additional examination was conducted. GADA were positive, that points to high risk of T1DM. Other studied indicators were in norm. Genetic testing of patients with APS1 in Belarus is not conducted.
Conclusion
It was shown that it is extremely important to supervise all children in family which already has a child with APS1. Families should be made aware of the potential later manifestations of the syndrome.

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GP69

Suspected medullary thyroid cancer in a patient with neuroendocrine tumor of left lung

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Introduction
Despite recommendations neuroendocrine tumors may still pose diagnostic and therapeutic problems. Patients are referred to specialized centers when their disease has already progressed to generalized stage.
Case report
A 64-year old male patient was referred to the Department of Endocrinology at the Pomeranian Medical University in 2013 because of liver metastases. His medical history included a surgical treatment of left lung tumor in 2006 with histopathology: *Typical carcinoid* (Ki67 12% - G2, T3N1M0). The patient has suffered from the symptoms of carcinoid syndrome for a few years. He has had abdominal pain for 1 year. Ultrasound and CT scan of the abdomen suggested the suspicion of liver metastases which was later confirmed by histopathology findings in core-needle biopsy specimen – neuroendocrine tumor with Ki 67 ranging from 17 to 31%. CT scan of the chest ruled out local recurrence and metastases in the right lung. Receptor scintigraphy - NET metastases. High levels of tumor markers were also observed (chromogranin 879 ng/ml, 5OHIO acid 181 mg/24 h, calcitonin 387 pg/ml, CEA 6.47, AFP 3.44 IU/ml). Ultrasound of the thyroid gland revealed several hypoechogenic foci in both lobes, their sizes ranging from 3 to 10 mm. A medullary thyroid cancer was suspected based on fine-needle biopsy and high calcitonin levels. Thyroidectomy was performed. Histopathology investigation revealed multiple foci of neuroendocrine tumor in both thyroid lobes, with the Ki67 proliferation marker ranging from 7 to 22%, ruling out the diagnosis of medullary cancer based on negative calcitonin staining. The patient was treated with somatostatin analogues with good clinical effect and with PRRT because of disease progression confirmed in imaging examinations.
Conclusions
High calcitonin levels and suspected medullary thyroid cancer in fine-needle aspiration biopsy of focal thyroid lesions sampled from a patient with NET do not rule out thyroid metastases associated with the underlying disease.

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Diabetes

GP70

The association between vitamin D metabolites and the DHCR7 rs12785878 polymorphism in German T2D patients

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Introduction
Hypercholesterolemia is frequently found in patients with type 2 diabetes (T2D). Cholesterol is metabolized from 7-dehydrocholesterol by 7-dehydrocholesterol reductase (DHCR7) from 7-dehydrocholesterol, a precursor of pre-vitamin D3. Therefore single nucleotide polymorphisms (SNP) in the DHCR7 gene could regulate cholesterol levels and concentrations of vitamin D metabolites (25(OH)D_3 or 1,25$(OH)_2D_3$). For this purpose we investigated the SNP rs12785878 located near the DHCR7 gene in German T2D patients and healthy controls (HC) as well as concentrations of vitamin D metabolites.
Methods
527 T2D patients and 654 HC were genotyped for the DHCR7 SNP rs12785878 by a Taqman assay. Additionally, 25$(OH)D_3$ and 1,25$(OH)_2D_3$ plasma levels of 76 T2D patients and 281 HC were measured by RIA.
Results
The homozygous TT genotype was significantly more frequent in T2D patients compared to HC (TT: 54.9 vs 50.2%; GT: 38.4 vs 37.8%, GG: 6.6 vs 12.1%, $P=0.007$), also the allele T (74.1 vs 69.0% OR $=1.22$; 95% CI: 1.02-1.46) in contrast to allele G (25.9 vs 31.0% OR $=0.82$; 95% CI: 0.68–0.98, $P=0.03$). T2D patients had significantly lower 25$(OH)D_3$ (median 12.6 vs 19.4 ng/ml $P=0.0001$) and 1,25$(OH)_2D_3$ levels (median 44.7 vs 51 pg/ml $P=0.001$) compared to HC. T2D patients with DHCR7 genotypes GG and GT had lower 25$(OH)D_3$ levels than those from HC with genotype GG and GT, and T2D patients with the TT genotype showed even lower 25$(OH)D_3$ (median 13.7 vs 20.9 ng/ml $P=0.002$) and 1,25$(OH)_2D_3$ levels (median 43.3 vs 52.3 pg/ml $P=0.001$) compared to HC with the same genotype.
Conclusion
Our results reveal an association of the DHCR7 SNP rs12785878 with German T2D patients. The allele T may predispose to the development of T2D. In addition, significantly lower VD levels were observed in T2D patients with the TT genotype. The dysfunction of DHCR7 may contribute to the complex pathophysiology of insulin action and or ß-cell secretion independent from its effect on VD deficiency being a risk factor for T2D development.

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GP71

A critical evaluation of the metabolic syndrome definition: why we should be more cautious

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Aim
We assessed in both men and women within different BMI- and age classes the prevalence of MetS and its individual components, since these specific estimates obtained simultaneously in a large western European population are lacking. Secondly, we measured as well how age-specific blood pressure (BP) cut-offs affect the prevalence of elevated BP and MetS.
Methods
Data of 74 531 western European participants, aged 18–79 years, were obtained from the Dutch LifeLines Cohort study. Men and women were categorized into three BMI classes and six age decades. MetS was defined according to the revised NCEP ATP III. Furthermore MetS was defined, using either the recommended cut-off values for elevated BP ($\geq$130/85 mmHg) or age-specific values ($\geq$140/90 mmHg for those aged $<$60 years, and $\geq$150/90 mmHg for those aged $\geq$60 years).
Results
According to the NCEP ATPIII 19.2% of men and 12.1% of women had MetS. Elevated BP and abdominal obesity were the most common MetS components in our population, dominating MetS prevalence especially in women, independent of BMI. In the MetS population, already 65–78% of normal weight women had abdominal obesity (overweight: 95–97% and obese: 100%), while in men this was still only 0–18% (overweight: 35–70% and obese: 93–99%). Applying age-specific BP cut-offs showed a great drop in the prevalence of elevated BP (especially among men $<$60 years and women $\geq$60 years) and MetS (in obese men: -9% and obese women: -7%).
Conclusions
The prevalence of MetS components varies strongly between men and women in an age- and BMI dependent manner. Our data indicates a disproportionate contribution of elevated BP to the prevalence of MetS when a conventional cut-off value of 130/85 mmHg is applied. For the MetS diagnosis, we suggest to use age-specific values for elevated BP as well as to establish new thresholds for abdominal obesity.

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GP72

Olfactory and gustatory functions in patients with non-complicated type 1 diabetes mellitus

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Introduction
Olfactory and gustatory dysfunction in patient with diabetes mellitus (DM) and its pathophysiology were studied in many previous studies. Some studies reported that there was a relationship between type 1 DM (T1DM) and olfactory and gustatory functions the presence of diabetic complications. However findings are limited and controversial. The aim of this study was to determine the relationship between olfactory and gustatory scores and patients with non-complicated T1DM. Another aim was to present evidence of the association between olfactory and gustatory scores and HbA1c values and disease durations.
Methods
The study included 39 out-patient non-complicated T1DM patients and 31 healthy individuals. Psychophysical olfactory tests were performed using the commercially available 'Sniffin' Stick' test kit. Taste function tests were carried out using 'Taste Strips' method.
Results
There were no significant differences in olfactory tests between two groups (odor thresholds: 8.63 ± 0.91 vs 8.55 ± 0.57, $P=0.66$; odor discrimination: 12.97 ± 0.80 vs 12.74 ± 0.79, $P=0.24$; odor identification: 13.81 ± 0.98 vs 13.72 ± 0.89, $P=0.69$; TDI score: 35.34 ± 1.94 vs 34.97 ± 1.4, $P=0.37$). There were also no significant differences in gustatory tests between two groups (bitter: 3.45 ± 0.51 vs 3.44 ± 0.50, $P=0.90$; sweet: 3.32 ± 0.48 vs 3.38 ± 0.49, $P=0.60$; salty: 3.13 ± 0.72 vs 3.10 ± 0.72, $P=0.88$; total score of taste: 13.16 ± 1.61 vs 13.13 ± 1.22, $P=0.92$). When dividing T1DM patients according to HbA1c values into three subgroups i) HbA1c values <7, ii) HbA1c values 7–9, iii) HbA1c values >9, olfactory tests and gustatory tests did not differ between groups ($P>0.05$). Comparison of gustatory and olfactory scores according to disease duration revealed that there were no differences between groups ($P>0.05$).
Conclusion
This study demonstrates that T1DM without complications is not associated with olfactory and gustatory dysfunction. We also found that gustatory and olfactory functions are not related with HbA1c values and disease duration. Further research is needed with regard to the underlying mechanisms to explain olfactory and gustatory dysfunction in T1DM with complications.

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GP73

Increased activation of ISCs isolated from diabetic mice

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Abstract withdrawn

GP74

A novel gene mutation in Berardinelli Seip Syndrome: Three case reports

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Introduction
Berardinelli Seip Congenital Lypodystrophy (BSCL) is a rare otosomal recessive disease characterized by major criteria which are lypoatrophy, acromegaloid features, hepatomegaly, hypertriglyceridemia, insulin resistance and minor citeria which are hypertrophic cardiomyopathy, psycomotor retardation, hirsutism, precocious puberty, long bone cysts, phlebomegaly. The presence of three major criteria or two major plus two minor criteria required for diagnosis of BSCL. We report three BSCL cases who are all from the same family and the same genetic mutation of BSCL 2 homozygote pQ94X (stop codon) which is encountered the first time in literature.
Case reports
The first case, 25 years old woman had appearance of acromegaloid face, hyperpigmentation on her skin, widespread acanthosis nigricans, diabetes mellitus, hepatosplenomegaly, prominent decrease of subcutaneous adipose tissue, hypertrophied limb and shoulder muscles. She had also chronic renal insufficiency requiring hemodialysis, cirrhosis of liver, pericardial effusion and hypertropy of left ventricul and interventricular septum. The second case is 20 years old man, the brother of the first one. He had acromegaloid face, darkening skin, acanthosis nigricans, hepatosteatosis, hepatomegaly, diabetes mellitus and hypertriglyceridemia. The third case is their cousin who is 16 years old man. He had similar face characteristic with them, hyperpigmented skin, acanthosis nigricans, hepatosteatosis, hepatomegaly, diabetes mellitus and absence of subcutaneous adipose tissue on entire body MRI. Genetic analysis of three patients showed BSCL 2 homozygote PQ94X(stop codon) mutation which is encountered the first time in literature.
Discussion
Although BSCL patients are born with typical phenotypic features, complications settle with the progression of the disease. A serious disease, BSCL should be followed and treated by multidisciplinary due to multiorgan impairments. In addition to symptomatically treatment of BSCL complications, leptin, which is a cytokine contributing to disease pathogenesis, replacement is becoming more important recently.

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GP75

Intact proinsulin level is associated with insulin resistance but not insulin secretory capacity in subjects with abnormal glucose tolerance

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Introduction
Proinsulin is a propeptide of insulin and C-peptide during physiological insulin production and is increased in patients with type 2 diabetes. Increased proinsulin in peripheral blood indicates impairment of cleavage capacity to process insulin within the beta cell. Recently, chemiluminescence assays have been developed that are able to specifically measure uncleaved intact proinsulin in peripheral blood. In this cross-sectional study, we investigated the relationship between intact proinsulin and insulin resistance and secretion in Korean adults.
Methods
We performed standard 75 g oral glucose tolerance test (OGTT) after an overnight fast in 388 subjects without history of diabetes. Glucose (0, 30, 60, 90, 120 min), insulin (0, 30, 60, 90, 120 min), C-peptide (0, 30 min), and fasting intact proinsulin were measured and insulin sensitivity and secretory indexes were calculated using the results of OGTT.
Results
Average age was 54.6 ± 11.8 years and 41.5% of the subjects were male. Intact proinsulin level was positively correlated with homeostasis model assessment insulin resistance (HOMA-IR) ($r = 0.504$, $P < 0.001$) and was inversely correlated with insulin sensitivity indexes (Matsuda index: $r = -0.445$, $P < 0.001$; OGIS: $r = -0.399$, $P < 0.001$). However, there were no significant correlations between intact proinsulin and insulin secretory indexes (HOMA-beta).Total subjects were stratified by glucose tolerance status; normal glucose tolerance (NGT, $n = 33$), prediabetes (impaired fasting glucose and/or impaired glucose tolerance, $n = 153$), and diabetes mellitus (DM, $n = 202$). Intact proinsulin level showed an increasing tendency with the deterioration of glucose tolerance ($P < 0.001$). In the NGT group, intact proinsulin level was correlated with acute phase insulin secretion (insulinogenic index) but not with the indexes reflecting insulin sensitivity. However, in the prediabetes and DM groups, intact proinsulin levels were inversely correlated with insulin sensitivity indexes (Matsuda index and OGIS index).
Conclusions
Intact proinsulin level increases with the deterioration of glucose tolerance and is significantly correlated with insulin resistance indexes. Moreover, intact proinsulin partly reflects beta cell function.

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GP76

Oxidative stress in the gestational diabetes mellitus mother and placenta

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Background and aims
The mechanisms underlying placenta oxidative stress co-existing with alterations in maternal-placenta interactions during gestational diabetes mellitus (GDM) are not well understood. We sought to evaluate the levels of oxidative stress markers and antioxidants in women with GDM, and to assess the impact on placenta.
Material and methods
Pregnant women (63 with GDM, 63 controls) were enrolled, together with 41 cases and 21 controls for the follow-up study. Oxidative stress markers and antioxidants were measured between the 24–29th week of gestation and 12 months post-delivery as well as in placentae from 6 controls and 6 GDM.
Results
Post-partum, we found significantly increased levels of lipoperoxides (LPO) ($P \leq 0.001$) and catalase ($P \leq 0.001$) and significantly decreased glutathione peroxidase (GPX) ($P = 0.003$) in both groups. Additionally, cases had lower levels of glutathione transferase (GST) ($P = 0.003$) and controls had lower levels of superoxide dismutase (SOD) ($P \leq 0.001$). Multiple regression analyses were performed to evaluate the influence of clinical and metabolic variables on post-partum status. The levels of post-partum oxidative stress were significantly related in the GDM group. Significantly increased levels of carbonyl protein ($p \leq 0.05$) and LPO ($p < 0.05$) together with reduced antioxidant enzyme activities of SOD ($p \leq 0.05$) and catalase ($p \leq 0.05$) were noted in GDM placenta.
Conclusions
We conclude that increased oxidative stress and reduction in antioxidant defence mechanisms occur in the circulation and placenta of women with GDM. Since these imbalances can lead to maternal complications, these variables need to be monitored carefully during GDM pregnancies.

Keywords: gestational diabetes mellitus, oxidative stress markers, antioxidants, placenta.

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GP77

Pancreatic damage induced by cigarette smoke: How does smoking affect the pancreatic functions?

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Background
Studies have shown that smoking may increase the risk of pancreatic disorders. This study aimed to evaluate the oxidative stress status, biochemical, pathological and immunohistochemical findings of rats exposed to the cigarette smoke, pathogenesis of smoking related pancreatic damage and usability of Alpha Lipoic Acid (ALA) for amelioration of cigarette' harmful effects on rat pancreas.
Methods
Twenty eight female, Sprague Dawley rats were randomly distributed into three groups. Sham group (S) (n = 8), rats given 0.1 ml of physiological serum by oral gavage for 8 weeks. Cigarette smoke exposed group (CSE) (n = 10), rats exposed to successive periods of cigarette smoke for 2 hours/day/8 weeks and given 0.1 ml of physiological serum by orally during the study. Cigarette smoke exposed and ALA treated group (CSE + ALA) (n = 10), animals exposed to cigarette smoke (2 hours/day/8 weeks) and simultaneously treated by 100 mg/kg/day ALA orally during the study. Total oxidant status (TOS), total antioxidant status (TAS) levels and oxidative stress index (OSI) were evaluated at the pancreas samples. Immunohistochemically insulin, glucagon, calcitonin gene related protein (CGRP), Caspase-3, hypoxia inducible factor-1 (Hif-1), Hif-2 and TNF-α expressions of pancreas were examined.
Results
Cigarette smoke caused statistically significant increase in serum amylase and glucose levels. At the histopathological examination the pancreases slight degenerative and apoptotic cells noticed both endocrine and exocrine part of the pancreas in CSE group. Immunohistochemical examination revealed marked increase in caspase-3, glucagon, Hif-1 and Hif-2, CGRP and TNF-α expressions while decrease in insulin secretion in some Langerhans islets in CSE group. ALA ameliorated biochemical and pathological findings in CSE + ALA group.
Conclusion
These findings clearly demonstrated that cigarette can cause damage in rat pancreas and ALA has ameliorative effect of cigarette induced lesions.
Keywords: Cigarette smoke, pancreas, pathology, biochemistry.
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GP78

Effect of alpha lipoic acid on high fructose corn syrup induced hepatic pathology

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Objectives
High-fructose corn syrup (HFSC) is used as an artificial sweetener. However, there is limited information about the metabolic effects. Fructose is implicated in the etiology of nonalcoholic fatty liver disease(NAFLD). Unfortunately, no therapy for NAFLD currently exists. The aim of this study was to investigate the hepatic lesion induced by chronic HFCS consumption and the protective effects of alpha-lipoic acid (ALA) on hepatic pathology.
Methods
In this study, 24 Wistar Albino, were randomly allocated into three groups. Groups were HFCS group and prepared 30% solution of F30 (24% fructose, 28% dextrose) was given in drinking water for 10 weeks. The ALA + HSCF group, same dose HSCF given this group and ALA (100 mg/kg per oral) administered the last 6 weeks of the experiment. No drug administered to the control group (CON). Each group consisted eight rats and at the end of 10 weeks, 24 h after the last ALA administration, they were killed.
Results
Statistically significant increase was observed in serum AST ($p = 0.023$) level in HFCS group. Tissue MDA ($p = 0.001$) levels were also increased while CAT ($p = 0.001$) activities were decreased in this group. Immunohistochemically caspase-3 ($p = 0.000$) expression were increased by HFCS significantly.
Conclusion
In ALA treated group all of these pathologic conditions were improved. HFCS induced hepatic toxicity by inducing oxidative stress and apoptotic activity and ALA was ameliorated these pathologic conditions. ALA may be alternative treatment to reduce the fructose-induced hepatotoxicity.
Keywords: alpha lipoic acid, corn syrup, hepatic damage, oxidative stress, pathology.
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GP79

Metagenomic analysis of saliva and biofilm microbiome of type 1 diabetics under continuous subcutaneous insulin infusion

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Introduction
The microvascular complications of diabetes and consequent autonomic neuropathy may cause changes in saliva's secretion and composition. Hyperglycemic levels can also contribute to various oral pathological changes due to alteration of fungi or bacterial flora and dental biofilm surface, leading to the onset of candidiasis, periodontitis and dental caries. The aim of this study was to determine total bacterial load of saliva and dental biofilm of diabetic patients under continuous subcutaneous insulin infusion and that of non-diabetics.
Methods
Twenty patients with type 1 diabetes under continuous subcutaneous insulin infusion were included and 20 non-diabetic subjects were randomized as age-sex-matched controls. Unstimulated whole saliva and dental biofilm were collected from all patients under fasting conditions (at least 2 h). DNA was extracted from samples adding Bacteria Lysis Buffer (Roche) plus Proteinase K. The mixtures were incubated during 1 h at 65°C, followed by an in house extraction protocol based in DNA precipitation and isolation with cold etanol. Total bacterial load was quantified by Real-time PCR (qPCR) using primers targeting conserved bacterial 16S rDNA sequence in the LightCycler 2.0 instrument (Roche) by SYBR green detection.
Results
Diabetic patients had a significantly higher saliva and biofilm total bacterial load than non-diabetic subjects. No significant correlation was found between total bacterial load and glycated hemoglobin A1C.
Conclusion
This study suggests that type 1 diabetic patients have a higher saliva and biofilm total bacterial load than non-diabetic individuals, regardless of metabolic control. The knowledge of the diabetic oral microbiome may pave the way to the redefinition of clinical protocols and to the creation of new public health policies related to this population.
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GP80

Study of serum fetuin-A in male patients with type 1 diabetes mellitus: association with insulin resistance and possible role of metformin therapy

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Type 1 diabetes mellitus (DM) is a multi system disease with both biochemical and anatomic/structural consequences. A number of components of the metabolic syndrome may be observed in patients with type 1 diabetes. It was suggested that treating obese adolescents with insulin resistance using metformin is an option for patients without response to traditional lifestyle change. It was reported that fetuin-A could inhibit insulin receptor tyrosine kinase activity and induced a lower-grade inflammation which resulted in IR.
Objective
To Measure serum fetuin-A level in type 1 DM male patients with and without IR and to study the Effect of metformin therapy on fetuin-A level and parameters of metabolic syndrome in type 1 DM male patients.
Study design
The study was conducted on two phases: *first phase*: a comparative study between three groups: Group 1:20 male patients with type 1 DM without IR. Group 2:20 male patients with type 1 DM with IR and Group 3:20 age and sex matched apparently healthy controls. *second phase*: interventional study, includes measurement of serum fetuin-A and other parameters of metabolic syndrome on patients included in group 2 after metformin therapy for 3 months.

Results
Group 2 had a significant higher BMI, waist:hip ratio (W:H ratio), fasting blood glucose (FBG), 2 h post prandial blood glucose (2 h PP BG), HBA1C%, Triglycerides (TG) LDL cholesterol, hs-CRP, and serum fetuin-A ratio and a significant lower eGDR and C-peptide ($P<0.001$). Serum fetuin-A had a direct significant correlation with BMI, waist circumference, W:H ratio FBG, 2 h PP BG,HBA1C%, LDL, cholesterol, TG, and hs-CRP and an indirect significant correlation with C-Peptide and e GDR. Patients in group 2 had significant improvement in eGDR, 2 h PP BG, HbA1C%, hs-CRP, and serum fetuin-A after metformin. EGDR was significantly correlated with HBA1C% and W:H ratio ($P<0.001$).
Conclusion
Patients with type 1 DM may have IR in association with insulin deficiency, those patients have higher fetuin-A levels, use of metformin may play a role in improvement of insulin sensitivity and decreasing insulin requirements in type 1 DM.

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GP81

Predictive variables of GLP-1 levels in postpartum reassessment of women with previous history of gestational diabetes

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Objective
To study the GLP-1 pattern of secretion after an oral glucose tolerance test (OGTT) in women in postpartum reassessment of previous gestational diabetes (GDM). To evaluate clinical and laboratory parameters that can influence GLP-1 secretion.
Patients and methods
Forty-eight women with a history of GDM were assessed one year after childbirth determining clinical and analytical characteristics and OGTT with 75 g. We measured glucose, insulin and GLP-1 (baseline, 30′, 60′, 120′). Women were classified according to the results of OGTT as healthy and prediabetic/diabetic patients.
Results
Patients mean age of 35 ± 5 years, BMI 29 ± 6 kg/m^2, SBP 117 ± 12 mmHg, DBP 77 ± 9 mmHg. Laboratory parameters: glucose 99 ± 16 mg/dl, insulin 9 ± 5 microU/ml, cholesterol 167 ± 31 mg/dl, HDL-c 48 ± 12 mg/dl, LDL-c 100 ± 23 mg/dl, triglycerides 95 ± 48 mg/dl, HbA1c 5.5 ± 0.38%. In postpartum analysis, 23 had normal reassessment and 25 pathological OGTT. There were no significant differences in levels of GLP-1 in both groups. GLP-1 AUC/AUC insulin ($r=-0.28$, $P=0.05$) increase GLP; AUC correlations between GLP-1/age ($P=0.05$, $r=0.28$) were observed 1/AUC insulin ($r=-0.38$, $P=0.01$) and numerical correlation between increased GLP-1/c-HDL ($r=-0.26$; $P=0.07$) and increase GLP-1/BMI ($r=-0.23$; $P=0.12$). The linear regression model showed insulin AUC ($r^2=0.1$, $P=0.04$) as predictor of GLP-1 AUC, and BMI ($P=0,00$), triglycerides ($P=0.01$) and c-HDL ($P=0.01$) and AUC insulin ($P=0.02$) as predictors of increased GLP-1 ($r^2=0.5$).
Conclusions
Women with GDM history and prediabetes/diabetes diagnosis in postpartum reassessment do not differ in GLP-1 secretion after OGTT compared to healthy subjects. The parameters related to GLP-1 response in postpartum OGTT are BMI, triglycerides, HDL-C and insulin AUC.

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GP82

Resistin gene polymorphism in offspring of patients with type 2 diabetes mellitus

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Background
Resistin is a hormone that potentially links obesity to T2DM. Several single nucleotide polymorphisms (SNPs) have been identified in the resistin gene (RETN). Polymorphism of RETN +299 (G>A) may contribute to increased resistin levels, which may be involved in the pathogenesis of T2DM.
Aim of work
To study the association between resistin gene +299 polymorphism and insulin resistance in non-diabetic offspring of T2DM.
Methods
This case control study included 60 volunteers divided into two groups:
Group A: Control group including 30 healthy individuals with negative family history of DM.
Group B: Offspring of patients with T2DM including 30 non-diabetic individuals with positive family history of DM. The latter group was further classified after OGTT into:
Group B1: 15 individuals with normal glucose tolerance
Group B2: 15 individuals with impaired glucose tolerance. All individuals had an estimation of serum resistin level by ELISA and RETN+299 polymorphism by PCR-restriction fragment length polymorphism.
Results
We found a statistically significant increase of serum resistin (AA genotype and combined GA+AA genotypes), decrease in GG genotype, increase of A allele ($P<0.03$) and increase in the indices of insulin resistance in the impaired glucose tolerant offspring as compared to the control individuals as well as normal glucose tolerant offspring. There was also a statistically significant association between hyperglycemia and resistin gene polymorphism at positions +299 (G>A). Moreover, a significant positive correlation was found between serum resistin level and insulin resistance in impaired glucose tolerant offspring.
Conclusions
The present study supports that RETN+299 G>A SNP and increase in serum resistin may have contributed to increased insulin resistance with subsequent susceptibility to T2DM in offspring of type 2 diabetic patients. Those carrying AA and combined GA+AA genotypes are more at risk.
Keywords**:** Resistin gene polymorphism; Insulin resistance; Type 2 diabetes mellitus; SNP.

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GP83

Does IGF2BP2 gene polymorphism have an effect on the development of gestational diabetes mellitus?

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Objective
Gestational diabetes mellitus (GDM) is a multifactorial disorder with environmental factors and genetic modifiers. IGF2BP2 gene polymorphisms are shown to be involved in T2DM and diabetic nephropathy. Here, we aimed to document the association between IGF2BP2 gene polymorphism and GDM to understand the pathogenesis of GDM.
Design
Matched, case-control study.
Method
Ninety-three patients with GDM and 89 healthy pregnant subjects were involved. IGF2BP2 (rs1470579) polymorphisms were genotyped to examine the association between GDM and IGF2BP2 polymorphism.
Results
Although IGF2BP2 (rs1470579) polymorphism was more frequent in GDM group, this association was not statistically significant ($P=0.267$). We also examined the association between IGF2BP2 polymorphism and the clinical parameters. Subjects bearing the risk allelle '*c*' of IGF2BP2 gene had higher LDL levels when compared the genotype *aa* ($P=0.034$).
Conclusions
The contribution of the rare genetic variants such as IGF2BP2 (rs1470579) in the development of GDM differs across the ethnicites. Here in this study, IGF2BP2 (rs1470579) was not involved in GDM. The association between IGF2BP2 and LDL cholesterol levels may be attributable to the role of insulin-like growth factor system in lipid metabolism.

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GP84

Sitagliptin prevents kidney damage via modulation of NO and JAK/STAT pathways in streptozotocin-induced diabetes in rats

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Abstract withdrawn.

GP85

Impaired RBC deformability is associated with pancreatic beta cell dysfunction and diabetic retinopathy in patients with type 2 diabetes

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Red blood cell (RBC) deformability is an ability of RBC to change shape under stress, and it has been known to be decreased in diabetes. However, the role of RBC deformability is not determined in type 2 diabetes (T2D) yet. We attempted to clarify whether RBC deformability is related with diabetic complications. This was a cross-sectional study, and 452 T2D patients were enrolled. RBC deformability was measured by using a microfluidic ektacytometer, Rheoscan-D (Rheo-Meditech, Seoul, Korea), and expressed as elongation index at 3 Pa (EI@3P, %). 388 patients (mean age 60.37 ± 11.98 years, male 233) were finally included. When subjects were categorized into three groups by hemoglobin A1c (HbA1c; $<7\%$ vs $7 \leq < 9\%$ vs $\geqq 9\%$), mean EI@3P was significantly lower in the poorly controlled group (31.23 ± 1.60 vs 31.00 ± 1.82 vs 30.70 ± 1.64, $P<0.05$ by ANOVA). HOMA-B and insulinogenic index were positively correlated with EI@3Pa but not with HOMA-IR in multiple regression analysis. EI@3Pa was significantly lower only in patients with retinopathy than those without retinopathy (30.53 ± 1.95 vs 31.20 ± 1.53, $P=0.001$). Of quartiles from lowest EI@3Pa to highest (reference), the odds ratio for Q1 was 2.86 (95% CI 1.24, 6.62, $P=0.014$) after adjustment for age, gender, hypertension, smoking, duration of diabetes, GFR, and triglyceride. If EI@3Pa increase by 1%, the risk of diabetic retinopathy will decrease by 24.9%. These results suggest that impaired RBC deformability is related with decreased pancreatic beta cell function and the risk of diabetic retinopathy.

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GP86

Novel biomarkers of chronic kidney disease in diabetes

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Background and aims
Microalbuminuria (MA) is not specific predictor of early stages of chronic kidney disease (CKD) in diabetes. We investigate several markers that might be useful in assessing early kidney damage in T1DM and T2DM patients additional to MA.
Materials and methods
We examined 111 patients (T1DM/T2DM: 51/60) with AER <20 mg/l ($n=80$); <199 mg/l ($n=18$); $\geqq 200$ mg/l ($n=13$). Biomarkers of kidney damage (collagen IV), nephrin, podocin, cystatin C, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), uromodulin, tissue inhibitor of metalloproteinases-1 (TIMP-1) were measured by ELISA in the morning urine and fasting plasma; overnight AER by immunoturbidimetry assay; glomerular filtration rate (GFR) was estimated by standard MDRD formula. All measurements were done in a triplicate and blinded manner. Statistical analyses performed by STATISTICA 8.0, using a Mann–Whitney test, correlations were analyzed using Spearman correlation coefficients, differences were considered significant at $P<0.05$.
Results
In T1DM podocin increased prior to MA [0.17; 0.08; 0.084; $P<0.05$]; collagen's increase with CKD progression [3.86; 6.06; 8.663; $P<0.05$]. In plasma, we observed cystatin C increase [1060;1022; 2391; $P<0.05$]; significant increase of TIMP-1 observed at NA stage [2632; 2347; 2008; $P<0.05$]. Positive correlation was observed between the collagen with AER ($r=0.48$; $P=0.002$) and serum creatinine ($r=0.51$; $P=0.001$), KIM-1 with eGFR ($r=0.41$; $P=0.05$), NGAL with AER ($r=0.44$; $P=0.05$), uromodulin with eGFR ($r=0.49$; $P=0.05$). In T2DM, we observed significant distinctions in urine levels of podocin [0.192; 0.568; 0.084, p1-3, p2-3 <0.05]; nephrin increase NAvs.MA [0.661; 0.904, $P<0.05$], KIM-1 increase NAvs. MA [373.02; 434.47; 1109.08, $P<0.05$], NGAL increase NA vs MA [1.74; 2.185; 14.66, $P<0.05$]. Biomarkers also had positive correlation with standard markers: collagen with AER ($r=0.48$; $P=0.002$), cystatin C, podocin and uromodulin with eGFR ($r=0.48$, $P=0.002$; $r=0.39$, $P=0.015$; $r=0.49$, $P=0.0002$, respectively).
Conclusion
We suggest that urinary levels of podocin, collagen IV, nephrin might be candidates biomarkers for early detection of CKD in diabetes.

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GP87

Comparison of aqueous concentrations of angiogenic and inflammatory cytokines based on optical coherence tomography patterns of diabetic macular edema

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Introduction
The purpose was to compare aqueous inflammatory and angiogenic cytokine levels in diabetic macular edema (DME).
Methods
Aqueous samples were obtained from 50 eyes with DME and 12 normal eyes (control group). DME was classified according to the morphologic pattern based on optical coherence tomography: Diffuse retinal thickening (DRT; $n=19$), cystoid macular edema (CME; $n=17$), or serous retinal detachment (SRD; $n=14$). Aqueous samples were collected just before intravitreal injection and at the beginning of cataract surgery in the control group. Interleukin (IL)-6, IL-8, interferon-induced protein (IP)-10, monocyte chemotactic protein (MCP)-1, platelet-derived growth factor (PDGF)-AA, and vascular endothelial growth factor (VEGF) levels were measured by multiplex bead assay.
Results
The IL-6, IL-8, IP-10, and PDGF-AA levels differed significantly among the three groups of DME ($P=0.014$, $P=0.038$, $P=0.021$, and $P=0.041$, respectively). However, there were no differences between groups in aqueous concentration levels of MCP-1 and VEGF ($P=0.205$ and $P=0.062$, respectively). IL-6 ($P=0.026$) and IL-8 ($P=0.023$) correlated positively with central foveal thickness (CFT) in the CME group. None of the cytokine levels correlated significantly with CFT in any of the DRT and SRD groups.
Conclusions
Aqueous concentrations of cytokines varied according to the morphologic pattern of DME, which might explain the variable response to treatments such as intravitreal bevacizumab or triamcinolone injection.

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GP88

Effects of metabolic control on bone mineral density and markers of bone remodeling in adult patients with type 1 diabetes mellitus

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Introduction
Type 1 diabetes mellitus (T1DM) is associated with reduced bone mineral density (BMD) and increased bone turnover. However, data regarding the influence of glycemic control on bone are limited. The aim of this study was to evaluate BMD and bone remodeling markers in patients with T1DM in relation to changes in glycemic control.
Methods/design
We studied 107 patients with T1DM (Group-D) (mean age: $34+8.1$ years, M/F: 48/59) and 95 healthy controls (Group-C) matched for age, sex and BMI. Patients in Group-D were re-examined after one-year (FU). In both groups, we measured

glycated hemoglobin (HbA1c), BMD at lumbar spine (LS) and femoral neck (FN) by dual energy X-ray absorptiometry. Bone resorption was assessed by β-crosslaps and bone formation was assessed by serum levels of type 1 procollagen total N-terminal propeptide (TP1NP). Currently, fifty patients from Group-D completed the FU and repeated the measurements as baseline. Based on the current literature, BMD changes at LS more than 3% and at FN more than 6% are considered to be significant.

Results

In Group-D, mean duration of diabetes was 15.1 + 7.4 years and mean HbA1c was 8.2 + 1.3%. In Group-D, BMD (g/cm^2) and *T*-score were lower at LS and FN compared to Group-C (LS: 1.024 ± 0.201 vs 1.052 ± 0.143. $P = 0.04$, −0.3 ± 1.6 vs 0.9 ± 1.7, $P = 0.02$) (FN: 0.696 ± 0.121 vs 0.898 ± 0.112, $P = 0.042$, −0.1 + 1.5 vs 1.4 ± 1.0, $P = 0.038$). No significant difference in β-crosslaps and TP1NP was observed between the two groups. At FU in Group-D, 36/50 patients had > 0.5% reduction in HbA1c (Group-DR), 8/50 had about the same HbA1c (+0.4%) (Group-DS) and 6/50 had > 0.5% increase in HbA1c (Group-DI). At FU, Group-DR had 3.3% increase in BMD at LS and 5.6% at FN and TP1NP was significantly higher compared to baseline ($P = 0.043$).

Conclusion

T1DM is associated with reduced BMD but improvement of glycemic control appears to ameliorate BMD and bone turnover.

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GP89

Low serum high-density lipoprotein level is associated with proliferative retinopathy in patients with diabetes mellitus

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Introduction

Diabetes mellitus (DM) is a common chronic metabolic disease associated with serious complications. Diabetic retinopathy (DR) is one of the most common microvascular complications of DM. The aim of this study was to investigate the association between DR and dyslipidemia

Methods

A total of 1363 subjects were included in this retrospective study. The participants were divided into three groups, including a study group of 352 patients with diabetes and retinopathy, a control group of 553 patients with diabetes without retinopathy and a control group of 457 healthy subjects. The study group included 202 and 150 patients with non-proliferative (NPDR) and proliferative DR (PDR), respectively. Groups were compared according to the demographic properties, HDL, triglyceride, LDL, HbA1c and serum fasting glucose levels. MedCalc 15.8 (MedCalc Belgium) was used for the statistical analysis.

Results

Groups were comparable in terms of age and sex ($P > 0.05$ for each one). Not surprisingly, serum fasting glucose and HbA1c levels were high in patients with diabetes ($P < 0.05$, respectively). Serum HDL levels of the patients with DR were lower than those in diabetic patients without retinopathy ($P < 0.001$). Patients with PDR had lower HDL levels than patients with NPDR ($P = 0.011$). There was an association between low HDL levels and PDR (OR:2.1 Cl %95 1.4–3.1 $P = 0.003$).

Conclusion

In this study, we have found low serum levels of HDL in patients with PDR. Low serum HDL level is associated with atherosclerosis and other vascular problems. Diabetic patients with low serum HDL level may be more predisposed for retinopathy. Diabetic patients should be evaluated for dyslipidemia to delay the development of vascular complications.

Keywords: HDL, retinopathy, diabetes mellitus

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GP90

Assessment of metabolic markers (myostatin, IGF-1), associated with the state of the lean component in young adults with type 1 diabetes

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Background and aims

There is compelling evidence that the decline in appendicular muscle mass is a poor prognostic factor for the development of chronic complications of diabetes. In addition to chronic hyperglycemia, reduction of muscle component may be determined by metabolic disorders. Therefore, the aim of study was to assess the possible links between serum myostatin, IGF-1 and a reduction in muscle mass in type 1 diabetes mellitus (T1DM).

Materials and methods

Ninety-five patients with T1DM (60 women, 35 males) (mean age: 30.6 (24.9–37.5) years, duration of DM: 13 (7–20) years, age of manifestation: 17 (12–23) years, HbA1c: 8.2 (7.6–8.9%) and 55 (31 women, 24 men) controls. The research involved anthropometry of patients, general clinic examination, serum myostatin and IGF-1, dual energy X-ray absorptiometry using a program 'Body composition'.

Results

There was a reduction of lean component of the arms ($U = 248$; $P = 0.017$), legs ($U = 208$; $P = 0.002$), total appendicular ($U = 219$; $P = 0.004$) and total lean ($U = 259$; $P = 0.027$) component in men with T1DM. Differences of lean mass at women with T1DM were in the increase of lean component of arms ($U = 6774$, $P = 0.044$) and lean android ($U = 604$, $P = 0.008$). There were revealed comparable levels of serum myostatin (589 (457.26–826) and 675.38 (491.94–750.34), $U = 838$; $P = 0.98$) and IGF-1 (136.89 (101.13–177.97) vs 129.45 (107.93–222.46), $U = 695.5$; $P = 0.285$) in patients with T1DM and controls. Taking into account gender differences the content of lean component, men compared to women with T1DM showed significant high levels of myostatin (792.64 (557.03–972.83 529.23) vs (443.55–625.86) pg/ml, $U = 232.5$; $P = 0.006$) and lower content of IGF-1 (146.77 (121.2–231.36) vs 106.15 (96.28–138.67) ng/ml, $U = 227.5$; $P = 0.004$).

Conclusions

Elevated levels of myostatin in men with diabetes can cause more expressed loss of muscle mass. Higher content IGF-1 explains the increase in the lean component of the abdomen in women.

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GP91

Relationship between urinary metabolites and type 2 diabetes mellitus by proton nuclear magnetic resonance spectroscopy method (^{1}H-NMR)

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Proton nuclear magnetic resonance spectroscopy (^{1}H-NMR) was applied to investigate metabolic profile of type 2 diabetes mellitus (T2DM) patients and identify possible disorders of T2DM.

We investigate the potential relationship between diabetic retinopathy (DR), diabetic neuropathy (DN), estimated glomerular filtration rate (eGFR), anthropometric indicators (body mass index (BMI), waist circumference (WC), waist to hip ratio (WHR), waist to stature ratio (WSR)), HbA1c (%) levels and urinary metabolites in T2DM patients.

Serial urine samples of 334 healthy subjects and 388 T2DM patients with a history of diabetes <5 years were investigated by ^{1}H-NMR. The ^{1}H-NMR spectra have been recorded on a Bruker Avance DRX 400 MHz spectrometer. The results are evaluated in mmol/mol of creatinine.

A significant difference between the urinary excretion of valine ($P = 0.007$), alanine ($P < 0.0001$), γ-aminobuthyrate ($P = 0.001$), betaine ($P = 0.036$), citric acid ($P < 0.0001$), trimethylamine-N-oxide ($P < 0.0001$) and glycine ($P < 0.0001$) at the healthy individuals and T2DM patients was found. The values for 3-hydroxyisolateric acid ($P = 0.042$), citrate ($P = 0.019$) and γ-aminobuthyrate ($P = 0.037$) increase in T2DM patients with retinopathy vs without retinopathy. There was no correlation between DN and urinary metabolite picture in T2DM patients. We found significant correlation between eGFR and dimethylamine ($r = 0.194$, $P = 0.031$), gamma-aminobuthyrate ($r = 0.239$, $P = 0.049$), acetate ($r = 0.29$, $P = 0.035$) and pyruvate ($r = 0.275$, $P = 0.014$) in T2DM patients. Our analysis revealed significant decreased concentrations for citrate ($P = 0.005$), dimethylamine ($P = 0.013$) and glycine ($P = 0.009$) in T2DM patients with the increase of BMI. WC were positively correlated with gamma-aminobuthyrate

($r=0.42$, $P=0.01$) and dimethylamine ($r=0.39$, $P=0.03$) and, no correlation were observed between WHR, WSR and urinary metabolites in T2DM patients. Alanine ($P=0.003$), lactate ($P=0.015$) and 3-hydroxyisovaleric acid ($P=0.006$) increased with the increase of HbA1c levels.
Type 2 DM urinary metabolites are interesting in various aspects, such as providing clues for the mechanisms of the disease or potential early markers in diabetes.

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GP92

The effect of glucose variability on microvascular complications in type 1 diabetes

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Introduction
Evidence implicates oxidative stress as mediator of diabetic complications. Furthermore, glucose variability (GV) is associated with oxidative stress and inflammation; however, association between GV and diabetes complications remains to be established. Our aim was to assess GV in patients with and without microvascular complications (MVC).
Methods
We analysed 2454 and 6593 h of continuous glucose monitoring of patients with type 1 diabetes (T1D) and labile glucose control with or without MVC, respectively. Patients were matched for A1C. All data points were collected on iPro2™.
Most patients were females ($n=36$, 59%) and A1C was similar on both groups (7.7 ± 0.9 vs 8.0 ± 1.2%, $P=0.372$). Patients with MVC were older (36.9 ± 4.8 vs 27.1 ± 9.0 years, $P<0.001$) and had longer duration of T1D (22.7 ± 6.1 vs 15.4 ± 9.8 years, $P=0.011$) than patients without MVC. GV measured by standard deviation (3.5 ± 0.8 vs 3.5 ± 1.1, $P=0.937$), mean amplitude of glycaemic excursions (6.5 ± 1.2 vs 6.8 ± 2.5, $P=0.716$), mean of daily differences (3.8 ± 0.9 vs 3.9 ± 1.3, $P=0.796$) was similar between the patients with or without MVC, respectively. Interestingly, patients with neuropathy had higher GV measured by lability index (15.1 ± 7.6 vs 6.1 ± 3.6, $P=0.02$) and mean absolute glucose (3.4 ± 0.9 vs 2.3 ± 0.7, $P=0.033$) but they were significantly older (39.0 vs 29.3 years), had longer disease duration (27.0 vs 16.9 years) and poorer glycaemic control (A1C, 9.1 vs 7.9%) than patients without neuropathy.
Conclusion
GV was not consistently associated with higher burden of MVC. Though, prospectively designed studies targeting GV are needed to definitively clarify the importance of GV.

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GP93

High dose vitamin D treatment regulates the gene expression pattern in T helper cells of type 1 diabetes patients

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Dysregulated T helper cells and vitamin D (VD) deficiency are important factors in the pathogenesis of Type 1 diabetes mellitus (T1D). Therefore, we investigated the immune effects of high dose VD-treatment on gene expression (GE) pattern in T helper cells (Th) before and after VD-therapy in patients with T1D.
Methods
Seven T1D patients with $25(OH)D_3$ levels below 20 ng/ml received 3 months 4000 IU/d Vigantol oil. The $25(OH)D_3$ plasma concentration (using radio-immunoassay) and GE within Th cells (using GeneChip) were measured at baseline (V1) after 3 months treatment (V3). VD-therapy effects on the GE were evaluated using the differences between V1 and V3 (expressed in fold changes = FC) by the statistical computing environment R version 3.0.2.
Results
The $25(OH)D_3$ concentration increased in median from 14 to 38 ng/ml ($P=0.02$) after high dose VD. Furthermore, 48 annotated genes changed significantly in Th cells of patients with T1D after VD supplementation. Important to note, unique four genes that code for dual specificity phosphatase 2 (=*DUSP2*/FC:1.4; $P=0.05$), HAUS augmin-like complex, subunit 2 (=*HAUS2*/FC:1.3; $P=0.01$), jun B proto-oncogene (=*JUNB*/FC:1.6; $P=0.04$) and mannose-P-dolichol utilization defect 1 (=MPDU1/FC:1.4; $P=0.02$) showed a higher expression after VD treatment, in T1D patients. In contrast, 44 genes were down regulated: exemplarily, genes which code for interferon receptor 1 (=*IFNAR1*/FC: -1.3; $P=0.02$), nuclear distribution protein (=*NUDC* FC: -1.3; $P=0.04$) and zinc finger protein 830 (=*ZNF830* FC: -1.4; $P=0.02$).
Conclusion
The elevation of $25(OH)D_3$ induced by Vigantol therapy (4000 IU/day) leads to differential GE pattern in Th cells from T1D patients (four genes upregulated/44 genes down regulated). The Th cell response to vitamin D results in an upregulated gene set (DUSP2, *HAUS2*, *JUNB*, *MPDU1*) and a downregulated gene set (*IFNAR1*, *NUDC*, *ZNF830*). Our data suggest an indirect VD effect on both gene sets via activation of transcription factors such as activator protein 1 (AP-1) and signal transducer and activator and transcription family members (Stat1 and Stat3), respectively.

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GP94

Calculated creatinine clearance using the CKD-EPI-formula shows a reliable prediction and high correlation to 24-h-urine in patients with diabetes mellitus but underrates systematically potentially leading to withdrawal or no prescription of oral antidiabetics

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Introduction
To reliably assess glomerular filtration is of vital importance if oral antidiabetics are used. We compared the CKD-EPI model, a clinically established calculation model to assess creatinine clearance (CreaClear) with specimens from 24-h urine.
Method
Inpatients (university hospital) with diabetes mellitus received a 24-h urine collection (24hClear) or since 2013 calculated CreaClear using CKD-EPI-formula (EPI). From 2014 to 2015 values of 615 simultaneously. Implausible 24-h-specimens (Creatinine excretion <8 or >22 mmol/24h) were excluded (n = 268). Correlation (Cor) was calculated and mean values (MV) compared.
Results
Three hundred and forty-one persons were analyzed ($n=120$ diabetes type1 (DM1), $n=285$ type 2 (DM2), $n=12$ pancreas diabetes (DMpankr). Seventy-four (18%) had a 24hClear in the range from 40 to 60 ml/min (DM1 16%, DM2 81%, DMpankr 3%). Mean values and correlations were (EPI vs 24hClear ml/min, Cor (significance level), significance level *T*-test): whole group: 62.8 vs 75.1, Cor 0.88 ($P<0.001$), MV $P<0.001$; DM1: 82.1 vs 94.7 Cor 0.83 ($P<0.001$), MV $P<0.001$; DM2: 54.1 vs 66.0, Cor 0.87 ($P<0.001$), MV $P<0.001$; DMpankr 75.8 vs 97.1, Cor 0.85 ($P<0.001$), MV $P<0.001$. In 20% EPI was higher than 24hClear (DM1 27%; DM2 18%; DMpankr 0%). In regression analysis 24-h creatinine excretion is negatively associated with an overestimation of EPI ($P<0,001$).
Conclusions
Calculated values of creatinine clearance by the CKD-EPI-formula compared to values from 24-h urine collection from routine data were highly correlated. CKD-EPI produced lower values in 80% of the cases underrating in the range from 11(DM2) to 21(DMpancr) ml/min. This may lead to withdrawal or no prescription of oral antidiabetics, on the other hand preventing drug induced complications. The large difference of both methods in pancreas diabetes is caused by reduced muscle mass.

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GP95

Association between coping styles of adolescents with type 1 diabetes and metabolic control

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Introduction
Across different chronic diseases, it has been shown that problem focused coping is associated with better adjustment. The aim of the study was to evaluate the various coping behaviors of children and adolescents with type 1 diabetes (T1DM) and their association with metabolic control and duration of disease.
Methods
The study population consisted of 65 children and adolescents with T1DM (male/female: 22/43) with a mean (±s.d.) age of 12.6 (±5.2) years, disease duration of 4.8 (±4.4) years and HbA1c of 8.1 (±1.6)%, who attended the diabetic clinic of the University Department of a Tertiary Children's Hospital. The "Ways of Coping Questionnaire" (Lazarus and Folkman), adapted and standardized in Greek population, was completed by all adolescents, 36 fathers (67.9%) and 17 mothers (32.1%). Coping was categorized as: (i) active coping, (ii) seeking social support, (iii) wishful thinking, (iv) problem avoidance, (v) aggressive coping.
Results
There was a significant association between fathers' and adolescents' coping styles in respect of "active coping" ($r=0.41$, $P=0.016$) and "seeking social support" ($r=0.38$, $P=0.023$). Female adolescents used more the "seeking social support" way compared to males (1.92 ± 0.73 vs 1.39 ± 0.99, $P=0.041$). Duration of disease was positively associated with the "active coping" style ($r=0.36$, $P=0.014$). Regression analysis for metabolic control showed that greater use of "aggressive coping" ($P=0.014$) and lower use of "active coping" ($P=0.035$) were related to a significant increase in HbA1c, which means that more constructive behavior has a positive impact on metabolic control.
Conclusion
Active coping was associated with better metabolic control and longer diabetes duration in adolescents with T1DM. Female adolescents with T1DM used more the "seeking social support" strategy compared to males, which is also reported in healthy adolescents. Assessment of coping behavior might be useful in the identification of adolescents in need of particular support and counseling.

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GP96

How soon do we achieve glycemic control after bariatric surgery? A comparative study among laparoscopic sleeve gastrectomy, mini gastric bypass, and diverted sleeve gastrectomy with ileal transposition

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Background
Type 2 diabetes mellitus became a global problem during recent decades, and unfortunately medical treatment fails to provide adequate control in many obese diabetics. We aimed to perform a prospective comparative cohort study to investigate how soon patients achieve glycemic control after three different surgical options (sleeve gastrectomy (SG), mini-gastric bypass (MGB), diverted sleeve gastrectomy with ileal transposition (DSIT)) within the first 30 days postoperatively.
Methods
Medical charts of 251 obese, type 2 diabetic patients with a mean age of 52.84 ± 8.52 were used to assess daily changes in weight and plasma glucose levels. Patients had a mean diabetic duration of 13.09 ± 7.54 years, mean HbA1c of 8.82 ± 1.58%, and a mean BMI of 36.04 ± 5.76 kg/m^2.Surgery types consisted of SG (n=49), MGB (n=93) and DSIT (n=109). Primary end point was the day of mean fasting plasma glucose levels reaching below 126 mg/dl within 30 days after surgery.
Results
In the morning of surgery, mean fasting plasma glucose levels was 177.63 ± 51.3 mg/dl, while on the 30th day, it was 131.35 ± 28.7 mg/dl ($P<0.05$). According to the type of surgery, SG group did not achieve a mean plasma glucose level <126 mg/dl within the first 30 days, postoperatively. Mean plasma glucose level reaching <126 mg/dl was achieved on day 29 for DSIT (124.36 ± 20.21 mg/dl) and on day 30 for MGB (123.61 ± 22.51 mg/dl).
Conclusion
We observed differences in glycemic control following different types of surgery within the first 30 postoperative days. Patients in the SG group did not achieve a mean plasma glucose level <126 mg/dl. Mean fasting plasma glucose levels <126 mg/dl were achieved on day 29 for DSIT and on day 30 for the MGB. Multivariate logistic regression analysis identified preoperative BMI and postprandial C-peptide level as independent predictors of postoperative glycemic control in the DSIT group.

Keywords: Bariatric surgery; glycemic control; sleeve gastrectomy; mini-gastric bypass; diverted sleeve gastrectomy with ileal transposition.
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GP97

Real-world comparative effectiveness of liraglutide, exenatide once weekly and lisixenatide in patients with type 2 diabetes mellitus

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The improvement of glycemic control and body weight reduction by GLP-1 receptor agonist (GLP1RA) has been demostred in randomized clinical trials, but comparative studies of the efficacy of different GLP1RA in real world and clinical practice setting are limited.
Objectives
To compare the efficacy of liraglutide (LIRA), exenatide once weekly (EQW), and lisixenatide (LIXI) treatment in a real-world and clinical practice setting.
Methods
Prospective, longitudinal, multicenter, and not randomized study that compares HbA1c and body weight reduction in 135 patients with type 2 DM treated for six months with LIRA, EQW or LIXI. Data for continous variables are presented as mean (SD) and for categorical variables as percentajes.
Results
52.6% men, age 53.9 (9.7) years, 6.7% <1 years of evolution, 23.7% 1–5, 25.8% 5–10 and 41.5% >10, mean baseline weight 102.5 (18.6) kg, BMI 37.7 (5.9) kg/m^2, HbA1c 8.4% (1.4). 83 (61.4%) patients were treated with LIRA, 30 (22.2%) with EQW and 22 (16%) with LIXI. There were no differences between the three groups regarding the baseline parametres. After 6 months we observed change of Hba1c -1.09% (1.18) $P<0.001$ (-1.2%(1.4) LIRA, -1.1% (1.2) EQW, $P<0.001$ for both and -0.8%(1.8) ns LIXI). Weight -3.6 kg (4.1) (-3.9 kg (5.5) LIRA, -3.6 kg (4.1) EQW $P<0.001$ for both, -2.8 kg (3.6) LIXI ns). Composite end points was analized, 47.4% achieved HbA1c<7% (59.2% LIRA, 46.4% EQW, 35.3% LIXI), 45.2% weight reduction >3% (52.7% LIRA, 55.6% EQW, 41.2% LIXI), 25.9% both parameters (31.1% LIRA, 37.5% EQW 11.8% LIXI). No differences was observed between groups.6 (4.4%) patients were lost from follow up (four LIRA, two EQW) and 26 (19.3%) discontinued the treatment (14 (16.8%) LIRA, 1 (3%) EQW and 11 (50%) LIXI).
Conclusions
In a real-world setting, HbA1c improved similarly in patients initiating EQW or LIRA, and minor efficacy was observed in LIXI group. Weight reducction was similar in all groups of treatment. The biggest proportion of treatment discontinuation was observerd among members of the LIXI group.

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GP98

Efficacy and safety of SGLT2 inhibitor Canagliflozin in the treatment of type 2 diabetes mellitus in clinical practice

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In clinical trials, the SGLT2 inhibitor Canagliflozin inhibits renal reabsorption of glucose, increases its excretion and reduces hyperglycaemia in patients with type 2 diabetes mellitus (T2DM). The increase in glucosuria and diuresis produced, results in a reduction in weight and blood pressure (BP). Moreover, It may cause genital and urinary tract infections. However, does Canagliflozin behave in the same way in routine clinical practice?

Objective

To make a short-term assessment in routine clinical practice of the efficacy and safety of Canagliflozin in patients with T2DM.

Material and methods

Thirty-three T2DM patients of 60.4 ± 10.9 years of age and 13.6 ± 7.3 years of evolution (12 women, 21 men), with BMI > 30 kg/m^2, HbA1C $> 7\%$ and glomerular filtration > 60 ml/min, had Canagliflozin 100 mg/day added to their treatment in monotherapy ($n=2$), double therapy ($n=6$), triple therapy ($n=7$), oral antidiabetic drugs (OADS) + basal Insulin ($n=5$), OADS + basal bolus ($n=10$); OADS + rapid insulin ($n=1$) and basal bolus ($n=2$). They were weighed and HbA1C, fasting glucose (FG), systolic BP (SBP) and diastolic BP (DBP) were measured, before and 3 months after adding Canagliflozin. A $P < 0.05$ was considered significant (SPSS, v. 20.0).

Results

At 3 months, a reduction in weight ($P < 0.001$), HbA1C ($P = 0.000$), FG ($P = 0.000$) and SBP ($P < 0.01$) was observed. Average reduction in weight was 3.45 ± 2.9 kg, $1.13 \pm 0.83\%$ in HbA1C, and 7.7 ± 8.6 mmHg in SBP; 69.2% achieved HbA1C $< 7\%$ with a reduction in weight and SBP. Only two genital (6%) and one urinary tract (3%) infections were observed.

Conclusion

In clinical practice and in the short-term, Canagliflozin added to the treatment of poorly controlled and obese T2DM patients, at any therapeutic level, was translated into a reduction in weight, HbA1C and SBP in more than 2/3 parts, with few adverse effects. Long-term studies with more number of patients should be conducted to find out whether the results are maintained.

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GP99

Liraglutide increases surfactant proteins (SPA & SPB) and angiotensin-converting enzymes (ACE & ACE2) expression in a rat model of acute lung injury by bleomycin

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Acute lung injury (ALI) is characterized by endothelial and epithelial damage, followed by inflammatory. Glucagon-like peptide-1 (GLP-1) is a gut-produced hormone with insulinotropic effects. GLP-1 receptor is expressed in the lung, and there implicated in the synthesis of surfactant proteins. We have previously shown that liraglutide (LIR), a GLP-1 receptor agonist, restores surfactant protein-B (SPB) levels, a limiting factor for survival, and also angiotensin converting enzymes (ACE and ACE-2), in a type-1 diabetes animal model. The aim of this work was to elucidate the effect of LIR in the production of surfactant proteins and ACEs in an animal model of ALI.

ALI was induced by a single intra-tracheal instillation of bleomycin (BLM, 2.5 mg/kg) on day 0 into rats. Rats were treated with liraglutide (100 μg/kg per 12 h sc.) or vehicle (0.9% saline) from day -1 to day 6, and sacrificed in day 7. Left lungs were extracted & weighted, and caudal lobes used for mRNA extraction.

BLM instillation increases left lung weight, revealing an inflammatory response with interstitial oedema. LIR treatment did not revert lung weight increase, since not attenuating inflammatory process. In agreement, BLM instillation decreases mRNA expression of surfactant proteins A and B (79%, $P = 0.021$ and 72%, $P = 0.002$ vs control group, respectively), which was prevented by the administration of LIR. ACE and ACE-2 expression levels were also markedly reduced after BLM instillation (68%, $P < 0.01$ and 70%, $P < 0.001$ vs control, respectively). Again, LIR administration restored the levels of both enzymes.

In conclusion, LIR restores surfactant proteins and angiotensin converting enzymes expression in the lung, in a rat model of ALI. This implicates that LIR could improve pulmonary functionality in ALI, regardless of the inflammatory response.

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Endocrine Nursing

GP100

The risk of obstructive sleep apnea and correlation with cardiovascular risk factors in patients with pituitary adenomas

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Introduction

Sleep disorders (SD) confer high cardiovascular risk (related to 52–70% of acute myocardial infarctions and strokes). Hypertension (HTN), diabetes (DM), weight gain, sleepiness, fatigue and depression have been correlated with obstructive sleep apnea (OSA). Patients with pituitary adenomas (PA) present with reported sleep dysfunction, fatigue and metabolic risk factors that may persist despite treatment

Aim

Assess the correlation between sleep disturbance (SD), depression, BMI, HTN, diabetes Mellitus (DM), pituitary deficiencies (PD), tumor size, diagnosis and risk of OSA for patients with PA.

Methods

A single institution, prospective assessment of patients presenting with PA using modified: Piper Fatigue Scale (PFS), Epworth Sleepiness scale (ESS), Beck Depression Inventory (BDI); Baseline BMI, tumor size (by MRI), HTN and DM assessed. The STOPBang Inventory was applied to stratify OSA risk. Diagnoses confirmed by biochemistry and/or histopathology. Statistical Analysis with PASW18.

Results

One hundred and fifty-seven patients (106F/51M; macroadenoma 74/micro 83) enrolled. Mean age 45 years, BMI 30.1 kg/m^2 (17.5% > 35); DM 20% (18F/12M); HTN 44% (40F/29M) 43.9% (40F/29M); Acromegaly 10% (16), Cushing's Disease (CD) 10%(16), NFA 40%(63), PRL 25%(39), RC 7%, other 7. Clinical Depression found in 36% of patients (mood disturbance 56%), SD 64% (ESS > 10, PFS > 2), and Pit Def > 1–40%. Higher SD, BMI and depression were correlated ($P = 0.001$) also BMI, DM and HTN ($P = 0.001$). SD, HTN, DM, PD, tumor size, were not correlated. Patients with CD had more SD ($P = 0.01$), depression ($P = 0.007$), DM ($P = 0.001$) and HTN ($P = 0.03$). Risk of OSA in PA was 57% (90/157, high risk in 17%) with highest risk in presence of DM + HTN.

Conclusion

Sleep disturbance in patients with PA is correlated with depression, BMI $>$ 30 kg/m^2 and associated with a moderate to high risk of OSA, particularly in the presence of diabetes plus hypertension. Evaluation of SD at baseline is warranted along with further research into sleep dysfunction post treatment, particularly related to metabolic indices.

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GP101

Waist to height ratio as a new marker of metabolic syndrome in type 2 diabetic patients

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Introduction

Metabolic syndrome is closely related to abdominal obesity. Classic anthropometric indices such as bmi and waist circumference have been used for the screening of metabolic syndrome.

Recently, it has been reported that waist to height ratio is more closely associated with insulin resistance.

The aim of the present study was to assess the relationship between waist to height ratio and components of metabolic syndrome among type 2 diabetic patients.

Methods

We conducted a cross sectional analysis in 121 type 2 diabetic patients (56 women and 65 men). We measured anthropometric parameters (body weight, height, waist circumference) of each patient. BMI was calculated as the body weight divided by the height squared. Waist to height ratio was calculated as the waist circumference divided by height.

Fasting blood specimens were collected to measure fasting glucose, HbA1c, total cholesterol and triglycerides.

Results

The mean age of the study participants was 57.76 ± 15.24 years. Waist to height ratio was 0.64 ± 0.08 in women and 0.55 ± 0.07 in men ($P < 0{,}001$). Statistic analysis showed significant positive correlations between waist to height ratio and respectively BMI ($r = 0.79$, $P < 0.001$), waist circumference ($r = 0.9$, $P < 0.001$), systolic blood pressure ($r = 0.28$, $P = 0.002$), diastolic blood pressure ($r = 0.218$,

$P=0.01$), total cholesterol ($r=0.3$, $P=0.001$) and triglycerides ($r=0.314$, $P<0.001$). However, There were virtually no correlations between waist to height ratio and fasting glucose ($r=-0.018$, $P=0.8$) nor with HbA1c ($r=-0.13$, $P=0.11$).
Conclusion
Based on the present findings, waist to height ratio may be useful to predict the presence of metabolic syndrome in type 2 diabetic patients.

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GP102

Influence of educational training course in improving the knowledge of diabetes mellitus among nurses of Diabetes Education Units in Albania

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Background
The involvement of nurses in diabetes patient education has an important contribution in the improvement in the quality of care provided. Experience and knowledge in diabetes and its management are crucial for teaching patients with diabetes effectively.
Material and methods
The aim of the study is to evaluate the effect of nurse Training Course in the improvement of the knowledge of diabetes among nurses. Ten Diabetes Education Unit's nurses, one per each Albania's regional hospital, aged from 25 to 55 years old, underwent the Training. To evaluate the diabetes knowledge a multiple-choice questionnaire was assessed, before the training (T1), immediately after (T2) and 6 months after the training (T3).
Results
The nurses, eight women and two men aged 35.5 $\pm$2.96 years old (median $\pm$ S.E.M), having 9$\pm$3.2 years of working experience from which 5.5$\pm$3.4 years were in endocrinology. The mean knowledge score before the training was 45$\pm$ 2.9 out of 100. It improved to 68.5$\pm$1.4 immediately after and to 66$\pm$1.4 points 6 months after the training. There was a statistically significant difference between T1 and T2 results $P=0.005$, between T1 and T3 $P=0.008$, and between T2 and T3 $P=0.025$. A significant correlation was observed between the T1 score and the working years ($r=6.667$, $P=0.05$) and T1 score and the years working in endocrinology ($r=0.729$, $P=0.026$).
Conclusion
We observed an improvement of the diabetes knowledge among the nurses participating the training course and a slight knowledge decrease 6 months after the course. Only the first test result was influenced by the number of years working in endocrinology. These preliminary results suggest the importance of continuous education in improving diabetes knowledge and giving a better diabetes care.

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GP103

Type 1 diabetes and attention deficit hyperactivity disorder: development of new educational material

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Background
Patients with type 1 diabetes and attention deficit hyperactivity disorder (ADHD) are more often absent from clinic visits than patients with diabetes type 1 without. If they come, they are often delayed, plasma glucose self-monitoring meters are not brought with, blood specimen collections are not done and difficulties in self-care are noticed. To achieve a stable blood glucose control, meals with a calculated amount of carbohydrates matched with a specific dose of insulin, in consideration of physical activity is desirable. Decreased ability of planning, perception of time, impulse control, setting goals and ability of organizing actions over long time, affects daily life in various levels and are the core symptom of ADHD.
Aims/method
First develop education materials for patients with ADHD aiming to improve the understanding and knowledge of personal diabetes care. Second to develop information material of ADHD and diabetes to all staff at the diabetes clinic. All material have been reviewed by a neuropsychologist.
Results
Education material with pictures for patients has been produced. An information booklet for staff about ADHD has been written, the importance of having a distinct structure of clinic visits has been highlighted. To meet the same health caregiver at every visit including limited amount of information are also key factors. Moreover, memory pens for insulin, SMS-reminders for insulin injections and visits at clinic, continuous glucose monitoring (i.e. FreeStyle Libre) and connecting the patient's own meter to a computer-assisted program for storing of glucose values (i.e. Diasend) are other important tools.
Conclusion
Patient information based on pictures and less written text is easier to process for people with ADHD. Continuity, in terms of contact with the same health professionals is desirable. We have just started to implement our new material and so far we have got positive feedback from our patients.

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GP104

Diabetic foot workshop to apply interactive learning method for nurses: working with real patient as a teaching strategy

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Background
One of important issues which should be taught by the multidisciplinary health care team in diabetes is related to the diabetic foot prevention and care. In this regard, nurses as one of team members are able to provide specific services to the patient including patient education and DF care. The aim of this study was to explore impact of work with "real patient" as a teaching strategy for nurses in the workshop.
Methods
Two days diabetic foot workshops are established for nurses by Endocrinology and Metabolism Research Institute focused on the nurses role in prevention and care of diabetic foot. This workshop was held four times in 2015 and120 nurse were participated totally. In fact, the main teaching method of DF workshop was doing education and dressing with "real patient" and other teaching methods consists of case study, role modelling and team work activity related to the diabetic foot prevention, education, management and rehabilitation. Pretest-posttest is selected as a method to compare and measure the participants' degree of changes. Data analyse was performed through using descriptive statistics and paired *t*-test by SPSS version 16.0.
Result:
Result showed that 89% of nurses were women and 85% had BS degree. There is strong evidence ($t=-2.345$, $P=0.021$) that working with real patient with diabetes as a teaching intervention improves marks of nurses. In this data set, it improved marks, on average, by $\sim$1.9 points. This result is at the 95% CI.
Conclusion
The interactive method of teaching with real patient who affected by diabetic foot in DF workshop improve nurses' knowledge and skill increase. It is clear those DF nurse specialists who pass this workshop successfully will be able to provide effective education and care.

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GP105

Short synacthen test – ESN only?

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In the National Health Service (UK), there are ever increasing demands to streamline care and develop patient pathways and guidelines as justification for any test or procedure. This is to ensure optimisation in patient care and experience.
The role of a specialist nurse focuses on ensuring appropriateness and swiftness of investigations, including providing a high level of clinical care which has its foundations on communication and education for the patient/carers.
Our aim was to determine if patients who had their short synacthen test (SST) done by someone other than the endocrine specialist nurse (ESN) encountered a negative impact on their experience and/or potentially standard of care and results.
Patients were contacted and had telephone interviews, in addition to a comprehensive review of their notes by the endocrine team.
65 patients had SST over a 6-month period. 33 (51%) of patients were contactable, and 8 (24%) of them had their tests carried out by the ESN.
87% of patients seen by the ESN had results documented in the notes, 63% had recorded actions taken. Following phone interviews 87% stated the test had been explained to them and were satisfied with care received.
52% of the patients not seen by the ESN had results documented in the notes, 60% had recorded actions taken. Following phone interviews 42% stated the test had been explained to them and 63% reported they had been satisfied with the care received.
Results showed that patients who were seen and treated by the ESN were significantly more likely to have their test explained to them and more likely to have their results documented in notes ($P = < 0.05$). There was also an increase in patient satisfaction ($P = 0.356$).
It was therefore concluded that it is advisable for the short synacthen test to be carried out by an ESN.

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GP106

Assessment of fall status and activity of daily living in older people with type 2 diabetes

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Background
Diabetes is considered as one of the most common chronic diseases. Since diabetes complications can lead to falls in the elderly and according to the fact that the risks associated with falling are multifactorial, the aim of this study was to explore the association between activity of daily living (ADL) and falling in older people with diabetes admitted to the selected hospitals of tehran university of medical sciences.
Methods
A case–control study was performed. The sample included 160 persons 60 years or older who suffering from type 2 diabetes. 80 participants with a history of falling and 80 participants without any history of falling during last year were matched by age and gender the associations of the ADL stage with a history of falling within the past year (none, once or multiple times) were explored using demographic and ADL questionnaire. Data analyse was performed through using descriptive statistics and independent *t*-test, χ^2 and logistic regression.
Results
Both groups of participants (83.8% of patients with and 85% of patients without a history of falling) had a moderate limitation in ADL. Independent *t*-tests and χ^2 analysis showed that there is not any significant correlation ($P < 0.938$) between falling and ADL.
Conclusions
This study showed that the level of ADL in diabetic elderly could not cause the fall alone. It seems that limitation of ADL, along with other fall risk factors such as fecal incontinence and hearing impairment cause falling in older patients suffered from diabetes type 2. Therefore, preventing falling must be considered in this group with pay attentions the set of risk factors together.

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GP107

Managing children with diabetes within the family: living in the orbit of diabetes

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Background
Diabetes is the disease of family and parents of children with diabetes face different problems which concerns meeting the developmental needs of children and daily control of children with diabetes.
Purpose
This article aims to explain how to manage diabetes around the child's life within the family.
Methods and materials
In this qualitative study, data was collected through semi-structured interview technique and was analyzed using Grounded Theory approach. The process of data collection was carried out by purposeful sampling. The participants included 13 individuals from nine families (11 parents and two children with diabetes). The research environment was health centers in Iran providing care to the families of children with diabetes. Data analysis was performed using Corbin and Strauss approach. Data was analyzed with using MAXQDA Software (version 10).
Results
The core category of "Living in the orbit of diabetes" addresses the story of how the family managing children with diabetes within the family which included Main categories 'shaping the children with diabetes', "the formation of diabetes family", and 'window to the endless orbit'.
Conclusion
The outcome of "Living in the orbit of diabetes" results capturing the control of children with diabetes in the family. The findings of the present study may play an integral part to help households with practicing appropriate strategies for the management of children with diabetes.
Keywords: family, managing of children with diabetes, 'living in the orbit of diabetes'

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GP108

Childhood leukemia survivors' experiences of long-term follow-up in an endocrine clinic: a focus group study

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Background
Survival rate after childhood cancer has improved markedly and today more than 80% of patients with a pediatric malignancy will become 5-year survivor. During the past years it has become evident that many childhood cancer survivors suffer from late complications due to the radiotherapy and chemotherapy. It is established that the largest childhood cancer group, the acute lymphoblastic leukemia (ALL) survivors, exposed to cranial radiotherapy are at particularly high risk of endocrine complications.
Purpose
To illuminate childhood ALL survivors experiences of long-term follow-up in an endocrine clinic.
Method
Data collection was carried out using semi-structured focus-group interviews. Fifteen ALL survivors were included in the study, divided into four groups. Data were analysed with conventional qualitative content analysis.
Results
The survivors experience of the care were captured in the theme: '*The need of understanding and support to manage daily life*'. It was shown that understanding of their situation, as well as support to manage daily life was fundamental for the survivors. On the other hand lack of understanding and support from the society was connected with fear for the future. The follow-up at the endocrine clinic was shown to be crucial for increasing the survivors understanding about late complications after surviving ALL. The past feeling of being out of control was replaced with increased self-confidence among the survivors.

Conclusion
The present results show that the leukemia survivors daily life was experienced as a struggle and a complicated issue to cope with for many survivors. The theme 'understanding and support to manage daily life' mirrors how the survivors are in need of knowing and support to handle and understand their complex situation after surviving childhood leukemia. Offering understanding and support with a holistic approach may be a way to strengthen the survivors healthiness, rather than focus on living with complications.

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Endocrine Tumours

GP109

Expression and mutational status of USP8 in tumours causing ectopic Cushing's syndrome

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Introduction
Mutations activating USP8 have been detected in a high proportion of pituitary adenomas causing Cushing's disease and have been linked to an increase of ACTH production in corticotroph cells. Whether *USP8* mutations are involved in the tumorigenesis of the ectopic Cushing's syndrome (ECS) caused by neuroendocrine tumors has not been studied.
Patients and methods
In this work we evaluate the role of USP8 in a series of 17 tumors from patients diagnosed with ECS by analyzing the expression of ACTH, EGFR and USP8 by immunohistochemistry, as well as the rate of mutations of *USP8* using Sanger sequencing. USP8 expression was related to different clinical parameters and its action was studied *in vitro*.
Results
USP8 was found to be widely expressed in all examined tumors, although at different levels. Sanger sequencing did not detect heterozygous mutations in the *USP8* gene. ACTH immunoreactivity was detected in 11/17 tumors (65%). The majority of ECS (12/17; 71%) had no or weak EGFR expression. No significant association was observed between USP8 immunoreactivity and clinical data, such as age, sex, BMI, hormonal levels or overall survival. Overexpressing USP8 and EGFR in the bronchial carcinoid cell line NCI-H727 – that does not synthesize ACTH – failed to trigger exogenous *Pomc* promoter activity.
Conclusions
Altogether these results suggest that, despite their role in pituitary tumors, neither USP8 nor EGFR are actively contributing to the ectopic production of ACTH.

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GP110

Thyroid dysfunction and ultrasonography features in patients with metastatic colorectal cancer treated with Regorafenib: preliminary results from a single centre prospective cohort study

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Introduction
Regorafenib, a Tyrosine kinase inhibitor (TKI) recently approved for the treatment of metastatic colorectal cancer patients previously treated with fluoropyrimidine-based chemotherapy, VEGF and EGFR inhibitors, may, like others TKIs produce hypothyroidism, but this effect has not been systematically evaluated so far.
Description of methods
Prospective evaluation of thyroid function, autoimmunity and morphology during treatment with Regorafenib. From November 2015, 14 consecutive patients (four males and ten females; mean age 64 ± 8.1) with metastatic colorectal cancer with comparable tumoral staging, normal thyroid function and no evidence of associated thyroid autoimmunity, were studied before and at monthly intervals after beginning Regorafenib at scheduled dose of 160 mg oral daily according to standard protocols. In all cases FT_3, FT_4, TSH and thyroid antibodies (TgAb and TPOAb) were measured together with clinical assessment and thyroid ultrasonography up to three months.
Results
Within 30 days of therapy, 6/14 patients (43%) became hypothyroid (TSH 5.8 ± 3.1, range 7–18.5) and TPOAb (199 and 88 IU/ml) became detectable in two patients (14%), who also showed the highest serum TSH concentrations (18.5 and 11 mUI/l).Thyroid volume significantly decreased in 8 (57%) patients (from 9.2 ± 2.1 ml before to 6.1 ± 1.7 ml 2 months after Regorafenib, $P < 0.01$ by paired Student *t*-test), together with the appearance of mild hypoechogenicity and a significant reduction of parenchymal thyroid vascularity ($P < 0.05$).
Conclusions
These preliminary data indicate that Regorafenib, similarly to other TKIs inhibitors, may rapidly cause rapidly hypothyroidism in about one half of patients, and probably trigger thyroid autoimmunity. Further studies are needed to characterize longer-term effects on thyroid function-autoimmunity and to assess whether hypothyroidism may have a prognostic value as a biomarker of clinical response.

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GP111

Implication of Filamin A in pulmonary neuroendocrine tumors aggressiveness and progression

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Pulmonary neuroendocrine tumors (PNTs) comprise a spectrum of neoplasms, ranging from low grade carcinoids to the highly malignant small cell lung cancers. Several studies identified cytoskeleton protein Filamin A (FLNA) as determinant in cancer progression and metastasis. To date, the role of FLNA in PNTs aggressiveness and progression is still unknown.
To address this question, we decided: i) to evaluate FLNA expression in PNTs ranging from typical carcinoids to small cell lung carcinomas; ii) to manipulate FLNA expression in order to assess its possible influence on cell proliferation, cell adhesion and migration in PNTs cell lines (H727 cells) and primary cultures; iii) to focus on the possible interaction between FLNA and Rap1, a small GTPase implicated in the regulation of cell polarity and migration.
FLNA is highly expressed in PNTs with high malignant grade, this expression being the highest in small cell lung carcinomas. Interestingly, FLNA silencing reduces cyclin D1 levels in PNTs cells and H727 cells (-53 ± 3 $P < 0.01$ and -48 ± 13, $P < 0.05$ vs C-siRNA, respectively) and cell proliferation in H727 cells ($-56\% \pm 10$, $P < 0.01$). In addition, FLNA-silenced H727 cells were characterized by a reduction in cell migration ($-25 \pm 9\%$, $P < 0.05$ vs C-siRNA) and by an increase in cell adhesion ($+86 \pm 19$ $P < 0.05$ vs C-siRNA), thus confirming that FLNA is involved in the control of cell motility. Interestingly, FLNA and Rap1 co-localized in cellular protrusions and FLNA knocking down induces a significant increase in Rap1 expression ($+72 \pm 17\%$, $P < 0{,}01$ vs C-siRNA).
In conclusion, these results demonstrated that FLNA is involved in mediating PNT progression thus providing a possible diagnostic and therapeutic target.

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GP112

Presence and clinical-histological correlates of ghrelin and somatostatin systems components in gastroenteropancreatic neuroendocrine tumors and lung carcinoids

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Neuroendocrine tumors (NETs) are uncommon neoplasms with increasing incidence and limited therapeutic options, wherein identification of new diagnostic/prognostic/therapeutic biomarkers is urgently required. Alterations in somatostatin (SST)/cortistatin (CORT) and ghrelin systems have been associated to development/progression of several cancers. Thus, we evaluated expression levels of SST/CORT/ghrelin system components in gastroenteropancreatic-neuroendocrine tumors (GEP-NETs) and lung carcinoids (LC), and explored their putative relationship with clinical/histological characteristics in an observational retrospective study with 90 GEP-NET patients (51.7%-G1, 36.7%-G2, 11.7%-G3), 81 LC patients and 20 controls. Clinical/histological characteristics of GEP-NET and LC patients were, respectively: mean age 54 ± 17/54 ± 15 years; 53.3%/50.6% males; 37.7%/19.2% incidental tumors; 34.4%/7.5% functioning tumors; 46.5%–25% metastatic at diagnosis; and 34.1%–19.4% mortality rate. Expression levels of SST/CORT/ghrelin systems components were assessed by quantitative-PCR using formalin-fixed paraffin-embedded samples. Results indicated that mortality in GEP-NETs patients correlated with metastasis, SST immunostaining, and relapsed disease, and tended to correlate with vascular/nerve invasion. Similarly, in LC patients, mortality was related with relapsed disease and metastasis, but also with tumor diameter, gender, tobacco exposure, weight loss, and constitutional syndrome. Quantitative-PCR studies revealed that the vast majority of SST/CORT/ghrelin systems components were expressed in GEP-NETs and LCs and displayed clinical correlates. Thus, for example, SST, CORT and receptor sst4 expression was lower in GEP-NETs from patients without family tumor history. Interestingly, sst2 and sst3 expression was correlated with tumor-free surgical borders, while sst5 expression correlated with vascular and nerve invasion. Additionally, truncated sst5TMD4 expression was higher in functioning/symptomatic, and metastatic tumors. In LCs, ghrelin expression was inversely associated with vascular invasion and with recurrence, while expression of its receptor GHSR1a was higher in non-functioning and metastatic tumors. Altogether, these data reveals a notable, widespread expression of key SST/CORT/ghrelin systems components in GEP-NETs and LC, where they display clinical-histological correlates, which could provide novel, valuable markers for NET patient management.

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GP113

FOXM1 as chemo-sensitizing target in neuroendocrine lung tumors

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Introduction
Neuroendocrine tumors of the lung (BP-NETs) are fairly rare tumors with very heterogeneous behavior and molecular characteristics. They are very heterogeneous concerning their malignancy, ranging from slow proliferating carcinoids (typical (TC) and atypical carcinoids (ATC)) to very aggressive large cell neuroendocrine carcinomas (LCNEC) and small cell lung cancers (SCLC). For the highly proliferative BP-NETs, combined chemotherapy is the standard therapy option, whereas for the lung carcinoids, Everolimus has recently been assessed in the Radiant-4 study as moderately effective concerning time to progression. Nevertheless the treatment options are limited and unsatisfactory. The cell cycle and DNA damage response (DDR) regulator FOXM1 has been lately demonstrated to be associated with grading in BP-NETs tumor biopsies and to be targetable by proteasome inhibition *in vitro.*
Purpose
The experimental (RNAi) and pharmacological (bortezomib) inhibition of FOXM1 was studied to assess the chemo-sensitizing effect of targeting FOXM1.
Material and methods
TC, ATC, large-cell NEC, small-cell NEC and a NSCLC cell line were treated with siRNA against *FOXM1* or bortezomib, cisplatin or a combination of cisplatin and either siRNA or bortezomib versus controls. The efficacy and molecular effects were studied by proliferation analysis, western blot, flow cytometry and multiplexed gene expression analysis (Nanostring technologies).
Results
In *TP53* wildtype carcinoids, knockdown of FOXM1 induced an enhanced induction of apoptosis and reduced mitosis after cisplatin therapy versus controls. Bortezomib, which shows several additional effects on DDR, strongly induced G2 arrest and reduction of mitosis in the cell lines. When combined with cisplatin, the G2 arrest turned into increased induction of apoptosis in the majority of the cell lines.
Conclusion
Targeting FOXM1 and Bortezomib treatment enhance the effect of cisplatin-chemotherapy in BP-NET *in vitro*.

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GP114

Proteomic and pathway analysis of adrenocortical cancer in an *in vivo* xenograft study

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Background
Few effective medical treatment options are available for adrenocortical carcinoma (ACC). Intensive efforts are therefore going on for exploring novel pathways and treatment targets.
Objective
To perform a proteomic and pathway analysis on a 9-cisRA (9-cis retinoic acid) and mitotane-treated ACC xenograft model.
Methods
43 male SCID mice xenografted with NCI-H295R cells were treated in four groups (i. control, ii. 5 mg/kg 9-cisRA, iii. 200 mg/kg mitotane, iv. 9-cisRA + mitotane) for 28 days. Protein isolates from three tumor samples from each group were subjected to SDS-PAGE separation followed by LC-MSMS analysis. After the normalization and statistical analysis of the data, one protein was chosen for validation by Western-blotting. For pathway-analysis David 6.7 was used.
Results
47 significant protein-level changes were found in the 9-cisRA + mitotane group relative to the control. By considering literature data, the SET protein was validated as being significantly down-regulated in the combined treatment group relative to the untreated control. SET protein was weakly expressed in human ACC samples, but not in benign adenomas, parallelling our xenograft data. Pathway analysis indicated the potential interaction of significantly affected proteins with p53- and Wnt-pathways that are known to be relevant in ACC pathogenesis. Processes linked to ribosome and proteasome were also identified as potentially affected.
Conclusions
The SET protein appears to be a novel player in ACC biology, but its pathogenic relevance along with the other pathways need to be confirmed in further studies. 9-cisRA might represent a novel treatment modality in ACC that could be used as an additive to mitotane.

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GP115

Loss of cells expressing the T-box transcription factor TBX1 might be associated with a quiescent phenotype in parathyroid tumours

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Embryonic transcription factors have been involved in tumourigenesis. The transcription factor TBX1 regulates the embryonic parathyroid cells fate. Indeed, it has never been investigated in human adult parathyroids. Here, expression, function and regulation of the *TBX1* gene were analyzed in adult normal and tumour parathyroid tissues. Immunohistochemistry identified 30–70% (mean ± S.E.M, 52.0 ± 7.3%) of cells expressing TBX1 at nuclear levels in normal parathyroid glands ($n=5$). About a half of parathyroid tumours [12 parathyroid carcinomas and 13 adenomas (PAds)] had reduced TBX1^{+} cells (0–15%), showing deregulated *TBX1* mRNA levels. Immunofluorescence on PAds-derived cells identified a subset of cells co-expressing TBX1 and PTH. Western blot analysis on fractioned proteins from PAds ($n=11$) showed that PAds expressed the 53 kDa isoform C of the TBX1 gene mainly at nuclear level. TBX1 function was investigated in HEK293 cells, which express the gene. Stable silencing of *TBX1* gene in HEK293 cells reduced nuclear TBX1 protein to 30% of basal levels and increased the proportion of cells in the G0/G1 phase (from 38.2 ± 6.7% to 50.2 ± 9.1%, $P=0.04$), suggesting that loss of TBX1 induced cell cycle arrest. Consistent with the promotion of cell cycle arrest, *TBX1* silencing increased *CDKN2A/p16* and *CDKN1A/p21* mRNA levels and decreased *ID1* (inhibitor of DNA binding 1) levels both in HEK293 and PAds-derived cells, where any significant change in both *GCM2* and *PTH* levels could be detected by TBX1-silencing. During embryonic development, *TBX1* is regulated by the activation of the Wnt/β-catenin pathway. Short-term (8 h) 10–20 mM lithium chloride treatment induced β-catenin nuclear accumulation and inhibited *TBX1* mRNA levels in five out of seven PAds cell preparations. Moreover, PAds samples with reduced TBX1 protein levels showed significantly higher *AXIN2* mRNA levels, a marker of β-catenin transcriptional activity (median, IQR; 0.16, 0.05–0.65 vs 1.57, 0.38–2.93; $P=0.03$, $n=11$). In conclusion, the embryonic transcription factor TBX1 is expressed in a subpopulation of adult parathyroid cells, which is reduced in half of tumours. Reduction of TBX1 expression is associated with cell quiescence, a feature that might be in line with the extremely low cell proliferation rate described in parathyroid tumours.

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GP116

Differential expression of protein kinase A catalytic and regulatory subunits in adrenocortical adenomas

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Background

Heterozygous activating somatic mutations in the catalytic subunit α (Cα) of Protein Kinase A (PKA) underlie 30–40% of cortisol producing adrenocortical adenomas (CPA). The activity of the catalytic subunits α,β,γ is controlled by the regulatory subunits (Iα,Iβ, IIα, IIβ). Previous reports found uncommonly reduced levels of RIIβ in CPA compared to other adrenocortical tumors.

Aim

Investigating a possible correlation between Cα mutational status and RIIβ expression levels.

Methods

We performed immunohistochemistry staining of all PKA regulatory subunits and Cα on FFPE tissue from normal adrenal glands ($n=12$), adrenocortical adenomas ($n=87$ including 40 CPA, of which 18 Cα-mutated) and adrenocortical carcinomas (ACC, $n=35$). mRNA ($n=19$) and proteins ($n=24$) from CPAs were isolated to perform qPCR and immunoblotting. Functional experiments were performed in the ACC cell line NCI-H295R.

Results

RIIβ expression was strongly reduced in Cα mutated CPAs, especially in tumors harboring the frequent L206R mutation ($n=13$, mean expression: 0.4 ± 0.5 vs 1.5 ± 0.7, $p<0.05$). Similar results were observed for RIα (1.8 ± 0.9 vs 2.6 ± 0.6, $p<0.05$) but not for the other regulatory subunits. Cα levels were not influenced by the mutations. mRNA expression of all subunits was unchanged in CPA$^{Cα\text{-}wt}$ compared to CPA$^{Cα\text{-}mut}$. Since no significant changes in mRNA expression were observed, downregulation of RIIβ and RIα seems a post-transcriptional event. However, in NCI-H295R cells, proteasome inhibition did not save RIIβ from degradation, rendering other degradation pathways more likely. Furthermore, we found different expression patterns of the PKA subunits in normal adrenal glands, overlapping zoning, with low RIIβ in the cortisol producing *Z. fasciculata*. The expression pattern of PKA subunits in normal adrenal glands indicates possible particular roles of these subunits on differentially regulating hormone secretion.

Conclusion

We demonstrate for the first time, that mutations in PKA Cα lead to post-transcriptional downregulation of the main regulatory subunits in adrenocortical tissues enhancing Cα catalytic activity leading to increased cortisol production.

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GP117

FSH supplementation increases the growth of PC-3 human prostate cancer cell xenograft in gonadotropin-suppressed nude mice

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Gonadotropin-releasing hormone (GnRH) analogues are now the standard hormonal treatment for prostate cancer. A fundamental difference between GnRH agonist and antagonist treatment is the permanent suppression of both gonadotropins (LH and FSH) by antagonist, while a rebound in FSH is associated with agonist treatment. The benefits of antagonist include the immediate onset of action and profound long-term suppression of FSH, suggested to be an independent growth factor in prostate cancer. To determine the potential benefit of permanent FSH ablation in treatment of prostate cancer, we studied the effect of the GnRH antagonist degarelix, in the presence and absence of FSH supplementation, on androgen independent PC-3 human prostate cancer cell xenograft tumour growth in intact and gonadectomised nude mice.

Our experiments demonstrate that degarelix treatment suppresses tumour growth in both intact and gonadectomised nude mice compared to non-treated controls ($P<0.0001$), indicating that the effect is mediated by gonadotropins rather than androgen suppression. Degarelix also effectively suppressed LH and FSH in both groups of mice, and testosterone in intact mice. The observed suppression of PC-3 cell xenograft tumour growth by degarelix treatment was significantly inhibited by concomitant FSH treatment. Quantitative polymerase chain reaction demonstrated LHR and FSHR mRNA in the xenograft tumours, but not in cultured PC-3 cells. Hence, *in vivo* conditions are needed for gonadotropin receptor expression of PC-3 cells. In conclusion, we provide experimental evidence that FSH may function as a direct growth promoter of prostate cancer cells, suggesting that combined FSH and LH suppression by GnRH antagonist could offer an advantage over the isolated LH suppression achieved by GnRH agonist upon prostate cancer treatment.

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GP118

Expression and regulation of the early embryonic stem cell genes in parathyroid tumours

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An embryonic gene signature has been suggested in parathyroid tumours. We investigated the expression of early embryonic stem cell (ESC) genes in parathyroid tumours. *POU5F1/OCT4*, *SOX2* and *NANOG* transcripts were detected in almost all parathyroid adenomas (PAds; $n=22$) and atypical PAds ($n=3$), besides the variable expression of ESC genes *KLF4*, *EGR1*, and *REX1/ZFP42*. OCT4, SOX2 and NANOG proteins expression were analyzed by immunohistochemistry in archival series of tumours and normal parathyroid glands. Parathyroid carcinomas ($n=8$) had more NANOG-expressing cells (mean positive cells 40%) compared to PAds ($n=11$; mean positive cells 10%), while PAds ($n=22$) showed a higher proportion of SOX2-expressing cells, though SOX2-expressing cells occurred in half of tumours. PAds-derived cells expressing the pluripotency genes were negative for PTH immunostaining. The ESC pluripotency is regulated by the Wnt/β-catenin and by the bone morphogenetic proteins (BMP) signalling. Active β-catenin highly accumulated at membrane and cytoplasm levels in normal glands ($n=4$) and in PAds ($n=16$), though PAds were heterogeneous showing parenchymal zones where cells had very low active β-catenin levels confined at membrane. Despite the absence of robust nuclear accumulation, β-catenin is transcriptionally active in parathyroid neoplasia: treatment of PAds-derived cells ($n=6$) with 10–20 mM Lithium Chloride increased the Wnt gene targets *AXIN2, DKK1, ZEB1,* and modulated the expression of POU5F1/OCT4, *SOX2* and *NANOG* mRNA levels depending on the time course of β-catenin activation. Investigating samples from 25 PAds, we observed that PAds expressing *AXIN2* ($n=6$) had abundant NANOG, *SOX2* and *WNT5A* transcripts. Moreover, stimulation of PAds-derived cells for 24 h with 50 and 100 nM BMP4 induced significant increases in *ID1/inhibitor of DNA binding 1* (about threefold the basal levels) and *Gremlin* transcripts suggesting that PAds-derived cells are responsive to BMP signalling. Nonetheless, any effect could be detected on ESC genes transcripts levels by a short term BMP pathway activation. In conclusion, parathyroid tumour cells expressed the ESC genes, whose expression might be modulated by deregulated β-catenin.

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Neuroendocrinology

GP119

Hypoxia-inducible factor 1α triggers growth hormone synthesis in acromegalic tumors

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Acromegaly is caused by excessive growth hormone (GH) secretion frequently due to GH-secreting pituitary tumors. Acromegalic tumors (ACRO) display reduced microvascular density versus normal pituitaries, suggesting they are under hypoxic conditions. Under hypoxia, tumors gain a survival advantage by stabilizing the transcription factor known as hypoxia-inducible factor 1 alpha (HIF1a). Western blot screening of ACRO ($n=40$) revealed significantly higher HIF1a protein levels compared to NFPA ($n=18$) and normal pituitary ($n=6$), indicating a role for HIF1a specifically in acromegalic tumorigenesis.

This study investigates the role of HIF1a in ACRO pathophysiology. HIF1a overexpression and hypoxia (1% O_2) increased GH secretion and promoter activity in the GH-secreting GH3 cell line, while knocking down HIF1a blunted these effects. GH transcription is positively regulated through the cAMP cascade, which activates CREB and subsequently GH transcription. HIF1a overexpression in GH3 cells maintained forskolin-induced CREB phosphorylation and increased cAMP responsive element (CRE) transcriptional activity, while HIF1a knockdown abrogated these effects. These effects were abolished by inhibiting CREB, revealing the importance of CREB.

Further analysis revealed that the effects of HIF1a overexpression on GH and CRE transcriptional activity were abrogated when HIF1a was co-expressed with a dominant-negative mutant of PKA, indicating that the target of HIF1a is located within, or upstream of PKA. Real-time PCR screening of PKA-associated proteins revealed the regulatory subunit IIb (PRKAR2B) as a probable HIF1a target gene, as HIF1a overexpression significantly repressed PRKAR2B mRNA expression, while HIF1a knockdown reversed this effect. Furthermore, the stimulatory effects of HIF1a overexpression on GH promoter activity could be suppressed by selectively overexpressing PRKAR2B.

Taken together, our results demonstrate that HIF1a overexpression as it is found in somatotrophinomas is involved in the overactivation of the cAMP pathway transcriptionally repressing the PRKAR2B subunit. Therefore, targeting HIF1a may sensitize tumor cells to pharmacological therapy in patients with acromegaly.

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GP120

High-resolution spatiotemporal analysis of Somatostatin Receptor Type 2 (SSTR2) – Filamin A (FLNA) interaction by single-molecule imaging

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SSTR2 is one of the main pharmacological target for GH-secreting pituitary adenomas treatment and the cytoskeletal protein FLNA plays an important role in tumor responsiveness by regulating SSTR2 expression and signaling. Single-Molecule Imaging was used to investigate the spatial distribution of FLNA-SSTR2 at the plasma membrane level and the involvement of FLNA in SSTR2 mobility, receptor clustering organization/internalization. This method is based on labeling SNAP/CLIP-tagged proteins (SNAP-tagged SSTR2, CLIP-tagged FLNA) and on total internal reflection fluorescence (TIRF) microscopy to visualize single particles on the surface of living cells. First, we observed dynamic and transient FLNA-SSTR2 interactions along actin fibers in transfected CHO cells. As far as SSTR2 mobility was concerned, no differences were found in SSTR2 average speed between basal and 100 nM BIM23120 stimulated CHO cells. However, an increase of the immobile receptors fraction ($2.17\% \pm 0.21\%$ vs $6.05\% \pm 0.69\%$) has been observed after SSTR2 agonist stimulation (this population of static receptor is the one that likely undergo internalization). To evaluate the contribution of FLNA in the enrichment of the immobile SSTR2 population, we assessed experiments with the FLNA dominant negative mutant that prevents SSTR2-FLNA binding (FLNA 19-20), but no differences were found with respect to negative control (FLNA 17-18). This result was confirmed in human melanoma cell lines M2 (FLNA-deficient) and A7 (FLNA-expressing). In conclusion, the spatiotemporal behavior of SSTR2 and SSTR2-FLNA interactions have been characterized for the first time by means high-resolution strategy. The interaction between FLNA and SSTR2 resulted to be extremely dynamic along actin filaments, but FLNA does not seem to be involved in SSTR2 receptor mobility. Since SSTR2 tended to cluster on FLNA fibers in stimulated cells, further experiments are required to better investigate the possible role of FLNA in the regulation of SSTR2 clusterization/internalization processes.

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GP121

Expression of dopamine (DA) D2 receptors (D_2R) in corticotroph cells is responsible for the switch of hypothalamic regulation of ACTH secretion to DA in lactating rats

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Hypothalamic regulation of pituitary adrenocorticotropic hormone (ACTH) secretion switches to dopamine (DA) with a parallel loss of DAerg control of alpha-melanocyte-stimulating hormone (α-MSH) release in lactating dams. It has been also shown that dephosphorylation/inactivation of tyrosine hydroxylase (TH) in terminals of DA neurons at the median eminence is required not only for suckling-induced PRL release but also for ACTH responses. The aim of the present study was to further investigate the regulatory switch of ACTH with special emphasis on potential changes at the level of anterior lobe (AL) and the neuro-intermediate lobes (NIL) of the pituitary gland in lactating rats. AL and NIL cells obtained from ovariectomized (OVX) and lactating rats were cultured *in vitro*. Levels of PRL, ACTH and α-MSH were measured by RIA from culture media, with and without DA treatment. In cells obtained from OVX rats, ACTH secretion was not sensitive to DA, but both PRL and α-MSH were blunted. In contrast, on AL cells obtained from lactating rats, DA treatment resulted in an inhibition in both PRL and ACTH secretion but had no effect on α-MSH. ACTH immunohistochemistry and D_2 DA receptors (D_2R) *in situ* hybridization techniques were combined to investigate whether DA inhibition of ACTH secretion is due to the expression of D_2R on corticotropes. It was found that expression of D_2R was much higher in both the AL and the NIL of lactating dams compared to OVX animals. Combination of *in situ* hybridization with immunohistochemistry revealed co-localization of D_2R with ACTH in a subpopulation of corticotropic cells of lactating animals. Therefore, the release of ACTH from corticotropes can be regulated by hypothalamic DA in lactating animals. This subpopulation of cells may also be responsible for the higher basal activity of the hypothalamo-pituitary-adrenal system and the stress hyporesponsiveness during lactation.

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GP122

Lipid content and ATP metabolism in the liver of patients with acromegaly

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We have recently shown that patients with growth hormone (GH) excess (acromegaly) exhibit inadequately low intrahepatic lipid content (IHL) despite marked insulin resistance. GH might increase mitochondrial oxidation capacity thereby counteracting ectopic lipid accumulation; however, up-regulation of mitochondrial function has been reported in early stages of non-alcoholic fatty liver disease. Up to now, data on mitochondrial activity in patients with acromegaly are missing.

Patient population and methods

Magnetic resonance spectroscopy (MRS) for determination of ATP synthesis (k) by the saturation transfer technique and IHL by 1H-MRS was performed in four patients with active acromegaly (AKRO; two newly diagnosed, two uncontrolled after surgery, 43 ± 3 years, BMI: 31 ± 3 kg/m^2, IGF1: 715 ± 128 ng/ml) and five healthy controls matched for age and BMI (CON: 37 ± 2 years, BMI: 31 ± 2 kg/m^2).

Results

As expected, IHL was markedly lower in AKRO compared to CON (0.7 ± 0.3 vs 4.6 ± .3%, $P = 0.05$). In contrast to our initial hypothesis, mitochondrial function was lower in AKRO (ATP synthesis (k): 0.21 ± 0.02 vs 0.33 ± 0.02 1/s, $P = 0.003$). In the whole group, IHL was tightly correlated with K ($R = 0.78$, $P = 0.014$).

Discussion

Consistent with the suggestion that mitochondrial function of the liver adapts to the prevailing lipid load, ATP synthesis was lower in patients with active acromegaly and also low hepatic lipid content was observed in acromegaly compared to matched controls. In contrast to short-term animal studies, GH excess does not up-regulate hepatic energy metabolism in patients with GH-excess.

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GP123

A placebo-controlled study to assess the dose-effect of COR-005, a novel somatostatin analogue on plasma glucose regulation compared to octreotide in healthy male subjects

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Somatostatin analogues (SSAs) approved to treat acromegaly tend to suppress postprandial insulin/glucagon secretion and can worsen glucose tolerance. COR-005, a novel SSA, is under investigation for treatment of acromegaly. In rodents, COR-005 effectively inhibits GH secretion with 10,000-fold greater potency compared with insulin release suppression. We sought to determine for the first time the effects of COR-005 on postprandial glucose in humans.

The pharmacodynamic effects of single subcutaneous doses of COR-005 300, 900, and 1800 μg, octreotide 300 μg and placebo on glucose, insulin and glucagon dynamics were investigated for 4 h after intake of a mixed meal in eight healthy male subjects using a randomized cross-over design. Following COR-005 300 and 900 μg, there were slight increases in maximum blood glucose concentrations (9.76 ± 1.00 and 9.73 ± 1.31 vs 7.56 ± 0.93 mmol/l) and in the 4-h blood glucose $AUEC_{Glucose}$ compared to placebo (26.13 ± 2.18, 28.86 ± 3.82 vs 23.02 ± 1.83 mmolxh/l). A higher increase was observed after injection of COR-005 1800 μg and the highest after octreotide 300 μg ($AUEC_{Glucose}$: 33.56 ± 4.71 and 38.69 ± 5.79 mmolxh/l). Octreotide significantly suppressed plasma insulin and glucagon secretion compared to placebo ($AUEC_{Insulin}$ 15.56 ± 2.02 vs 44.29 ± 10.65 μUxh/ml and $AUEC_{Glucagon}$ 135.5 ± 55.1 vs 363.2 ± 40.9 pgxh/ml) whereas COR-005 caused only a dose-dependent delay in insulin and glucagon secretion but had no significant effect on $AUEC_{Insulin}$ or $AUEC_{Glucagon}$.

After intake of a mixed meal, COR-005 single doses up to 900 μg had no significant effect on total insulin and glucagon secretion compared to placebo and a marginal effect on blood glucose. COR-005 1800 μg less strongly inhibited postprandial insulin and glucagon compared to octreotide. COR-005 might offer a reduced risk of hyperglycemia relative to other SSAs currently used to treat acromegaly.

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GP124

Endothelial damage and thrombotic response in patients with cured Cushing syndrome

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Introduction

Clinical observational studies have reported the persistence of a high cardiovascular risk in patients with cured Cushing's syndrome (CCS) compared

with controls of the same age, gender and BMI. It is still at debated whether this is due to the persistence of comorbidities, hormone deficiencies or chronic changes induced by hypercortisolism. The aim of this translational approach was to investigate the interplay in CCS of the cardiovascular disease in vivo and the endothelial activation and thrombogenicity *in vitro* occurring in response to sera of CCS.

Methods

Cross-sectional study in CS patients and controls and *in vitro* endothelial damage atherothrombotic model. Subjects: I. Cured CS (CCS) ($n=10$) at minimum 2 years after cure and without hormone deficiencies and II. Active CS (ACS) ($n=10$), III. Controls (CTR) ($n=10$) matched for age, sex, sexual hormonal status (females, premenopausal) and also by BMI and cardiometabolic profile. We evaluated in vivo: the cardiometabolic clinical and analytical profile; endothelial dysfunction (FMD) and body composition (DEXA). Endothelial cells (EC) were exposed for 24 h or have been cultured for 7 days with the different seras (groups I, II, III) to evaluate the inflammatory EC response (VCAM, ICAM; NfKB) and the reactivity (VWF) of the extracellular matrix (ECM).

Results

Active CS patients have a clinical, subclinical and *in vitro* proatherothrombotic phenotype. EC exposed to CCS sera displayed augmented expression of ICAM1 ($P=0.04$), VCAM1 ($P=0.05$), a higher synthesis of sub-endothelial VWF ($P=0.03$) and a higher EC reactivity towards circulating platelets: platelet adhesion ($P=0.04$) than CTRs of the same sex, age and BMI. NFκB is activated downstream.

Conclusion

This is the first translational study demonstrating that the sera of patients with cured CS have a deleterious atherothrombotic NFκB dependent potency on the endothelium inducing endothelial inflammatory activation and increased thrombogenicity.

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GP125

Cabergoline therapy in clinically nonfunctioning pitutiary adenoma: results of a clinical trial

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Nonfunctioning pituitary adenomas (NPA) are prevalent neoplams from pituitary. The best treatment is the surgical approach but residual tumours are common. For residual tumours the options are radiotherapy (RT) and re-surgery. There are no significant studies testing drugs in NPA. Due to the fact that these tumors express dopamine D2 receptors, dopamine agonists that may be useful in patients with NPA.

Methods

We selected 145 patients with residual tumor after surgery and imunohistochemical confirmation. Hormonal hypersecretion was excluded in all of them. RMI was performed 6 months after surgery to confirm residual tumour. After this time, the patients were randomized alternately in two groups: for cabergoline (Group A; $n=74$) or just clinical observation (Group B; $n=71$). RMI was performed at baseline and each 6 months by 24 months. Tumour residual volume and immunohistochemical expression was compared after 12 and 24 months. The tumour volume was calculated according by Lundin and Peterson (cm^3) and by a software program (Osirix). Tumor shrinkage $>25\%$ of baseline was considered significant. Any increase in tumor volume during follow-up was considered relevant. Ecocardiography was performed as a safety measure.

Results

Group A (CAB) showed tumor reduction in 20.89% of patients and tumor increase in 7.46%. Stabilization of residual tumour was observed in 71.64%. In group B, reduction was observed in 4.91%, tumour progression in 16.39% and no changes in 78.68%. Significant differences was observed in tumor reduction (A > B; $P<0.01$) and tumor progression (B > A; $P=0.02$). Stabilization was similar between two groups ($P=0.4$). No echocardiography alterations were observed between baseline, 12 and 24 months (Ao, Pulm, Mitral, Tric: $P=$NS). Imunohistochemical profile was not different between two groups and not related to tumor progression or reduction.

Conclusions

Cabergoline was a effective alternative to radiotheraphy or resurgery in NPA. Residual tumour reduction was observed in 1/5 of patients. The immunohistochemical profile is not predictive of response to cabergoline. Cabergoline did not show cause changes in heart valves in this study.

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GP126

Abnormal hypothalamus and related brain regions in Prader–Willi syndrome evaluated in vivo by diffusion tensor imaging (DTI)

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Introduction

Prader–Willi syndrome is a genetic disorder characterized by hypotonia, intellectual disabilities, obesity and behavioral disturbance. Patients present with several neuroendocrinological abnormalities, such as growth hormone deficiency, hypogonadotropic hypogonadism, and hyperphagia, as the result of possible involvement of the hypothalamo-hypophyseal system. Diffusion tensor imaging (DTI) is a noninvasive MRI technique capable of providing quantitative indices of brain structure integration. To our knowledge, there is only one study in PWS patients using DTI and it was not focused in the hypothalamo-hypopshyseal region.

Materials and methods

Twenty patients (11 males, 9 females, aged 28.3 ± 7.4 years) with PWS and twenty age- and gender-matched controls (11 males, 9 females, aged 28.1 ± 7.0 years) were recruited. MRI data were acquired from all participants using a 1.5-Tesla system. Diffusion-weighted scans were obtained using spin-echo single-shot echo-planar sequences of 25 directions with a B-factor of 1000 s/mm^2. Images were preprocessed and fractional anisotropy (FA) maps were calculated using Functional MRI of the Brain (FMRIB) Software Library 5.0 (FSL).

Results

Based on a voxel-wise approach, we found a significant reduction in FA values in a number of brain regions in PWS compared with controls. Relevantly, FA was significantly reduced in the entire hypothalamus (H) region and in nearby structures including the lenticular nucleus (LN) (bilateral), amygdala (A), the sub-genu part of the anterior cingulate cortex (CC) and the cranial-ventral aspect of the striatum (S). R LN 79.9 ml, (x,y,z) 20, 4, -9, T5.00; L LN -23, 3, -12 T4.65; H 4, -11, -3, T5.25; A -12, -8, -21, T5.61; AnteriorCCsub-genu, -5,17,-12, T4.80; L cranial-ventral S -16, 22, -6, T4.17 and R cranial-ventral S 16, 21,-2, T4.31.

Conclusion

DTI results confirm the presence of an abnormal hypothalamus that could contribute to explain endocrinological abnormalities and hyperphagia pathophysiology in these patients.

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GP127

Hypothalamic GRK2, via GPR54, modulates puberty onset

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The G protein-coupled receptor (GPCR) kinase 2, GRK2, is a ubiquitous serine/threonine protein kinase that is able to phosphorylate and desensitize the active form of several GPCR. Compelling, as yet limited, evidence from *in vitro* studies have suggested a potential role of GRK2 in mediating desensitization of Gpr54, the canonical receptor for kisspeptins that is abundantly expressed in GnRH neurons. Yet, although kisspeptins have been universally recognized as essential regulators of puberty and fertility, the physiological role of GRK2 in modulating kisspeptin signalling *in vivo* remains completely unexplored. We report herein a series of expression and functional analyses addressing the putative role of central (hypothalamic) GRK2 in the regulation of puberty, as major developmental event under the control of kisspeptins (and related factors). Expression analyses revealed a gradual increase of GRK2 mRNA and protein levels in the hypothalamus during postnatal maturation, especially in the preoptic area, where most GnRH neurons reside. Of note, models of delayed puberty, due to postnatal under-nutrition or manipulation of neonatal sex steroid milieu, displayed an exaggerated increase of hypothalamic GRK2 expression. In addition, intracerebro-ventricular (icv) injection of a GRK2 inhibitor enhanced LH and FSH secretion in response to acute kisspeptin-10, but not to NKB, administration. Furthermore, chronic icv administration of a GRK2 inhibitor caused an advancement of puberty onset, evidenced by earlier vaginal opening and first ovulation, together with increased ovarian and uterus weights. Alike, central GRK2 inhibition partially rescued the delay in puberty onset caused by postnatal under-nutrition. Altogether, our results demonstrate that GRK2 regulates hypothalamic Gpr54 signalling in vivo and provide conclusive evidence for a crucial role of GRK2 in the fine tuning of pubertal timing, likely via modulation of kisspeptin actions, in normal and metabolically or hormonally compromised conditions.

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GP128

Latest results from the PATRO adults study of Omnitrope® for the treatment of adult patients with growth hormone deficiency

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Introduction
PATRO adults is an international, longitudinal, non-interventional study of the long-term safety and efficacy of recombinant human growth hormone (rhGH; Omnitrope®, Sandoz). The study will provide additional data on the long-term safety of rhGH in adult patients with severe GH deficiency (GHD). Here, we present safety data from an interim analysis.
Methods
Eligible patients are adults who are receiving treatment with Omnitrope® and have provided informed consent. Patients treated with another rhGH before starting Omnitrope® therapy are eligible for inclusion. The primary objective is to assess the safety and efficacy of Omnitrope® in adults treated in routine clinical practice, with particular emphasis on the risk of glucose intolerance or diabetes and normalisation of IGF-I levels.
Results
As of November 2015, 996 patients have been enrolled in the study; 548 (55%) have received previous GH treatment. Mean (s.d.) age of subjects is 50.0 (15.2) years, and mean (s.d.) BMI is 29.4 (6.1) kg/m^2. To date, 1772 AEs have been reported in 539 (54%) patients, with 273 (15%, in 164 [16.5%] patients) regarded as serious. One-hundred-and-ten AEs (6%) in 67 (6.7%) patients were suspected as drug-related. These included 18 nervous system disorders, 17 general disorders/administration site conditions, 16 musculoskeletal/connective tissue disorders and two investigations (increased IGF levels). A total of 22 SAEs in 20 (2%) patients were suspected as related to Omnitrope® treatment, including one incidence of diabetes mellitus. Of the 127 patients who have discontinued treatment, 31 did so due to an AE.
Conclusions
Based on this interim analysis, Omnitrope® treatment in adults with GHD is well tolerated in real-life clinical practice, both in rhGH-naïve and previously treated patients. The PATRO adults study will continue to provide important data on the diabetogenic potential and overall safety of long-term GH treatment in this population.

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Obesity

GP129

Direct effects of dopamine on mitochondrial thermogenesis in brown adipocytes

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Brown adipose tissue (BAT) is key in energy homeostasis. Catecholamines are critically involved in the regulation of BAT-thermogenesis, yet current research has focussed on noradrenaline and adrenaline. Some evidence suggests a role of dopamine (DA) in BAT-thermogenesis but the intracellular mechanisms have not been addressed. We applied our extensively characterised murine brown adipocyte cell line to address these questions.
D1-like and D2-like receptors were detectable at the protein level, as determined by immunoblotting. Treatment with DA caused an increase in cAMP levels. Oxygen consumption rates and uncoupling protein 1 levels increased, whereas the proton gradient at the inner mitochondrial membrane decreased after 24 h of DA-treatment. Mitochondrial mass (as determined by measurement of two mitochondrial proteins, TOMM20 and ATP synthase beta) also increased within this period of time. This was accompanied by an increase of PPAR gamma co-activator 1 alpha protein levels, a master regulator of mitochondrial mass. The D1-like receptor antagonist SCH 23390, but not the D2-like receptor antagonist Raclopride, abolished the DA-effect on the inner mitochondrial membrane potential (Delta Psi). Similar to DA, the specific D1-like receptor agonist SKF 38393 had an effect on Delta Psi after 24 h, whereas bromocriptine, a D2-like receptor agonist, had no significant effect. DA caused an increase of p38 MAPK phosphorylation and pharmacological inhibition of p38 MAPK abolished the DA-mediated effect on Delta Psi.
In summary, our study for the first reveals direct D1-like receptor and p38 MAPK-mediated increases of thermogenesis and mitochondrial mass in brown adipocytes.

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GP130

Hypothalamic inflammation in humans is not reversed by a profound weight loss and an improved insulin sensitivity due to bariatric surgery

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Introduction
Obesity is associated with hypothalamic inflammation (HI) in animal models. While MRI studies in humans also found an increased intensity in the MBH in obese subjects, it remains unclear (1) if HI causes neuronal death and (2) if HI reverses during weight loss.
Patients and methods
$n=50$ obese subjects and $n=50$ age- and sex-matched controls where examined. MRI scans including spectroscopy were performed. Also, detailed nutritional questionnaires, serum lipidomics, 16s rRNA microbiome sequencing data as well as array-based genotyping data were obtained. $n=10$ obese subjects underwent bariatric surgery followed by a second MRI.

Results
Obese subjects exhibit an increased intensity in the left, but not the right MBH compared to non-obese controls. The NAA/Cr ratio, a marker for neuronal cell count in spectroscopy, did not differ between the two groups indicating that the number of neurons might not be affected by the inflammatory process. After bariatric surgery, BMI and HOMA showed a significant improvement in the mean follow-up time of 3 months. However, the MRI intensity in the MBH did not change in the same time period, suggesting that bariatric surgery might not beneficially affect HI.
Conclusion
Obese human subjects exhibit an increased MRI intensity of the MBH suggesting HI. While HI is not reversed by a significant weight loss due to bariatric surgery, the finding that the number of neurons is not altered in the MBH by HI might suggest that the function of the MBH in terms of appetite regulation might be reversible.

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GP131

The liver of obese patients with hepatic steatosis exhibits a severe dysregulation of key splicing machinery components as compared to obese patients without hepatic steatosis

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Obesity, a disease that is growing at epidemic proportions worldwide, is caused by a combination of genetic and lifestyle factors. One of the most common pathologies associated with obesity is hepatic steatosis, an accumulation of fat within the liver that can progress to liver fibrosis, cirrhosis, and ultimately lead to hepatocellular carcinoma. There is emerging evidence that alternative mRNA splicing, the key mechanism providing transcript and protein diversity, is dysregulated in many tissues under adverse metabolic conditions, such as obesity and cancer. Moreover, the splicing variants generated within this process could contribute to the aggressiveness and comorbidities of these diseases. We hypothesized that an alteration in the splicing machinery could occur in obese patients with hepatic steatosis, which might ultimately be associated with the progression to hepatic fibrosis/cirrhosis/carcinoma. To address this question, an array of selected components of the major ($n=13$) and minor spliceosome ($n=4$), and associated splicing factors ($n=28$) was developed, and their expression levels were evaluated using a Fluidigm methodology, in a series of liver samples from obese (BMI >30) women with ($n=33$) and without ($n=9$) liver steatosis. Results revealed that expression of a number of relevant splicing factors (SRSF2, SND1, SRRM1, PTBP1, KHDRBS1) and spliceosome components (SF3Btv2, U2AF1, U2AF2, RNU6) was altered in steatosis vs non-steatosis liver tissues. Interestingly, some of these changes were associated with relevant clinical parameters, including glucose levels (i.e. SRSF2, U2AF1/2, KHDRBS1), gamma-glutamyltransferase (SRSF2, U2AF1, KHDRBS1), HDL (U2AF2, SND1) as well as with insulin, cholesterol, creatinine and HOMA-IR (i.e. RNU6). Finally, ROC analysis revealed that the expression of specific splicing factors, especially SRSF2, U2AF2, PTBP1 and RNU6, can clearly predict patients with or without hepatic steatosis. In conclusion, the expression of specific splicing machinery components is significantly altered in the liver of obese patients with hepatic steatosis. Ongoing studies would clarify the potential pathological implications of these findings, which could help to predict a worsening in steatosis, and may provide novel diagnostic biomarkers and therapeutic tools for this disease.

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GP132

The E_3 ubiquitin ligase MDM2 acts as a key determinant of hepatic VLDL-triglycerides and ketone body production in obesity

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Introduction
Obesity is a major risk factor for the development of hyperlipidemia and its related cardiovascular complications. Apart from its well-established role in cancer biology, the MDM2-p53 axis has been recently shown to regulate glucose and lipid metabolism. Our preliminary data indicated that MDM2 is dramatically induced in the liver of obese mice. In this study, we aimed to investigate the potential role of hepatic MDM2 in controlling systemic lipid homeostasis using a hepatocyte-specific MDM2 knockout (H-MDM2KO) mouse model.
Method
H-MDM2KO mice were generated by crossing $MDM2^{floxed}$ mice with transgenic mice expressing Cre recombinase under the control of albumin promoter. Eight-week-old male H-MDM2KO mice and its WT littermates were fed with a standard chow or a high fat high cholesterol (HFHC) diet for 24 weeks. Lipid metabolism and energy metabolism were measured during the 24-week monitoring period.
Results
Genetic deletion of hepatic MDM2 led to elevation of p53 level in the liver. H-MDM2KO mice and WT controls displayed similar body weight, lipid profile and energy metabolism under standard chow feeding. Despite of similar body weight and food intake, H-MDM2KO mice exacerbated obesity-induced hypertriglyceridemia and impaired fasting-induced ketogenesis when fed with HFHC. The elevated triglyceride levels in H-MDM2KO mice was due to VLDL-triglyceride production, whereas intestinal chylomicron-triglyceride synthesis or VLDL-triglyceride clearance were normal. QPCR analysis revealed that the genes involved in VLDL assembly such as ApoB and ketogenesis (HMGCL and HMGCS2) were upregulated in the liver of H-MDM2KO mice, whereas genes involved fatty acid oxidation (PPAR-alpha, MCAD and CPT1a) and lipogenesis (SCREBP1c and Lipin-1) were unchanged when compared to its WT controls.
Conclusion
Our results indicated that MDM2 is a key player in controlling VLDL-triglyceride secretion and ketogenesis, thereby maintaining lipid homeostasis. We will further investigate whether these MDM2 actions are mediated by p53 in the future.

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GP133

The ubiquitin-like pathway neddylation controls adipocyte differentiation, obesity and metabolism

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The ubiquitin-proteasome cascade has been described as a critical factor in adipocyte biology, insulin signaling and obesity, but the function of Nedd8, the ubiquitin-like protein with the closest homology to ubiquitin, remains unknown. Using 3T3-L1 preadipocyte cells, we found that MLN-4924, a specific neddylation inhibitor, blocks adipocyte differentiation. Screening for signaling and transcriptional factors driving adipogenesis, we found that neddylation blockade inhibits the expression of the master genes of adipogenesis, C/EBPα and PPARγ on RNA and protein levels. In 3T3-L1 mature adipocytes, MLN-4924 treatment reduced lipid droplets content without affecting lipolysis but fatty acids uptake, a process maintained by enzymes transcriptionally controlled by PPARγ. In adipocytes, MLN-4924 also strongly reduced C/EBPα and PPARγ expression as well as the expression of multiple downstream targets of PPARγ. Importantly, the PPARγ ligand, rosiglitazone reverted MLN-4924 effects on triglycerides lost. In addition, we performed a preliminary *in vivo* study in WT mice chronically treated with MLN-4924. Pharmacological blockade of neddylation *in vivo* prevented high fat diet (HFD)-induced body weight increase and reduced adipocytes hypertrophy. Furthermore, conditional adipocyte-specific neddylation-deficient ($Nae1^{Adipo\text{-}Cre\text{-}ERT2}$ KO) mice showed a decrease in body weight in obese (HFD 4 months) mice accompanied by changes in glucose tolerance.
Altogether, these results suggest that the inactivation of Nedd8 in fat cell precursors or mature adipocytes severely impairs adipocyte maturation and fat storage respectively by reducing C/EBPα and PPARγ levels.
Moreover, these observations demonstrate that neddylation, a new post-translational modification in adipocytes, is physiologically active in the regulation of adipocyte development, biology and metabolism.

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GP134

Prognostic factors and pathophysiology of diabetes remission after metabolic gastric bypass, sleeve gastrectomy and greater curvature plication: a randomized controlled trial

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Introduction
39% of morbidly obese patients have type 2 diabetes mellitus (T2DM) and 80% of them can achieve diabetes remission after bariatric surgery. However, there are few randomized studies comparing the metabolic results of different surgical techniques and the hormonal mechanisms involved.
Objective
To study and compare the improvement of T2DM and the hormonal pathways following three surgical techniques: metabolic gastric bypass (mGBP), sleeve gastrectomy (SG) and greater curvature plication (GCP).
Methods
Prospective, randomized controlled single-center study in patients with T2DM and morbid obesity. 45 patients aged 49.4 ± 7 years, BMI 39.4 ± 1.9 kg/m^2, initial HbA_{1c} 7.7 ± 1.9%; were randomly assigned (1:1:1) to the three surgical techniques. At baseline, one and 12 months a standard meal test was performed to determine GLP-1, GLP-2, PYY, ghrelin and glucagon concentrations.
Results
Twelve months after surgery, total weight loss was higher in mGBP compared with SG and GCP (−35.2 ± 8.1 vs −27.8 ± 5.4 vs −20.5 ± 6.8 kg, $P = 0.007$, $P < 0.001$, respectively). HbA_{1c} at one year was significantly lower in mGBP compared with SG and GCP (5.09 ± 0.62 vs 6.21 ± 0.82 vs 6.61 ± 1.30%, $P = 0.001$, $P = 0.001$). The percentage of patients with diabetes remission was higher in mGBP 80% vs 53.3% vs 20%. GLP-1 area under the curve (AUC) at month one and 12 was greater in mGBP than after SG and GCP. In the multiple regression analysis the absence of insulin treatment and the increase in GLP-1 AUC from baseline to month one were the factors associated with T2DM remission.
Conclusions
mGBP is the technique that has shown a higher rate of weight loss and T2DM remission. Factors associated with improved glycemic control are those that accompany a less evolved diabetes, and an enhanced secretion of GLP-1.

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GP135

Ventilatory anaerobic threshold six months after RYGB

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Introduction
Obesity is associated with high risk for coronary artery disease, high blood pressure, elevated serum cholesterol level, malignancy and Type 2 diabetes mellitus. After weight loss, especially after bariatric surgery there is improvement in blood pressure, metabolic parameters and ventilatory anaerobic threshold.
Material and methods
Ergospirometry (Shiller CS-200, Bruce protocol) was performed in 50 obese patients before and six months after R en Y gastric bypass. Baseline characteristics were: BMI 43.8 kg/m2, 43 ± 12.7 years of age (female $n = 37$, male $n = 13$). Changes in pulse rate, systolic blood pressure (SBP) in rest and maximal SBP, diastolic blood pressure in rest (DBP) and maximal DBP, ventilatory anaerobic threshold (VAT/VO2) and peak in oxygen consumption (VO2) were analyzed. Baseline VO2 less than 14 ml/kg per min was exclusion criteria for bariatric surgery.
Results
Change in pulse rate (98.7 ± 12.2 vs 88.01 ± 13.46/min) was significant ($P < 0.0001$). SBP in rest decreased (135 ± 14 vs 131 ± 13 mmHg) with significance $P = 0.017$. Max SBP decreased with high significance (181 ± 26 vs 162 ± 22 mmHg; $P < 0.0001$). DBP in rest also decreased (85 ± 8 vs 80 ± 9 mmHg; $P < 0.0001$) and max DBP decreased from 98 ± 12 to 92 ± 10 mmHg ($P = 0.002$). There was improvement in VAT/VO2 (17.8 ± 3.44 vs 20.86 ± 4.70 ml/kg per min; $P < 0.0001$) and in peak of oxygen consumption, VO2 (20.79 ± 3.63 vs4.97 ± 4.37 ml/kg per min; $P < 0.0001$).
Conclusion
Our results suggest that bariatric surgery could improve cardiorespiratory fitness. Ventilatory anaerobic threshold, oxygen consumption, pulse rate, maximal systolic and diastolic blood pressure as well as systolic and diastolic blood pressure in rest were improved six months after RYGB.

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GP136

A novel human fetal brown stem cell functional model to study brown adipogenesis

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The potential therapeutic applications of targeting brown adipose tissue open new clinical avenues in fighting against metabolic pathologies. However, due to the limited brown depots in adult humans, dramatically reduced after birth, solid cell models to study human brown adipogenesis and its pathophysiological regulation are urgently needed.
In our study, we characterized a novel human model of brown adipose stem cells, hfB-ASC, derived from fetal interscapular brown fat depots. After demonstration of the mesenchymal and stem nature of the isolated cells, we studied their differentiation potential, in particular, towards the brown lineage. Following *in-vitro* induced adipogenesis, these cells exhibit several features of brown fat cells, such as the elevated expression of mature and early brown markers, UCP-1 and PRDM16, respectively ($2^{-\Delta\Delta Ct}$: 2295 ± 864 and 19.3 ± 8.0 for UCP-1 and PRDM16), but not of white markers as leptin, compared to in-vitro differentiated white adipose stem cells. They maintain also a specific intrinsic differentiation program to functional brown adipocytes, and even spontaneously organize in organoid structures with brown features. Moreover, for the first time, we investigated the thermogenic and electrophysiological activity of the *in-vitro*-derived fetal brown adipocytes compared to their undifferentiated hfB-ASC precursors, in basal conditions and after acute administration of norepinephrine. Compared to adipocytes obtained from *in-vitro* differentiation of white adipose stem cells, brown adipocytes from hfB-ASC show a significantly increase in temperature vs. undifferentiated cells (Δtemperature: 0.30 °C ± 0.10, $P = 0.02$), as well as following acute administration of 10 μM norepinephrine (Δtemperature: 0.21 °C ± 0.20, $P = 0.02$).
In conclusion, starting from interscapular brown fat of human fetus, we developed and functionally characterized a novel physiological brown adipose stem cell model. This model may represent a unique opportunity for further studies on brown adipogenesis processes in humans, as well as the most suitable target to develop novel therapeutic approaches in order to stimulate brown activity in metabolic pathologies.

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GP137

Adipose tissue infiltration in normal-weight subjects and its impact on metabolic function

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Objectives
To study for the first time the differences in monocyte/macrophage infiltration, inflammation and adipogenesis in the subcutaneous and visceral adipose tissues of normal-weight subjects who differed in their degree of metabolic syndrome.

Methods
The study included 92 normal-weight subjects who differed in their degree of metabolic syndrome. Anthropometric and biochemical parameters were measured. RNA from subcutaneous and visceral adipose tissues was isolated, and mRNA expression of monocyte/macrophage infiltration (CD68, CD33, ITGAM, CD163, EMR-1, CD206, MerTK, CD64, ITGAX), inflammation (IL6, TNFα, IL10, IL1b, CCL2, CCL3) and adipogenic and lipogenic capacity markers (PPARgamma, FABP4) were measured. Additionally, cells derived from stromal vascular fraction from subcutaneous and visceral adipose tissues were isolated and expanded, and subsequently differentiated with an adipogenic media, measuring the mRNA expression of adipogenesis (PPARgamma, FABP4, ADRP, C/EBPalpha, LPL, LEP).
Results
Our data indicated a different degree of macrophage infiltration between adipose tissues, with a higher monocyte/macrophage infiltration in subcutaneous adipose tissue in metabolically unhealthy normal-weight subjects, while visceral adipose tissue remained almost unaffected. Moreover, adipogenesis function was decreased in patients with the metabolic syndrome in subcutaneous adipose tissue.
Conclusions
An increased macrophage infiltration of adipose tissue and its consequences, such as a decrease in adipogenesis function, may explain why both obese and normal-weight subjects can develop metabolic diseases or remain healthy.

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GP138

Dietary and weight loss effects on human gut microbiome diversity and metabolism

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Introduction
Changes in the gut microbiome have been associated with the development of obesity. The aim of the present study was to examine i) the effect of a formula based very-low-calorie weight loss diet (VLCD) on the gut microbiome of obese humans and ii) whether if potential changes are sustained during weight maintenance.
Patients and methods
The study consisted of 3 months VLCD (∼800 kcal/d) followed by 3 months of weight maintenance. 18 obese humans were examined (BMI 42.3 kg/m^2 (35.2–47.7)). A lean and an obese control group were included. Microbiome was characterized by performing high-throughput dual-indexed 16S rDNA amplicon sequencing of stool samples and subsequent analyses.
Results
At baseline, a difference in the Firmicutes/Bacteroidetes ratio was observed ($P=0.047$). The VLCD resulted in alterations in diversity from baseline to 3 months ($P=0.0053$). Acinetobacter is an indicator species for the observed effect (IndVal$=0.998$, $P=0.006$). Metabolic analysis revealed significant alterations of the bacterial riboflavin pathway from baseline to 3 months ($P=0.039$). However, the changes in diversity and bacterial metabolism induced by the VLCD diminished during the weight maintenance phase, despite sustained reductions in body weight and sustained improvements of insulin sensitivity.
Discussion
In obese humans a VLCD is able to beneficially alter both, gut microbiome diversity and metabolism, but these changes are not sustained during weight maintenance. This finding might in part explain the significant weight regain after VLCD- based therapies and might suggest additional measures to target the microbiome, e.g. fecal transplantation.

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Paediatric Endocrinology & Development

GP139

2nd year efficacy results of once-weekly administration of CTP-modified human growth hormone (MOD-4023): a phase 2 study in children with growth hormone deficiency

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Objective
Growth hormone (GH) replacement therapy currently requires daily injections. This may cause poor compliance, inconvenience and distress for patients. CTP-modified hGH (MOD-4023) has been developed for once-weekly administration in growth hormone deficient (GHD) adults and children. The 18 and 24 month efficacy of once-weekly subcutaneous (SC) administration of MOD-4023 was evaluated in a Phase 2 study in children with GH deficiency.
Design and methods
A one year, randomized, controlled Phase 2 study was conducted in 53 pre-pubertal children with GHD receiving once-weekly SC injections of one of three MOD-4023 doses (0.25, 0.48, and 0.66 mg/kg per week) vs daily hGH (34 μg/kg/day). Forty-six subjects were rolled over to continue with the same MOD-4023 dose in an open-label extension (OLE), which will routinely assess growth until marketing approval. Height velocity (HV) results during the 2nd year of MOD-4023 treatment for 45 patients were compared to historical controls (1). IGF-1 and IGFBP-3 were monitored as well.
Results
The analysis included 2nd year height velocity data for 45 patients. All three doses of MOD-4023 demonstrated promising 2nd year growth, while the two higher doses of MOD-4023 resulted in better growth in comparison to the lower dose of MOD-4023 (0.25 mg/kg per week), and in line with reported age- and GHD severity-matched historical control (1).
Conclusions
The efficacy of single weekly administration of MOD-4023 for the treatment of pediatric GHD patients was further confirmed during the 2nd year of treatment as part of the OLE of a Phase 2 study. This further affirms that a single weekly injection of MOD-4023 has the potential to replace daily hGH injections in children with GHD and provides additional efficacy data to support dose selection for OPKO's upcoming Phase 3 trial.

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GP140

Congenital adrenal hyperplasia: parents' experiences of treating their child's condition

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Patients with congenital adrenal hyperplasia (CAH) require life-long, daily glucocorticoid hormone replacement therapy. Currently, there is no licensed treatment for young patients and existing treatment requires adapting adult doses by crushing tablets. As primary caregivers, parents of young children with CAH often take on the responsibility for routine medication and adapting doses in times of stress or illness. There has been little research to date exploring parents' experiences and the challenges associated with treating CAH. The study was conducted by Genetic Alliance UK as part of the European Commission funded TAIN (Treatment of Adrenal Insufficiency in Neonates) Project, which aims to develop a new formulation of hydrocortisone for neonates and infants. Taking a mixed methods approach, Genetic Alliance UK captured the views of parents across three European countries. In 2014, 17 semi-structured interviews were conducted in the UK and analysed thematically. In 2015, an online survey was developed, piloted and disseminated widely to parents of children under the age of six in the UK, The Netherlands and Germany. Although parents reported that their child's condition was relatively well managed, many described a number of challenges associated with the treatment regime and made suggestions for how it could be improved. Interviewees experienced a 'latent anxiety' as well as disruption to their sleep, their daily routines and their work life. Many of the challenges were associated with the frequency of medication required and the importance of getting the right dose at the right time. Challenges were particularly acute for new parents when they left the supportive environment of the hospital.

The study has provided a unique insight into the wider impact of managing CAH, particularly from the perspective of parents. It has important implications for treatment in the future, and for the care and support provided to CAH families.

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GP141

Genomics and phenomics of Hashimoto's thyroiditis and dyshormonogenesis in hypothyroid children of South India

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Background
Dyshormonogenetic goiter and Hashimoto's thyroiditis are amongst the commonest causes of hypothyroidism in children and adolescents Worldwide. But, the genetic basis and their hypothyroid phenotypes are under-reported, especially from developing countries. In this context, we screened for dyshormonogenetic mutations in hypothyroid children with dyshormogenetic goiter (DH) and Hashimoto's thyroiditis (HT).
Material and methods
In this prospective multidisciplinary study, blood DNA of 42 hypothyroid children with dyshormogenetic goiter (DH) and Hashimoto's thyroiditis (HT) were studied with direct sequencing analysis for NIS, DUOX2 and TPO gene mutations. Detailed clinical, biochemical and follow-up data were analysed.
Results
Mean age of children was 11.35 ± 2.03 years (5–18). In the entire cohort, we detected 17/42 (40.4%) thyroid specific mutations. In HT, we detected eight mutations in 7/20 (35%) children of this cohort (six in *NIS* and two in *Tpo* genes). In DH, nine mutations in 8/22 (36%) children were detected. No mutations were observed in *Duox2* gene. All our mutations were localized in introns. Except for two homozygous polymorphisms, all other mutations were heterozygous in nature. Genotype-phenotype correlations shows statistically significant expression of autoimmune manifestations, goiter rate and positive family history.
Conclusions
NIS gene mutations were the most prevalent mutations in both HT and DH amongst South Indian children in this study. These mutations significantly influenced hypothyroid phenotypic traits such as severity of hypothyroidism, goiter rate, autoimmune associations and positive family history. More studies from varied geographic zones are needed to risk categorise hypothyroid phenotypes in children.

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GP142

Association between urinary magnesium and glycaemic control in children and adolescents with type 1 diabetes *mellitus*

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Background
Hypomagnesemia is common in patients with diabetes; possibly due to higher renal magnesium excretion in those patients. Hypomagnesemia seems to correlate with poor glycaemic control. The relationship between urinary magnesium (UMg) and glycaemic control is not known. We aimed to study the association between UMg and glycaemic control in a type 1 diabetes (T1D) pediatric population.
Methods
Study of a pediatric population with T1D attending the Pediatric Endocrinology Clinic at Hospital de São João, Porto, between May 2014 and April 2015. We prospectively included all patients with UMg in a first-morning-void urine sample. Glycated haemoglobin (HbA1c) was measured in a capilar blood sample using DCA 2000 analyser. Patients with good and poor glycaemic control (cut-off used: 7.5%) were compared. We studied the correlation between UMg and HbA1c using Spearman's rank correlation coefficient. A multivariate logistic regression model was built to study predictors of poor glycaemic control.
Results
We studied 48 patients. Mean age was 12 ± 4 years and 58.3% were male. Mean duration of T1D was 88 ± 43 months and mean HbA1c was 8.4 ± 1.4%. Median (IQR) UMg was 8.46 (5.36–12.33) mEq/l. Twelve patients (25%) had good glycaemic control. Patients with good glycaemic control were more frequently on *Continuous Subcutaneous Insulin Infusion* (CSII) (7 (58.3%) vs 7 (19.4%); $P = 0.02$) and had lower UMg (5.6 (3.1–7.7) vs 9.4 (6.8–12.4) mEq/l; $P = 0.01$). There were no differences in serum magnesium levels. UMg had a weak positive correlation with HbA1c ($\rho = 0.30$; $P = 0.04$) and T1D duration ($\rho = 0.28$; $P = 0.05$). UMg was a predictor of poor glycaemic control OR: 1.40 (95% CI: 1.05–1.85), $P = 0.02$; independent of age, T1D duration and CSII use.
Conclusions
UMg is an independent predictor of poor glycaemic control. Per each mEq/l increase of UMg there is a 40% higher risk of poor glycaemic control.

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GP143

Adolescent girls with hyperandrogenism – epidemiology and clinical features

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Hyperandrogenism in adolescent girls is medical and social problem, including hirsutism, seborrhea, severe acne, alopecia and hyperclitoridism.
Purpose
To study the frequency and clinical peculiarities of the hyperandrogenism (HA) in adolescent girls.
Patients and methods
The study included 2369 girls (aged 11–19 years). Patients were subjected to the clinical examination, ultrasound examination. Index of hyperandrogenism (HAI) were calculated (the Ferriman–Gallwey score).
Results
The investigation shows that 341 (14%) girls had HA. In 100% adolescents with HA had *acne*, *seborrhea* and menstrual disorders. Results showed that dysmenorrhea (99%) and hypermenstrual syndrome (80%) highly prevalent among patients with HA. Girls with HA observed median Ferriman–Gallwey scores of 13 (range: 7–18). The macromastia was found in 20 (9%), breast hypoplasia in two girls. The dysplasia of mammary glands (mastopathy) was diagnosed in all patients with macromastia. The morbid obesity (BMI ≧ 40 kg/m^2) was diagnosed in 26 (8%) girls with HAI > 12. In 99% adolescents with HA was found ultrasound signs multifollicular ovaries, in two girls had ultrasound signs polycystic ovary syndrome.
Conclusions
This study has shown that HA have been diagnosed in every tenth adolescent girls. The clinical features in girls with HA were hirsutism, menstrual disorders and multifollicular ovaries. The multifollicular ovaries in adolescents are indication for observation.

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GP144

Leptin directly stimulates parathyroid hormone secretion

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A relationship between obesity, plasma leptin concentration and primary hyperparathyroidism has been previously reported. To test the hypothesis that leptin directly stimulates parathyroid hormone (PTH) secretion, *in vivo* and *in vitro* experiments were conducted. In the *in vivo* studies leptin (200 μg/kg, ip) was administered to lean and obese (mutants that do not express active leptin

receptor) Zucker rats. The *in vitro* experiments were carried out by exposing rat parathyroid glands to increasing concentrations of leptin (0, 0.1, 0.25, 0.5, 1, 2 and 4 μg/ml). After leptin administration, PTH increased progressively in the lean but not in the obese rats reaching a maximum at 60 min (from 34.5 ± 3.7 pg/ml to 113.9 ± 23 pg/ml, $P = 0.01$) and then returned to baseline by 180 min. Changes in PTH after leptin administration were not associated with changes in $1,25(OH)_2$-vitamin D, fibroblastic growth factor 23 (FGF23), calcium or phosphorus. Moreover, *in vitro*, a dose-dependent increase in PTH secretion that started at leptin = 0.25 μg/ml and kept rising until reaching a zenith at leptin = 2 μg/ml was identified. In conclusion, the results of the present study demonstrate a direct stimulatory effect of leptin on PTH secretion and suggest the existence of an endocrine axis between adipose tissue, where leptin is mainly produced, and the parathyroid glands.

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GP145

Impact of fetal exposure to testosterone on fetal insulin sensitivity tissues – a morphological and molecular approach

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Polycystic ovary syndrome (PCOS) is the most common cause of infertility in reproductive aged women affecting ∼5–10% of women of reproductive age worldwide. PCOS patients are characterized by infertility disorders, obesity, insulin resistance and hyperandrogenemia that persists during pregnancy. This finding allowed to suggest the hypothesis that this intrauterine environment could affect the fetus, reprogramming the insulin sensitivity of the offspring. We have developed an ovine model to study the reprogramming effect of testosterone (T) during pregnancy in order to emulate the hyperandrogenemia observed in PCO pregnant mothers. The objective of this work was to assess the morphometry of fetal tissues and the mRNA expression of key molecules in the insulin pathway of insulin sensitivity tissues in ovine female fetal tissues exposed to T in utero. Pregnant Suffolk-down sheep were treated with 30 mg T propionate twice weekly from day 30–90 of pregnancy and 40 mg from day 90 to 120 of pregnancy. Pregnant control sheep received the vehicle of T. At 120 days of pregnancy and under bioethical procedures, female fetuses were obtained by cesarean surgery. Fetal skeletal muscle, visceral adipose tissue and pancreas were collected for morphological (HE and NADH-Tr stain) and RNA expression of insulin receptor (IR), insulin receptor substrate 1 and 2 (IRS-1, 2), AKT, PKC and glucose transporters (GLUT2 and GLUT4). Control and T- fetuses showed similar pattern in the development of skeletal muscle (number of fibers, CSA and proportional phenotype of fibers), adipose tissue (area and perimeter of adipocyte) and pancreas (islet area and number of islets). On the other hand, there was higher expression of IR signaling factors and GLUT2 and GLUT4 in pancreas. These results provide evidence that T induces transcriptional activation of insulin signaling in our animal model of PCOS without effect on morphological organogenesis.

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GP146

Breast development in male-to-female transgender patients after one year cross-sex hormonal treatment

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Background
In male to female transgender patients breast development is a key part in the process of feminization using cross sex hormone therapy. In the Endocrine Society's clinical guideline 'Endocrine treatment of transsexual persons' the onset of breast growth is estimated as 3–6 months after starting cross sex hormone treatment. The maximum breast growth however is seen after 2–3 years. But how much growth, in centimeters or cup-sizes, we can expect is not clear. With this in mind we want to objectify the breast growth after one year of cross sex hormone treatment in male to female transgender patients.
Objective
To examine the absolute increase in breast circumference corrected for chest circumference in male to female transgender subjects included in the ENIGI database who are treated with cross sex hormone therapy for 1 year.
Methods
All male to female transgender subjects included in the ENIGI database who have been treated with cross sex hormones for 1 year are eligible for this study. According to the ENIGI protocol patients are examined in the outpatient clinic every 3 months. During this outpatient clinic visits several features are examined and measured including breast and chest circumference. Missing values we imputed with multiple imputation(ICE) in Stata.
Results
One-hundred-forty-two male to female subjects are eligible for this study. Mean breast circumference increased from 93.9 (s.d. 11.6) cm to 97.2 (11.1), while chest circumference remained stable (88.6 (10.7) cm). The mean difference between breast and chest diameter after one year was 7.5 (3.0) cm. This implicated a C-cup (16–18 cm) in 2%, B-cup (14–16) in 4%, A-cup (12–14) in 8% and AA-cup (10–12) in 10% of the patients. After 1 year, 76% had a breast-chest difference smaller than 10 cm.
Conclusions
Our study shows a modest breast development after 1 year. Future studies need to determine whether breast circumference is an accurate method to estimate breast development during cross sex hormone treatment and what the effects are on longer treatment. Furthermore, a topic of interest is which factors influence breast development in transgender treatment.

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GP147

Prenatal metformin treatment prevents estradiol increase and partially improves ovarian function in offspring of obese mothers

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Obesity epidemic is one of the major concerns in the world. Worryingly, a high percentage of pregnant women have obesity, which could imply several consequences. Maternal obesity leads to different abnormalities in pregnancy and delivery. In addition, recent studies show that the offspring of obese mothers has an increased probability to suffer cardiovascular, metabolic and reproductive diseases. We have previously demonstrated that exposure to a high fat diet is related to obesity, liver dysfunction, increased serum estradiol, advanced puberty and ovarian follicular alterations in the progeny. We aimed to determine if metformin prevents this developmental reprogramming produced by a high fat diet exposure. Sprague Dawley rats were distributed in three groups: Control diet (13% Kcal in fat); High Fat Diet (HF) (60% Kcal in fat, Research Diet, USA) and HF + Metformin (60% Kcal in fat + metformin 150–200 mg/kg in tap water). Diet was administered for 1 month previous to pregnancy, during pregnancy and nursing. Metformin was administered from 1 week previous to pregnancy until weaning of the offspring. Metformin did not affect the weight gain during pregnancy and failed in prevent increased weight in offspring of obese mothers. At postnatal day (PND) 14 metformin tended to prevent the estradiol increase while at PND60 metformin significantly prevented the estradiol increase. Coherently, hepatic CYP3A2 (enzyme that metabolizes estradiol) decreased in offspring obese mothers and this decrease was prevented by metformin treatment. The generation of ovarian cyst was also prevented by metformin in offspring of obese mothers. In conclusion, metformin prevented some reproductive alterations triggered by maternal obesity on the offspring.

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GP148

Adrenal dysregulation in children who were born extremely premature – a pilot study

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Introduction
The prevalence of hypertension in children and adolescent who were extremely preterm newborns (EP; $\leq$32 gestational weeks) has been found to be higher than in those born at term. The causes have not been well characterized. Studies support that adrenal dysregulation might be a consequence of prematurity.
Objectives
To determinate if children who were EP had higher adrenal hormones and vascular remodeling biomarker than term newborn ($\geq$38 gestational weeks).
Design, subjects and methods
A pilot – cross sectional study was design. Children from the community were invited ($n=235$, range 5.1–15.5 years old); twelve were EP (gestational age between 30 and 32 weeks) and 223 were born at term (gestational age between 38 and 40 weeks). Anthropometric characteristics and aldosterone, plasma renin activity (PRA), aldosterone/PRA ratio (ARR), cortisol and cortisone were measured. Metalloproteinasa 2 (MMP-2) activity was measured as a vascular remodeling biomarker.
Results (median)
Both groups were comparables in age (10.2 vs 11.6 years; $P=0.075$), BMI-SDS (1.13 vs 1.18; $P=0.434$), height-SDS (0.48 vs 0.23; $P=0.434$) and blood pressure corrected by gender, age and height (systolic index 1.09 vs 1.06, $P=0.184$ and diastolic index 1.11 vs 1.10 $P=0.797$). EP newborn vs term newborn showed similar aldosterone (ng/dl): 7.6 vs 6.2 ($P=0.439$) and PRA (ng/ml per h): 2.16 vs 2.3 ($P=0.779$) but higher ARR (3.9 vs 2.6 $P=0.039$) and higher MMP-2 activity (Arbitrary units): 1.88 vs 1.50 ($P=0.009$). No statistical differences in cortisol, cortisone and cortisol/cortisone ratio were observed.
Conclusions
This pilot study showed that children who were extremely preterm newborn have higher ARR and vascular remodeling than children born at term, despite similar blood pressure. Future studies to assess the importance of these findings in early prevention of hypertension are warranted.

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Pituitary – Clinical

GP149

Impact of AIP and Gαi-2 proteins on clinical features of sporadic GH-secreting pituitary adenomas

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Introduction
In sporadic acromegaly, downregulation of AIP protein of the adenomas associates with invasive tumour features and reduced response to somatostatin analogue treatment. AIP is a regulator of Gαi signaling, but it is not known how the biological function of the Gαi pathway is controlled.
Aim
To study somatic GNAS and AIP mutation status, AIP and Gαi-2 protein expressions, Ki67 proliferation indices, and clinical parameters in patients having primary surgery because of acromegaly at a single centre between years 2000 and 2010.
Results
Sixty patients (F/M 31/29, mean age 49 (median 50), mean follow-up 7.7 (range 0.6–14.0) years) underwent primary surgery. Of the 60 adenoma specimens, four (6.8%) harboured an AIP and 21 (35%) an activating GNAS (Gsp+) mutation. All adenomas stained positive for Gαi-2, and 55/56 AIP mutation negative adenomas stained positive for AIP protein. Altogether 13/56 (23%) adenomas had low AIP protein levels, and 14/56 (25%) low Gαi-2 staining. A regression model including Gαi-2, Ki 67 proliferation indices and GH (measured 3 months after surgery), best explained the variance in the AIP protein level ($P=6.03\times10^{-9}$). The majority (43%) was explained by Gαi-2 level only. Gsp+ status was not related to AIP or Gαi-2 protein levels, but associated with lower KNOSP grade ($P=0.0018$, $r=0.332$), tumours restricted to the sella ($P=0.026$, $r=0.320$), and higher preoperative prolactin concentrations ($P=0.0017$, $r=0.032$). However, the associations were not significant after correction for multiple testing.
Conclusions
We demonstrate, for the first time, that AIP protein expression associates with Gαi-2 protein intensities in sporadic somatotropinomas. This may indicate a synergetic effect on somatostatin signaling. Low AIP protein levels associate with higher proliferation activity and higher postoperative serum GH, indicating more aggressive adenomas. The AIP mutation rate of 6.8% is fairly high and probably reflects the genetic composition of the Finnish population.

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GP150

Treatment of acromegaly increases BMD but reduces Trabecular Bone Score – a longitudinal study

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Background
Bone turnover is increased in active acromegaly. Despite normalization of bone turnover after treatment, the risk for vertebral fractures remains increased. Gonadal status, but not bone mineral density (BMD) is correlated to vertebral fracture incidence. Trabecular and cortical bone are differentially affected by GH and IGF-1. The trabecular bone score (TBS) is related to bone microarchitecture and provides further information not captured by BMD measurement.
Methods
This longitudinal study included 38 patients with acromegaly consecutively recruited between 2005 and 2015. Dual-energy X-ray absorptiometry (DXA) scans and blood samples for measuring bone turnover (PINP, CTX1) were acquired at baseline and 1 year after transsphenoidal surgery. TBS was analysed at L1-L4 with TBS iNsight software.
Results
Following treatment, the mean TBS decreased by 3.0% ($\pm$7.0), from 1.33 ($\pm$0.15) to 1.29 ($\pm$0.14); $P=0.007$, whereas BMD L1-L4 increased by 3.2% ($\pm$4.9) from 1.20 ($\pm$0.19) to 1.24 ($\pm$0.20) g/cm^2; $P<0.001$. The changes in BMD and TBS were not correlated ($P=0.87$).
TBS change in men was –4.5% ($\pm$6.7%; $P=0.003$) and in women –0.3% ($\pm$6.8%; $P=0.85$). There was a trend towards a difference in changes between men vs women ($P=0.063$).
Mean BMD L1-L4 increased in men +0.050 ($\pm$0.051; $P<0.001$, but not in women +0.016 ($\pm$0.061; $P=0.36$) g/cm^2, ($P=0.073$ for interaction depending on gender).
BMD increased in ultradistal radius and total body (all $P<0.01$). The increase of BMD was associated with a decrease in PINP and CTX1 ($P<0.001$) and with lower levels of PINP and CTX1 at follow-up ($P<0.02$).
Conclusion
Treatment of acromegaly impacts TBS and BMD at L1-L4 in different manners. The reduction of bone turnover markers predicts the increase in BMD. The DXA changes in bone parameters were more pronounced in men. Alterations in trabecular bone architecture may explain the persistent fracture risk despite the increase in BMD after disease control.

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GP151

Longitudinal assessment of response to treatment with oral octreotide capsules in patients with acromegaly: post-hoc analysis of a phase 3 trial

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Introduction
Although biochemical markers of acromegaly disease activity, including GH and IGF1, may fluctuate from day-to-day, biochemical treatment response in clinical trials is generally monitored using single-point analyses. Accordingly, longitudinal evaluations may assess patient status more accurately. In a phase 3 trial, oral octreotide capsules (OOC) demonstrated sustained composite endpoint GH and IGF1 response for $\leq$13 months in 151 patients with acromegaly previously managed with somatostatin analog injections (IGF1 $<1.3\times$ ULN and GH $<$2.5 ng/ml). Here we report longitudinal IGF1 and GH analyses from this trial.
Methods
Trial design comprised core (dose escalation [DE] + fixed dose [FD]; $\leq$7 months) and extension ($\leq$13 months) periods. IGF1 was assessed monthly; mean integrated GH was assessed upon up-titration and at the beginning and end of each period. For the primary study endpoint, response was determined by a composite including IGF1 and GH at End-of-Treatment (EoT). In this *post hoc* analysis, longitudinal IGF1 and GH are expressed as time-weighted average (TWA) incorporating all measurements; response is defined as a composite including TWA IGF1 $<1.3\times$ ULN and TWA GH $<$2.5 ng/ml.
Results
At end of core period, 108/151 patients (72%) achieved response by TWA, vs 98/151 (65%) per initial EoT composite endpoint analysis. Of patients who entered FD ($n=110$), 88 (80%) completed the core period (7 months) and achieved response by TWA, vs 82/110 (75%) per EoT analysis. Of patients who entered FD as responders by protocol ($n=91$), 86 (95%) maintained TWA response through extension ($\leq$13 months), vs 77/91 (85%) per EoT analysis.
Conclusions
Based on a composite using TWA IGF1 and TWA GH, OOC demonstrated a greater response vs the single-point analysis at EoT. Analyses incorporating all evaluations may provide more accurate and clinically meaningful assessments of overall treatment response than single-point evaluations. Therefore, ongoing studies using OOC evaluate response using all evaluations.

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GP152

Effects of hydrocortisone substitution on blood pressure – results from an RCT

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Background
Patients with secondary adrenal insufficiency show increased risk of cardiovascular disease. Higher doses of glucocorticoid replacement are related to an unfavourable metabolic profile. In the absence of randomized controlled trials assessing the effect of hydrocortisone dose on haemodynamics and blood pressure regulation, we determined effects of a higher vs a lower glucocorticoid replacement dose on blood pressure, the renin-angiotensin-aldosterone system (RAAS) and sympathetic activity.
Materials and methods
Forty-seven patients treated for secondary adrenal insufficiency participated in this randomized double blind cross-over study (Clinicaltrials.gov identifier: NCT01546922). Patients were randomized to receive 0.2–0.3 mg hydrocortisone/kg body weight followed by 0.4–0.6 mg hydrocortisone/kg body weight or *vice versa*, both for 10 weeks. Each treatment period was followed by a study visit including measurement of blood pressure and collection of fasting blood samples.
Results
The higher dose of hydrocortisone resulted in a mean (s.d.) increase in body weight of 0.5 (1.7) kg ($P=0.045$), an increase in systolic blood pressure of 5 (12) mmHg ($P=0.011$) and a borderline significant increase in diastolic blood pressure of 2 (9) mmHg ($P=0.050$). A median [interquartile] plasma potassium decrease was observed of -0.1 [-0.3; 0.1] mmol/l ($P=0.048$). Furthermore, the higher dose of hydrocortisone led to a decrease in plasma renin concentrations of -1.4 [-4.7; 1.2] pg/ml ($P=0.015$), a decrease in aldosterone levels of -27 [-101; 9] pmol/l ($P=0.020$) and a decrease in aldosterone-to-renin ratio (ARR) of -2.6 [-5.6; 1.4] pmol/ng ($P=0.047$). In addition, a decrease of -0.104 [-0.242; 0.016] ($P=0.001$) nmol/l in plasma normetanephrine concentration was found on the higher dose of hydrocortisone, while metanephrines remained unchanged.
Conclusion
The higher dose of hydrocortisone led to an increase in systolic and diastolic blood pressure accompanied by a suppression of the RAAS and in sympathetic activity. This suggests that hydrocortisone affects multiple pathways involved in blood pressure regulation even at concentrations generally considered to be physiological.

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GP153

Once-monthly injection of pasireotide LAR reduces urinary free cortisol (UFC) levels in patients with Cushing's disease: Results from a randomised, multicentre, phase III trial

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Background
Twice-daily formulation of pasireotide, a pituitary-directed therapy, is approved for treatment of Cushing's disease. Here we present data from a phase III study designed to evaluate the more convenient once-monthly long-acting release (LAR) formulation of pasireotide (approved for acromegaly) in patients with Cushing's disease.
Methods
Patients with persistent, recurrent, or de novo Cushing's disease (not candidates for surgery) and baseline mean UFC (mUFC) $\geq$1.5-$\leq 5\times$ULN (mean of three 24-h UFC collections) were randomised (double-blind) to pasireotide LAR 10 mg or 30 mg; at month 4, dose could be increased to 30 mg or 40 mg, respectively, if mUFC $>1.5\times$ULN. Patients ($N=150$; baseline median mUFC $2.4\times$ULN) were stratified for analysis by screening mUFC: stratum 1 (mUFC $\geq$1.5-$<2\times$ULN) and stratum 2 (mUFC 2-$5\times$ULN). The primary efficacy endpoint was the proportion of patients with mUFC $\leq$ULN at month 7, regardless of dose titration.
Results
The primary efficacy response rate was 41.9% (95%CI, 30.5–53.9%) and 40.8% (95%CI, 29.7–52.7%) in 10 mg ($n=74$) and 30 mg ($n=76$) dose groups, respectively. In stratum 1 (milder disease), 52% (13/25) patients in both 10 mg and 30 mg groups had mUFC $\leq$ULN. In stratum 2, 36.7% (18/49) and 35.3% (18/51) patients in 10 mg and 30 mg groups, respectively, had mUFC $\leq$ULN. Median percentage decrease in mUFC from baseline to month 7 was 48% in both dose groups. Two deaths reported in the 30 mg group (cardiorespiratory failure and pulmonary artery thrombosis) were not considered drug-related. The safety profile of pasireotide LAR was consistent with that of twice-daily pasireotide. Fifty (68%) and 61 (80%) patients experienced hyperglycaemia-related adverse events in the 10 mg and 30 mg groups, respectively; of these 2 (2.7%) and 3 (3.9%) patients discontinued.
Conclusions
Results from this phase III study in patients with Cushing's disease show that pasireotide LAR treatment effectively lowers UFC levels with a tolerability profile similar to the twice-daily subcutaneous formulation, and provides a convenient monthly administration schedule.

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GP154

Outcome predictors in profound hyponatremia – a prospective 12-month-follow-up study

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Introduction
Hyponatremia is the most common electrolyte abnormality in clinical practice and given its impact on mortality and morbidity a relevant medical condition. Nevertheless little is known about factors influencing long-term outcome.
Methods
This is a prospective observational 12 months follow-up study of patients with profound hyponatremia ($\leq$125 mmol/l) admitted to the medical emergency department of two tertiary care centers in Switzerland between 2011 and 2013. We analysed the association of different clinical and laboratory parameters with following three outcomes: 1-year-mortality, rehospitalisation and recurrent profound hyponatremia.
Results
Median [IQR] initial serum sodium (s-sodium) level of the 281 patients included (median age 72 years [61-80]) was 120 mmol/l [116–123]. During the study-period 58 (20.6%) patients died. The majority (56.2%) was hospitalized at least once again, 28.5% even repeatedly. Recurrent hyponatremia was observed in 42.7%, being profound again in 16%. Beside relevant comorbidities (assessed by the Charlson Comorbidity Index) the following two parameters revealed significant association with the main outcome mortality – also after multivariate adjustment: 'initial s-sodium level' (Odds Ratio [OR] 1.14, 95% Confidence Interval [CI] 1.01-1.29, $P=0.036$) and 'corrected s-sodium $\geq$135 mmol/l at discharge' (OR 0.47, 95% CI 0.23–0.94, $P=0.034$).
Severity of hyponatremia showed an inverse correlation with mortality. Thus, we compared patients with s-sodium levels $\leq$120 mmol/l to those with levels $>$120 mmol/l; the latter had a significant higher mortality rate than patients with lower s-sodium levels (27.8% vs 14.8%, $P=0.0078$). Also etiology of hyponatremia differed: patients with s-sodium level $\leq$120 mmol/l were more likely to have drug induced hyponatremia (49% vs 29.4%, $P=0.0008$), whereas hypervolemic hyponatremia was more common in patients with initial s-sodium level above 120 mmol/l (15.9% vs 7.7%, $P=0.033$).
Conclusion
Hyponatremia goes along with a high 1-year-mortality, recurrence and rehospitalisation rate. The inverse correlation of hyponatremia-severity and mortality emphasizes the importance of the underlying disease, which rather determines outcome than hyponatremia itself.

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GP155

Plasma apelin concentrations in patients with polyuria-polydipsia syndrome

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Background
Apelin and arginine-vasopressin (AVP) are antagonists in the regulation of body fluid and osmotic homeostasis. So far there exist no data about apelin levels in patients with polyuria-polydipsia syndrome (PPS).
Methods
Plasma apelin and copeptin concentrations were measured in 15 patients with complete central diabetes insipidus (cDI), in seven patients with complete nephrogenic diabetes insipidus (nDI) and 19 patients with primary polydipsia (PP) and were compared to those in 113 healthy volunteers.
Results
Median plasma apelin levels were highest in patients with nDI (413 pmol/l (IQR 332; 504), $P=0.01$) and lower in patients with PP (190 pmol/l (172; 215), $P<0.001$) or cDI (209 pmol/l (174; 241), $P=0.02$) compared to healthy volunteers (254 pmol/l (225; 311)). Plasma apelin to copeptin ratio in patients with PP (53 pmol/pmol (38; 92), $P>0.9$) was similar to healthy volunteers (57 pmol/pmol (37; 102)). In contrast, apelin to copeptin ratio was higher in patients with cDI (89 pmol/pmol (73; 135), $P=0.02$) and lower in patients with nDI (7 pmol/pmol (6; 10), $P<0.001$) compared to healthy volunteers.
Conclusion
In PP, normal plasma apelin to copeptin ratio attests a normal water homeostasis. In contrast, in patients with cDI or nDI the increased or decreased apelin to copeptin ratio, respectively, reflects a disturbed osmotic and body fluid homeostasis.

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GP156

Natural history of a large cohort of pituitary incidentalomas in Italy

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In this observational, retrospective, multicenter study, we analyzed data from 300 patients with pituitary incidentaloma followed in two Italian Hospital Center. We observed a predominance of female patients (65%), with an a mean age at diagnosis of 49 years (higher in men than women, 57 vs 45 years old). The main reason to perform imaging were neurological symptoms not related to the presence of adenomas (56%). Most cases were microadenomas (56%), and macroadenomas were more frequent in males than females (75 vs 28%).
The first hormonal evaluation showed at least one pituitary deficiency in 21% of patients (35% of macroadenomas vs 10% of microadenomas). Hormonal follow up (median 3 years, range 0–27) showed a worsening in pituitary function in 7% of patients (7% of microadenomas vs 9% of macroadenomas). Radiological follow up (median 3 years, range 0–32) showed an increase of dimension in 27 patients (more frequent in macroadenomas, 33 vs 10%) and a reduction in 16% of cases. However, radiological and biochemical modification were concordant only in the 69% of patients; in six patients we witnessed a deterioration of pituitary function in presence of an adenoma stable or in reduction. Overall, 66 patients underwent surgery; in 58 cases surgical indication was formulated at diagnosis, while in eight patients during follow up due to growth of the lesion.
In our population, accordingly with the data available in literature, macro-adenomas are more frequently found in males, and more prone to volumetric growth over time. Hormonal function is altered in about 1/5 of patients at diagnosis, with further deficit onset during the follow up; these changes are not always in agreement with radiological changes, remarking that, besides radiological assessement, a periodical biochemical follow up is also needed in these patients.

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GP157

Prevalence of acromegaly in patients referred for sleep apnea syndrome (SAS): results of ACROSAS Study

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Introduction
Acromegaly is a rare disease (estimated prevalence 40–125 cases per million) resulting from GH/IGF1 hypersecretion, mostly by pituitary adenomas. SAS has a prevalence of up to 80% in acromegalic patients. The high frequency of acromegaly-related comorbidities and delayed diagnosis although effective treatments exist, make it necessary a screening of acromegaly in at risk populations.
Aim
In a national multicenter study, to determine the prevalence of acromegaly in patients referred for SAS.
Patients and methods
Patients referred at Grenoble university hospital and in ten private practice centers for SAS suspicion were recruited consecutively from November 2013 to October 2014. Clinical data and co-morbidities were collected via an electronic case report form of French Sleep Observatory (OSFP). Patients had polysomnography/respiratory polygraphy and systematic serum IGF-1 determination. When serum IGF1 levels were elevated for age and sex, IGF1 level and GH during OGTT were performed and patients with GH/IGF1 hypersecretion had MRI of the pituitary and were examined by an endocrinologist for definite diagnosis of acromegaly.
Results
873 patients with suspected SAS were included: 817 patients had IGF1 and 755 had polysomnography or respiratory polygraphy. SAS (Apnea/Hypopnea Index >15/h) was present in 567 patients and absent (AHI <15/h) in 188 patients. SAS patients were men (68%), older (54 ± 12 vs 48 ± 13 years, $P<0.0001$), had higher BMI (31.4 ± 6.6 vs 29.0 ± 6.0 kg/m^2, $P<0.0001$) and lower IGF1 levels (142 ± 63 vs 162 ± 61 ng/ml, $P<0.0001$). 5 SAS patients had a 10% increase of IGF1 above the upper limit of normal and two SAS patients had acromegaly due to GH-secreting pituitary macroadenoma.
Conclusion
The prevalence of acromegaly is greater than 35/10 000 in our patients with SAS and higher than in the general population. Further studies are needed to evaluate the cost-effectiveness of IGF1 screening in patients with SAS.

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GP158

Differentiated pharmacokinetics of levoketoconazole (COR-003), the single 2S,4R-enantiomer of ketoconazole, a new investigational drug for the treatment of Cushing's syndrome

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Ketoconazole is a 50/50 racemic mixture of two enantiomers (2S,4R and 2R,4S) used off label in the US for the treatment of endogenous Cushing's syndrome by virtue of adrenal cortisol synthesis inhibition.
COR-003 (levoketoconazole) is the more potent single (2S,4R) enantiomer of ketoconazole (KTZ) to inhibit adrenal cortisol synthesis and is currently being investigated in a multinational Phase 3 study for the treatment of endogenous Cushing's syndrome.
In a three period cross-over study in 24 healthy subjects dosed with ketoconazole at an oral dose of 400 mg QD, plasma concentrations of the two enantiomers were measured on Day 5 after 4 day QD oral dosing with 400mg ketoconazole and a single 80-mg dose of atorvastatin on Day 5. Maximal plasma concentrations of the 2S, 4R enantiomer were about three-fold higher (6.1 µg/ml, coefficient of variation 40.7%) than those of the 2R, 4S enantiomer. This pattern was also observed in a Phase 2a study in 37 patients with type 2 diabetes mellitus dosed for 14 days with 400 mg QD oral ketoconazole. PK data of KTZ, COR-003 and 2R, 4S were modeled using a population approach with the software package NONMEM version 7.2. PK modeling of KTZ, COR-003 and 2R, 4S suggested dose-proportional exposure for all analytes and linear PK, and revealed a greater clearance of 2R, 4S and a monophasic plasma-time curve of COR-003 in contrast to KTZ with two peaks.
Study treatments were safe and well tolerated. Headache, nausea, diarrhea, and back pain were the most frequently reported AEs.
Taken together, PK data show that COR-003 reaches higher plasma concentrations with reduced clearance compared to 2R,4S, potentially indicating reduced hepatic metabolism. Mechanistic nonclinical studies are being conducted to further investigate the differentiated PK profile of COR-003 and implications for hepatotoxicity and efficacy.

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GP159

The partner perspective of the impact of pituitary disease: results from a focus group study

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Background
Patients with pituitary disease demonstrated Quality of Life (QoL) impairment. From other chronic diseases it is known that partners of patients also report impairments in QoL. Furthermore, it is observed that well-being of patients is associated with the well-being of their partners. To date, no data are available on the well-being of partners of patients with pituitary disease. Therefore, the aim of the present study was to explore well-being of partners of patients with pituitary disease.
Methods
Four independent focus groups of 4–6 partners of patients with pituitary disease (Cushing's disease, non-functioning adenoma, acromegaly, prolactinoma) were conducted. In two sessions, these groups of partners discussed the impact of the pituitary disease on their own lives. Verbatim transcripts were analysed using a grounded theory approach.
Results
Partners reported the negative influence of pituitary disease on their own lives, including worries (related to the pituitary disease and the medical treatment), coping difficulties (uncertainty about comforting or encouraging the ill partner, problems with adaptation, high sense of responsibility, differences in coping styles), relationship issues (changes the in relationship, communication with ill partner, viewing the ill partner differently, issues regarding sexuality, issues with the desire to have children), social issues (difficulties in communication about the disease, lack of sympathy from environment, changes in social network, negative impact on family, negative impact on work) and unmet needs regarding care (insufficient information, no recognition for certain complaints, dissatisfaction about aspects of medical care).
Conclusion
This first explorative focus group study in partners of patients with pituitary disease elucidates the negative impact on their lives. This study emphasizes the importance of not only paying attention to the psychosocial impact of patients during medical consultation, but also to their partners. Furthermore, information obtained in this study can be used for the development of a disease-specific questionnaire for partners of patients with pituitary disease, in order to further quantitatively assess their well-being, as well as for optimizing psychosocial care not only for patients, but also for their partners.

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GP160

Anthropometric factors have significant influence on the outcome of the GHRH-arginine test – establishment of normative data

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Background
Adult GH deficiency (GHD) is diagnosed by provocative testing of GH secretion. To improve diagnostic accuracy of GHRH plus arginine (GARG) testing, we

evaluated the influence of age, BMI, and sex. Furthermore, we aimed to established normative data for an automatic immunoassay specifically measuring 22kD human GH.
Methods
Eighty-seven patients with hypothalamic-pituitary disease and 200 healthy controls were enrolled. Controls were prospectively stratified for sex, age (18–30, 31–50, ≥51 years), and BMI (<25 {lean}, 25-29.9 {overweight}, ≥30 kg/m^2 {obese}), with at least ten subjects in each subgroup. All participants received GHRH (1 μg/kg i.v.) and L-arginine (30 g via 30 min infusion), with blood sampling over 120 min. GH was measured by immunoassay (iSYS, IDS). ROC analysis identified cutoffs with ≥95% specificity for GHD.
Results
In controls, multiple stepwise regression analysis revealed that BMI (21%, $P<0.0001$), sex (20%, $P<0.0001$), and age (5%, $P<0.001$), accounted for 46% of GH peak level variability during GARG. Fifty-one patients with ≥2 additional pituitary hormone deficiencies were considered GHD, the remaining 36 patients were GH sufficient (GHS). Comparison of peak GH during GARG (GHD vs GHS+controls) revealed an overall cutoff of 3.9 ng/ml (sensitivity 86%, specificity 95%). BMI-adjusted cutoffs were established for males and females (lean: 6.5 vs 9.7 ng/ml; overweight: 3.5 vs 8.5 ng/ml; obese: 2.2 vs 4.4 ng/ml).
Conclusion
BMI and sex account for most of the variability of peak GH levels during GARG. Consequently, the diagnostic accuracy of the GARG test is significantly improved by use of adjusted cutoffs. Especially gender differences during GH stimulation testing may require more attention for the correct diagnosis of GHD.

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GP161

Evaluation of MRI T2-signal intensities of GH-secreting pituitary macroadenoma in treatment-naïve acromegalic patients receiving primary treatment with lanreotide autogel (LAN-ATG) 120 mg

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Introduction
Pituitary MRI T2-signal intensity may be associated with the response to somatostatin analogue therapy in acromegalic patients. Here, we explore how best to evaluate MRI T2-signal intensity of GH-secreting pituitary macroadenoma using data from the PRIMARYS study (NCT00690898; EudraCT2007-000155-34).
Methods
PRIMARYS assessed tumour volume reduction (TVR) on MRI in treatment-naïve acromegalic patients with GH-secreting pituitary macroadenoma receiving monthly LAN-ATG 120 mg primary therapy over 1 yr. In this additional post hoc analysis, pituitary MRI T2-signals from 85 acromegalic patients were evaluated at baseline and during treatment. T2-signal intensity was defined as hypo-/iso-/hyper-intense based on comparison of adenoma/normal cerebral parenchyma, according to a qualitative method (visually comparing tissues); and two quantitative methods using ratio of signal intensities of region-of-interests in either tissues (adenoma vs grey matter only (first method) or vs grey matter and white matters in adjacent lobes (second method)). Here, we present the results of baseline MRI evaluations according three methods.
Results
A greater proportion of patients' macroadenoma were categorized as hypointense using the qualitative method (59%) than the quantitative methods (36 and 20%) (Table 1). In addition, more of the patients showing full hormonal control or tumoural response had hypointense macroadenoma using the qualitative than using the quantitative methods (Table 1). There were no notable differences in baseline demographics between groups. The exception was a trend towards smaller TV in the hypointense group observed with all three methods; this was most evident, albeit still non-significant, on the qualitative method (mean (95% CI) TV, mm^3: hypointense, 2041 (1435–2647); isointense, 3280 (2120–4441); hyperintense, 8533 (0–23843)).
Conclusion
A simple qualitative method could be used to identify MRI T2-signal hypointensity in treatment-naïve acromegalic patients with GH-secreting pituitary macroadenoma, which could be associated with later favourable responses to LAN-ATG primary therapy. Regression analyses are ongoing to determine associations between T2-signal intensity and treatment response.

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Table 1 Hormonal control (GH ≤2.5 ng/ml and IGF-1<ULN) and tumour response (TVR ≥20%) at last visit according to baseline MRI T2-signal intensity.

	Qualitative method			Quantitative first method			Quantitative second method		
T2-signal intensity	Overall (*n*=85)	Hormonal control (*n*=30)	Tumoural response (*n*=53)	Overall (*n*=85)	Hormonal control (*n*=30)	Tumoural response (*n*=53)	Overall (*n*=85)	Hormonal control (*n*=30)	Tumoural response (*n*=53)
Hypointense, *n* (%)	50 (59)	20 (67)	38 (72)	31 (36)	14 (47)	25 (47)	17 (20)	8 (27)	14 (26)
Isointense, *n* (%)	31 (36)	8 (27)	13 (25)	44 (52)	13 (43)	25 (47)	40 (47)	14 (47)	26 (49)
Hyperintense, *n* (%)	4 (5)	2 (7)	2 (4)	10 (12)	3 (10)	3 (6)	28 (33)	8 (27)	13 (25)

GP162

Hippocampal and cerebellar atrophy in patients with Cushings disease

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Objective
Cushing's disease (CD) may cause atrophy of different regions of the human brain, mostly affecting the hippocampus and the cerebellum. This study evaluates the use of 3-T MRI of newly diagnosed patients with CD to detect atrophic degeneration with voxel-based volumetry.
Methods
Subjects with newly diagnosed, untreated CD were included and underwent 3-T MRI. Images were analyzed using a voxelwise statistical test to detect reduction of brain parenchyma. In addition, an atlas-based volumetric study for regions likely to be affected by CD was performed.
Results
Nineteen patients with a mean disease duration of 24 months were included. Tumor markers included adre-nocorticotropic hormone (median 17.5 pmol/l), cortisol (949.4 nmol/l), and dehydroepiandrosterone sulfate (5.4 μmol/l). The following values are expressed as the mean±S.D. The voxelwise statistical test revealed clusters of significantly reduced gray matter in the hippocampus and cerebellum, with volumes of 2.90±0.26 ml (right hippocampus), 2.89±0.28 ml (left hippocampus), 41.95±4.67 ml (right cerebellar hemisphere), and 42.11±4.59 ml (left cerebellar hemisphere). Healthy control volunteers showed volumes of 3.22±0.25 ml for the right hippocampus, 3.23±0.25 ml for the left hippocampus, 50.87±4.23 ml for the right cerebellar hemisphere, and 50.42±3.97 ml for the left cerebellar hemisphere.
Conclusion
Patients with untreated CD show significant reduction of gray matter in the cerebellum and hippocampus. These changes can be analyzed and objectified with the quantitative voxel-based method described in this study.

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GP163

Medical treatment of macroprolactinomas Escalation and de-escalation of dopamine agonist dose

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Background
Cabergoline (CAB) is the most effective dopamine agonist (DA) used for the treatment of macroprolactinoma. Few data on the dose of CAB necessary for achieving and maintaining normal prolactin (PRL) levels are available. We aimed to study these parameters in a large series of patients with macroprolactinomas
Methods
We retrospectively analysed the clinical, biochemical and imaging features at diagnosis and the treatment response to CAB (dose necessary for normalizing and thereafter for maintaining normal PRL levels on long term) in 260 patients (125F) with macroprolactinomas followed at the Service d'Endocrinologie et des Maladies de la Reproduction in Hôpital Bicetre Hospital, Le Kremlin-Bicêtre, France.

Results
At diagnosis, the median [min; max] age, PRL level and maximal tumor diameter was 32.7 [10.6; 83.1] years, 680 [6; 38000] ng/ml and 20 [10; 110] mm, respectively. PRL levels were normalized in 68.4% of patients under CAB treatment. Weekly mean (SD) CAB dose necessary for normalizing and thereafter for maintaining normal PRL levels were 1.30 (1.02) and 0.74 (0.62) mg ($P \leq 1.10^{-4}$), respectively. CAB dose de-escalation was tried in 84 (53.5%) of the 153 patients in whom CAB succeeded to normalize PRL levels. This dose de-escalation was successful in 77 out of 84 patients (91.7%). The main differences between patients in which dose de-escalation was tried and the others are the duration of CAB treatment ($P \leq 1.10^{-4}$), the duration between the introduction of CAB and the time of PRL normalization ($P = 0.05$) and the tumor volume at time of PRL normalization ($P = 0.02$).
Conclusion
The dose of CAB necessary for maintaining normal PRL level on long term is lower than the dose necessary for normalizing PRL levels. Dose de-escalation after normalization of PRL levels is possible and potentially useful when considering the potential side effects of the drug which depends on its cumulative dose.

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GP164

Ipilimumab-induced hypophysitis in melanoma patients: a single centre experience

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Ipilimumab, a monoclonal antibody against CTLA-4, is licenced for the treatment of metastatic melanoma (dose of 3 mg/kg for four cycles intravenously). It can cause immune-related adverse reactions (IRAEs) in multiple organs, with hypophysitis the most common endocrine IRAE. We carried out a retrospective analysis of 171 ipilimumab-treated patients in one centre for endocrinopathies.
Results
Nine cases (six female, mean age 64 years, range 42–76) of ipilimumab-induced hypopituitarism were identified (incidence 5.3%). Mean time to hypophysitis was 64 days (17–188 days, mean 3.4 cycles) post-commencement of ipilimumab. All patients were identified at clinic visits or presented acutely; fatigue, headache and blurred vision were the most common symptoms. At diagnosis, three patients were hyponatraemic; hormone deficiencies were: eight cortisol (no recovery), eight TSH (four recovered), seven gonadotrophin (three recovered), no DI. Seven patients had IGF-1 measured (two high, two low). Five patients had low TSH (0.03–0.54;NR0.55–4.78 mU/l) with low normal fT4 (12.7–15.5; NR10–22 pmol/l) the month before diagnosis. Five patients' MRI scans demonstrated enlarged pituitary; follow-up scans showed normal pituitary in three, one reduced pituitary size and one empty sella. Four patients had additional IRAEs (three colitis, one dermatitis, one hepatitis). Four patients received high dose glucocorticoids (2-methylprednisolone, 2-dexamethasone), with no difference in hormone recovery, however one developed diabetes mellitus and another steroid psychosis. No other endocrinopathy was diagnosed.
Discussion
In our series, the incidence of ipilimumab-hypophysitis was approximately 5%. Cases occurred from the first cycle to several months after treatment completion. A normal pituitary on MR does not exclude hypopituitarism. The low TSH documented a month prior to clinical presentation may be a valuable marker of early hypophysitis and represent an opportunity for earlier diagnosis. Treatment with high dose glucocorticoids (as recommended by manufacturers) is of uncertain value and can lead to side effects. Hypopituitarism is rarely reversible and not a reason to discontinue ipilimumab.

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GP165

Remission, recurrence and control rates in patients with ACTH-dependent Cushing's syndrome– a monocentric, retrospective analysis

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Introduction
Transsphenoidal surgery is the gold standard in Cushing's disease and recurrence is a major risk. We wondered which impact remission and recurrence might have on control rates of hypercortisolism and conducted a systematic analysis of our cohort of patients with Cushing's syndrome after undergoing surgical therapy.
Methods
We analysed the course of the disease in 74 patients with ACTH-dependent Cushing's syndrome (63 Cushing's disease (CD); 11 ectopic Cushing's syndrome (ECS)). All patients underwent surgery as first line therapy and in cases where relapse occurred, each received further therapy. The outcomes of interest were biochemical remission/control, clinical remission and recurrence, with evaluations conducted annually from the time of first treatment (follow-up time: 1–38 years).
Clinical remission was defined by the absence of Cushing stigmata. Biochemical remission/control was defined as normal urinary free cortisol levels, normal salivary cortisol levels at midnight and/or cortisol <1.8 µg/dl after 1 mg overnight dexamethasone suppression test. Data analysis was conducted using the Kaplan-Meier method.
Results
In patients with CD the biochemical control rates at 1, 2 and 3 years were 77.2, 81.8, and 77.2%. In contrast, patients with ECS showed considerably higher remission rates with 88.8% at 1 year and 100% at 2 and 3 years. The cumulative recurrence free remission rate in CD was 71.4% at 1 and 2, and 54.2% at 5 years. In patients having second transsphenoidal surgery the remission rate was poor with 50% at 1 and 2 years, and 40% at 5 years.
Conclusions
The outcome of patients in remission 1 year after initial surgery is associated with higher remission rates in the long term, while the absence of remission after 1 year, or the occurrence of early relapse are related to a noticeably poorer outcome.

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GP166

Auditory changes in acromegaly

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Introduction
Certain sensory system functions are affected somehow in acromegaly, however auditory complications have not been identified in detail yet. It is possible that widespread changes in acromegaly may also affect auditory system. We aimed to determine the changes involving auditory system in cases with acromegaly.
Methods/design
Otological examination of 41 cases with acromegaly (active $n = 22$, inactive $n = 19$) were compared with that of age and gender-matched 42 healthy subjects (HS). All cases in acromegaly group (AG) underwent examination with pure tone audiometry (PTA), speech audiometry for speech discrimination (SD), tympanometry, stapedius reflex (SR) evaluation and otoacoustic emission (OAE) tests whereas the control group had only otological examination and PTA. Additionally, previously performed paranasal sinus computed tomography of all cases with acromegaly and control subjects were obtained to measure the length of Internal Acoustic Canal (IAC).
Results
In AG and HS PTA values were 20 (15–30) and 13 (12–15) dB in right ears ($P < 0.001$) and, were 20 (13–28) and13 (12–15) dB in left ears ($P < 0.001$). SD scores in AG and HS were 92 (84–96)% and 96 (92–96)% in right and, 92 (84–96)% and 96 (92–96)% in left ($P = 0.002$). IAC width in AG was narrower compared to that in CG (In AG 4.5 (4.1–5.3) mm and in CG 4.9 (4.4–6.2), $P = 0.04$ for right ears. In AG 4.5 (4.2–5.4) mm and in CG 5.2 (5–7) mm $P = 0.009$ for left ears). PTA values of AG in left ears had positive correlation with GH and IGF1 levels ($r = 0.4$, $P = 0.02$ and $r = 0.3$, $P = 0.03$). Thirteen (32%) cases in AG had hearing loss, 7 (54%) was sensorineural type and 6 (46%) was conductive type hearing loss.
Conclusion
Acromegaly may cause certain changes in auditory system. These changes may be multifactorial causing both conductive and sensorioneural defects.

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GP167

Sleep apnea in patients with acromegaly – prevalence, diagnosis and risk factors

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Introduction
Patients with acromegaly have an increased mortality, mainly due to cardiovascular and respiratory diseases. Sleep apnea is related to hypertension, stroke and cardiovascular diseases and is reported to occur in 11–30% of acromegaly patients, according to retrospective studies based on diagnostic ICD-codes. However, in smaller prospective studies sleep apnea is found in about 70% of patients with active acromegaly and 40% after biochemical control. This difference raises the suspicion that sleep apnea may be an underdiagnosed complication of acromegaly.
Methods
This was a prospective cross-sectional multicenter study of 260 patients (128 women) with acromegaly registered in the Swedish Pituitary Registry. At a single outpatient visit (2013–2014), previous diagnosis and treatment for sleep apnea and cardiovascular diseases were assessed, data on smoking and anthropometry were collected, IGF1 concentrations were measured and the Epworth Sleepiness Scale was completed. Patients with clinical suspicion of undiagnosed sleep apnea were referred for sleep studies.
Results
75/260 (29%) patients were previously diagnosed with sleep apnea. In 57% of these sleep apnea was diagnosed before acromegaly was diagnosed. After screening (Epworth Sleepiness Scale) and sleep studies, sleep apnea was found in another 20 (8%) patients, resulting in a total prevalence of 37%. The risk for sleep apnea (after adjustment for age and gender) was increased with higher BMI, IGF-1 and index finger circumference. Sleep apnea was not significantly associated with stroke/TIA, diabetes or hypertension.
Conclusion
Sleep apnea is a frequent complication in acromegaly related to overweight and IGF-1. Awareness of this complication is good in Sweden. However, a simple screening questionnaire and subsequent sleep study revealed previously undiagnosed sleep apnea in 8% of the patients. Screening for sleep apnea is recommended in acromegaly patients especially those with high BMI and IGF-1. In addition, collaboration between sleep clinics and endocrinology departments may enhance earlier diagnosis of acromegaly.

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GP168

Dynamics of adrenocorticotropin after stimulation with metyrapone (DYNAMO)

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Purpose
To investigate the kinetics of adrenocorticotropin (ACTH) following oral metyrapone administration and describe differences between ACTH-deficient and non ACTH-deficient subjects.
Methods
Patients from a tertiary endocrine center at a University Hospital in Munich, Germany, were tested. Metyrapone (Metopirone, HRA Pharma, France) was administered with a dosage of 40 mg/kg bodyweight at 0800 h. Consecutive levels of ACTH were determined at 0, 60, 120, 180, and 240 min. Patients were categorized according to their need of glucocorticoid substitution. The study was approved by the local Ethics Committee with a limitation to 25 patients.
Results
Of 25 patients, 15 (60%) were female. Mean age was 52.3 years (range 21–79). ACTH (mean (± S.D.)) was 12.3 (±8.7) pg/ml before stimulation and 104.7 (±114.9), 84.9 (±65.4), 82.2 (±65.1), and 102.7 (±83.5) pg/ml at 60, 120, 180, and 240 min, respectively. Cortisol (mean (±S.D.)) was 10.6 (±5.1) µg/dl before stimulation and 2.6 (±2.1), 1.7 (±0.9), 1.6 (±0.9), and 1.6 (±0.9) µg/dl at 60, 120, 180, and 240 min, respectively. There was an 8.51-fold and a 7.65-fold rise in ACTH compared to the basal level ($t=0$) at 60 and 120 min, respectively. Analyzing groups as categorized by the course of clinical follow up (±13.6 months; range 0–39 months), there were significant differences in ACTH concentrations at 60 min (166.2 vs 21.3 pg/ml; $P<0.001$) and at 120 min (121.8 vs 27.7 pg/ml; $P<0.001$). Using ROC analysis of those patients who remained free of glucocorticoid substitution with ACTH at 60 min, and ACTH at 120 min, AUCs of 0.83 ($P=0.007$) and 0.92 ($P=0.001$) were achieved, respectively.
Conclusion
In contrast to previous reports, we found a significant rise in ACTH concentration as soon as one hour after oral metyrapone administration. Early ACTH values seem to estimate the pituitary corticotrophic function.

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Receptors & Signalling

GP169

Chemotherapy resistance and metastasis-promoting effects of thyroid hormone in hepatocarcinoma cells are mediated by suppression of FoxO1 and Bim pathway

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide, and systemic chemotherapy is the major treatment strategy for late-stage HCC patients. Poor prognosis following chemotherapy is the general outcome owing to recurrent resistance. Recent studies have suggested that in addition to cytotoxic effects on tumor cells, chemotherapy can induce an alternative cascade that supports tumor growth and metastasis. In the present investigation, we showed that thyroid hormone (TH), a potent hormone mediating cellular differentiation and metabolism, acts as an anti-apoptosis factor upon challenge of thyroid hormone receptor (TR)-expressing HCC cells with cancer therapy drugs, including cisplatin, doxorubicin and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). TH/TR signaling promoted chemotherapy resistance through negatively regulating the pro-apoptotic protein, Bim, resulting in doxorubicin-induced metastasis of chemotherapy-resistant HCC cells. Ectopic expression of *Bim* in hepatoma cells challenged with chemotherapeutic drugs abolished TH/TR-triggered apoptosis resistance and metastasis. Furthermore, *Bim* expression was directly transactivated by *Forkhead box* protein *O1* (*FoxO1*), which was negatively regulated by TH/TR. TH/TR suppressed FoxO1 activity through both transcriptional downregulation and nuclear exclusion of FoxO1 triggered by Akt-mediated phosphorylation. Ectopic expression of the constitutively active FoxO1 mutant, FoxO1-AAA, but not FoxO1-wt, diminished the suppressive effect of TH/TR on *Bim*. Our findings collectively suggest that expression of *Bim* is mediated by FoxO1 and indirectly downregulated by TH/TR, leading to chemotherapy resistance and doxorubicin-promoted metastasis of hepatoma cells.

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GP170

Altered exression of circadian clock genes in polyglandular autoimmune syndrome type III

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Introduction
CLOCK system is a highly conserved, ubiquitous molecular 'clock' which creates internal circadian rhythmicity under the influence of light/dark information. CLOCK system is regulated by the coordinated activation/inactivation of several transcription factors, including the CLOCK, the BMAL1 and other essential regulators, such as the Pers, Crys and RORs. The present study aimed to evaluate the circadian rhythm of clock-related genes expressed in patients with polyglandular autoimmune syndrome type III (PASIII).
Methods
Sixteen patients diagnosed with PASIII and nine healthy controls were enrolled. Patients and controls were age and gender-matched. All patients had normal adrenal function. We analysed mRNA and protein expression by real-time PCR and western blot analysis of CLOCK-related and glucocorticoid receptor (GR) genes isolated from the peripheral blood mononuclear cells (PBMCs) from blood

samples drawn at 0800 and 2000 h. At the same time, plasma *cortisol and ACTH* were also measured by chemiluminescence. Statistical analysis were performed with spss,vs 20.

Results

Our data showed a significant increase in the evening to morning *CLOCK*, *GR*, *BMAL1*, *ROR* and *PER3* mRNA expression ratio ($R_{pm/am}$) in patients compared to controls ($P=0.006$, $P=0.04$, $P=0.004$, $P=0.02$ and $P=0.004$ respectively). In patients the amplitude of cortisol circadian variation ($\Delta F_{0800–2000\ h}$) demonstrated a significant positive correlation with the $R_{pm/am}$ of *CLOCK*, *BMAL1* and *Per 3* expression ($P=0.033$, $P=0.02$ and $P=0.03$ respectively) whereas in controls $\Delta F_{800–2000\ h}$ presented a significant negative correlation with the $R_{pm/am}$ of *CLOCK* and *BMAL1* ($P=0.07$ and $P=0.007$). No significant correlation was found between $\Delta F_{800–2000\ h}$ and *GR* or *ROR* expression, neither in patients nor in controls.

Conclusions

These findings suggest that there is an abberant expression of clock-related genes in patients with PASIII compared to healthy controls. Daily pattern expression of five circadian clock genes was disrupted in patients with PAS III indicating a possible association with the pathogenesis of the disease.

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GP171

Zebrafish as a new model to study *in vivo* the functional consequences of human THRA variants

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Introduction

Since 2012, different heterozygous mutations in the *THRA* gene have been described in patients with resistance to thyroid hormone alpha (RTHα). The associating symptoms are reminiscent of untreated congenital hypothyroidism (growth retardation, psycho-neuromotor disorders, delayed bone development and bradycardia) but with raised T3/T4 ratio and normal TSH levels. All genetic abnormalities act in a dominant negative (DN) manner against functional receptors due to reduced T3-binding or defective interaction with corepressors or coactivators of the ligand-binding domain. Therefore, RTHα patients present variable sensitivity to TH treatment. We previously described that zebrafish embryos expressing a DN form of *thraa* recapitulate the key features of RTHα, and that zebrafish and human receptors are functionally interchangeable.

Methods

In this work, we present a simplified model obtained by direct mRNA microinjection into zebrafish eggs of several human *THRA* variants (D211G, A263V, A382PfsX7, E403X and F397fs406X). Using a series of molecular and analytical approaches (WISH, IHC, ELISA) we studied the embryonic development of cardiovascular, skeletal and nervous systems, which are directly involved in the T3-dependent TRα action. Additionally, thyroid and pituitary function, as well as the T3 and T4 contents were analysed.

Results

All *THRA*-injected embryos show defects in several tissues of variable entity: altered cardiovascular development, incomplete formation of cartilages and bones, reduced number motorneurons that is reflected by defective zebrafish locomotion. Furthermore, changes in deiodinases expression (high *dio2*, low *dio3a* and *dio3b* levels) in presence of normal thyroid and pituitary markers, could explain the high T3/T4 ratio observed in *THRA*-injecting embryos, as in RTHα cases. Interestingly, the treatment with high T3 dose efficiently rescue most of these defects only in D211G- and A263V-injected embryos, conserving part of the T3-binding activity and transactivation properties.

Conclusion

Zebrafish represent a new '*biotool*' to delineate the functional impact of new *THRA* variants *in vivo*.

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GP172

Increased 17beta-hydroxysteroid dehydrogenase type 1 mRNA level is correlated with poor prognosis in endometrial cancer

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Endometrial cancer (EC) is estrogen dependent and several enzymes control the local availability of these steroids by activating (i.e. aromatase, sulfatase, 17beta-hydroxysteroid dehydrogenase type 1 – HSD17B1) or deactivating estrogens (sulfotransferase, 17beta-hydroxysteroid dehydrogenase type 2 – HSD17B2). Imbalances in these enzymes are implied in EC development.

In the present study, it is evaluated whether imbalances in these enzymes are also associated with EC prognosis.

Tumour tissue collected directly after hysterectomy of 175 EC patients was included; 141 endometrioid (49 Grade I, 53 Grade II and 39 Grade III) and 34 non-endometrioid tumour types. Most tumours were estrogen receptor positive (72%). The mRNA levels of aromatase, sulfotransferase, sulfatase, HSD17B1 & HSD17B2 were measured using micro-array analyses. Patients were clustered according to the mRNA enzyme levels using quartiles.

It was observed that patients with high HSD17B1 mRNA levels (4th quartile) had a significantly poorer prognosis compared with patients with low HSD17B1 levels (1st, 2nd and 3th quartiles) ($P=0.007$). No significant correlation in the levels of HSD17B2, aromatase, sulfotransferase, sulfatase and patient prognosis was observed.

In conclusion, high HSD17B1 mRNA level, predicted to increase the availability of local estrogens, is correlated with poor prognosis in EC patients. Hence, HSD17B1 is a potential prognostic marker. Validation of these results in independent cohorts is required.

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GP173

The changing 'steroid metabolome' across the spectrum of non-alcoholic fatty liver disease

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Introduction

Dysregulated glucocorticoid (GC) metabolism has been implicated in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). NAFLD extends from simple steatosis, to inflammation (steatohepatitis/NASH), fibrosis and consequent cirrhosis. It is often regarded as the hepatic manifestation of the metabolic syndrome and is independently associated with increased liver and cardiovascular mortality. Changes in GC metabolism have thus far been described in small numbers of patients. 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) regenerates active cortisol (F) from inactive cortisone (E), whilst A-ring reductases 5α and 5β reductase (5αR/5βR) inactivate cortisol to dihydro and subsequently tetrahydro metabolites (THF/5αTHF). Both pathways are implicated in the development and progression of NAFLD.

Methods

Using gas chromatography/mass spectrometry, we analysed steroid metabolites in spot urine samples (corrected for urinary creatinine) in a large cohort of patients with biopsy proven NAFLD/NASH ($n=39$) alongside patients with cirrhosis ($n=44$), and compared them to healthy controls without liver disease ($n=58$).

Results

Total urinary cortisol metabolites were significantly different across all three groups allowing discrete separation ($P<0.0001$), with the highest levels seen in patients with NASH. Interestingly, 11β-HSD1 activity (reflected by the THF+5αTHF/THE ratio) was significantly increased in patients with cirrhosis in comparison to NASH or healthy controls ($P<0.0001$). A-ring reductase activity (THF/5αTHF ratio) did not differ significantly across the three groups. Using computerized machine learning analysis, we identified distinct clusters of patients, with complete separation between those with cirrhosis and healthy controls (ROC AUC=0.99).

Conclusion

We have identified steroid metabolic pathways that appear differentially regulated across the spectrum of NAFLD. This not only offers the potential to identify discrete targets amenable to intervention, but through the adoption of an unbiased computational approach, we have raised the possibility of utilizing this technique as a non-invasive assessment of the stage and severity of liver disease.

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GP174

5β-reductase (AKR1D1) is a regulator of glucose homeostasis in human hepatocytes and development of model systems to define its role in metabolic liver disease

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Non-alcoholic fatty liver disease is the hepatic manifestation of the global epidemic of metabolic disease. Steroid hormones, including glucocorticoids and sex steroids, regulate metabolic phenotype, and in addition, bile acids have recently been identified as potent metabolic regulators. 5β-reductase (AKR1D1) is predominantly expressed in the liver and is a crucial regulator of steroid hormone clearance as well as bile acid synthesis. Its role in pathogenesis of metabolic disease has not been examined. We have therefore developed systems to define the enzymology of human AKR1D1 in cell free assays, to determine the impact of manipulation of AKR1D1 expression and activity in human hepatocyte models and we propose that AKR1D1 regulates glucose flux in human liver. B21 bacteria cells were transformed with an AKR1D1 construct and recombinant protein extracted and purified. A high-throughput assay was developed to determine AKR1D1 activity, substrate specificity and enzyme kinetics. AKR1D1 activity was inhibited by Finasteride (selective 5αR2 inhibitor), but not Dutasteride (non-selective 5αR inhibitor). AKR1D1 mRNA expression was characterized in four different hepatoma cell lines (Hep3b, HepG2, C3A and Huh7.0) as well as primary cultures of human hepatocytes. Over-expression and siRNA knockdown of AKR1D1 in HepG2 cells were performed and confirmed using qPCR. Changes in gene expression were paralleled by functional activity as measured by cortisone clearance and tetrahydrocortisone generation using GC/MS. AKR1D1 knockdown increased the mRNA expression of the glucose transporters GLUT1 and GLUT9, as measured by qPCR (GLUT1: 0.6 ± 0.1 vs 1.71 ± 0.1, $P < 0.05$; GLUT9: 0.58 ± 0.05 vs 1.35 ± 0.08, $P < 0.05$). In addition, AKR1D1 knockdown also increased the extracellular glucose concentration in the cell culture media (3.7 ± 0.33 vs 5.36 ± 0.5 umol/mg, $P < 0.05$) with evidence of enhanced gluconeogenesis through increased PEPCK mRNA expression (0.13 ± 0.03 vs 0.36 ± 0.01AU, $P < 0.05$). AKR1D1 over-expression did not impact upon cellular metabolic phenotype. We have characterised human AKR1D1 in cell-free systems and in established liver cell models. Furthermore, we have successfully manipulated AKR1D1 expression and activity and identified it as a potent regulator of glucose homeostasis within human hepatocytes.

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GP175

Differential roles of estrogen receptors (ERα and ERβ) in seminiferous epithelium: in vivo agonist studies in adult rats

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Estrogen, through its receptors, plays an important role in regulation of spermatogenesis. The importance of estrogen is highlighted with the reports that environmental estrogens have deleterious effects on spermatogenesis and have been associated with declining sperm counts in men. Although estrogen receptors (ERα and ERβ) have been localised in the seminiferous epithelium; their precise roles are yet unclear as *in vivo* estradiol treatment would signal through both the ERs. It is important to understand the effects of activation of estrogen signaling through both the receptors since several environmental estrogens have different binding affinities to the two ERs. Hence we had developed *in vivo* selective ER agonist administration models in adult male rats to decipher the individual roles of the ERs. Treatment with both ERα and ERβ agonists decreased sperm counts after 60 days of treatment. This study was aimed at understanding the factors contributed, by the two ERs, to the decreased sperm counts. Treatment with ERα agonist causes an arrest in differentiation of round spermatids into elongated spermatids, mainly due to down-regulation of genes involved in spermiogenesis by activation of estrogen signaling through ERα. ERβ agonist administration reduces sperm counts due to spermiation failure and spermatocyte apoptosis. Spermiation failure observed was due to defects in tubulobulbar complex formation because of decrease in expression of genes involved in actin remodelling. The increase in spermatocyte apoptosis could be due to increase in oxidative stress conditions and decrease in anti-apoptotic genes. Our results suggest that the ERs regulate distinct aspects of spermatogenesis. ERα is mainly involved with regulation of spermiogenesis, while ERβ regulates spermatocyte apoptosis and spermiation. Activation of estrogen signaling through either of the receptors can affect their respective processes during spermatogenesis and lead to low sperm output. These observations can be useful in understanding potential effect of environmental estrogens on spermatogenesis.

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GP176

Luteinizing hormone and human chorionic gonadotropin (hCG) action on the same receptor results in different *in vitro* intracellular signaling in mouse primary Leydig cells

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Luteinizing hormone (LH) and human chorionic gonadotropin (hCG) are two glycoprotein hormones regulating development and reproduction. Despite binding the same receptor (LHCGR), they elicit different intracellular signaling. *In vitro* non-equivalence of hCG and LH was previously demonstrated in human primary granulosa cells. The aim of this study is to compare the effects of LH and hCG in mouse primary Leydig cells *in vitro*, naturally expressing the murine receptor (l hr). Although hCG is absent in mice, lhr retains the ability to binds both these human gonadotropins and shares 80% identity with the human LHCGR. Testis from 3/5-months-old C57BL6 mice were collected and Leydig cells were isolated by density gradient, plated and treated by increasing doses of recombinant LH and hCG (1 pM–100 nM range). We evaluated cAMP production and testosterone synthesis by ELISA, ERK1/2 and CREB phosphorylation by Western blotting, gene expression by real-time PCR. Despite no different gene expression and testosterone production was found, hCG is about 10-fold more potent than LH in inducing cAMP accumulation (hCG $EC_{50} = 18.64 \pm 10.14$ pM; LH $EC_{50} = 192.00 \pm 53.96$ pM; Mann–Whitney's *U*-test; $P < 0.05$; $n = 4$) and higher levels of ERK1/2 (hCG: 6646.1 ± 1492.1; LH: 2214.1 ± 464.8 – relative units) and CREB (hCG: 2318.3 ± 495.9; LH: 1360 ± 395.3 – relative units) (means ± S.E.M.) (Two-way Anova and Bonferroni post-test, $P < 0.05$; $n = 4$) phosphorylation at the highest dose used (100 nM). We demonstrated that hCG and LH treatment results in quantitatively but not qualitatively different signaling in Leydig cells *in vitro*, differing to that previously described in human primary granulosa cells naturally expressing the human receptor. The high levels of cAMP/PKA and pERK1/2 activation induced by hCG may rely on not complete aminoacids identity (about 75%) between the LHCGR and lhr hinge regions, which are fundamental for proper hormone binding and signal transduction. Our results support that LH and hCG are not equivalent at molecular levels.

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GP177

Characterization of the signaling and testicular functions of bone morphogenetic protein 8

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Previous studies have indicated that targeted depletion of *Bmp8* in mice can cause the reduction of germ cells in the postnatal testis and this further leads to male infertility, indicative of its importance in the maintenance of spermatogenesis. However, except the genetic impacts, no direct signaling pathway of BMP8 in cells has been interpreted *in vitro* due to the lack of functional BMP8 proteins. To solve this, we firstly generated different constructs for producing the recombinant BMP8 proteins in the prokaryotic and eukaryotic expression systems. With the bioactive recombinant BMP8 proteins generated, we found that BMP8 is able to activate the BMP signaling by promoting the phosphorylation of Smad1/5/8. In the reporter assays using HEK293T cells, overexpression in combination with knockdown experiments indicated that ALK3 and ALK6 of the type I receptors and ACVR2A and BMPR2 of the type II receptors can be the candidates to form the receptor complex for conducting BMP8-driven signaling. BMP8 was shown to be expressed in the testis of neonatal mice by immunoblotting and its expression is further localized in spermatogonia by immunofluorescence staining. In addition to characterization of the receptor identities of BMP8 in spermatogonia, we also found that BMP8 is able to induce differentiation of spermatogonia by increasing Kit expression. It also suppressed the expression of the GDNF-mediated self-renewal genes. Thus, our findings conclude that BMP8, capable of promoting spermatogonia differentiation at least, participates in the completion of spermatogenesis.

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GP178

Salivary testosterone to androstenedione (T/A4) ratio is significantly higher in PCOS patients and accompanied with an adverse metabolic phenotype

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Background
The aim of this study was to evaluate salivary androgen measurements via liquid chromatography-mass spectrometry as a non-invasive tool for the diagnosis of polycystic ovary syndrome (PCOS) and the assessment of metabolic health.
Methods
Saliva and serum samples of 274 patients with PCOS fulfilling Rotterdam criteria and 51 BMI-matched, premenopausal, healthy controls were analysed for steroid hormones using liquid chromatography/mass spectrometry. The ratio of testosterone to androstenedione (T/A4 ratio) in saliva and serum was assessed and correlated with parameters of metabolic health.
Results
Serum and saliva levels of testosterone and androstenedione are significantly higher in PCOS patients ($P<0.001$ each). PCOS patients also show significantly higher free testosterone and free dihydrotestosterone levels in serum, as well as a higher free androgen index ($P<0.001$ each). Testosterone to androstenedione ratio is significantly higher in saliva from PCOS patients compared to saliva from healthy, BMI-matched controls ($P<0.001$), whereas no significant difference for the T/A4 ratio in serum was found. Only in PCOS patients, salivary T/A4 ratio is significantly higher in patients with obesity ($P=0.001$), metabolic syndrome ($P=0.004$), insulin resistance ($P=0.016$) and glucose intolerance ($P=0.038$) compared to PCOS women without the respective metabolic alterations.
Conclusions
Assessing salivary androgens and calculating the salivary T/A4 ratio could be a novel, non-invasive tool for the diagnosis of PCOS. Further, a higher T/A4 ratio is linked with an adverse metabolic phenotype in PCOS patients.

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Reproduction & Endocrine Disruption

GP179

Urinary bisphenol A in PCOS women and its relation to steroid hormones

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Bisphenol A (BPA) is an environmental estrogen found in plastic material such as bottles, food package, dental material, etc. It is known to have many negative effects on human health and its exposure is associated with endocrine disorders including polycystic ovary syndrome (PCOS). Some studies found significantly higher serum and urinary levels of BPA in PCOS women, however its association with steroid hormones is still controversial.
Aim
The aim of this study was to compare urinary BPA concentrations between PCOS and healthy women and to assess the relationship between BPA and steroid hormones in PCOS group.
Subjects and methods
Study groups consisted of 69 PCOS women and 38 healthy age matched women without endocrine disease. BPA concentrations were measured in urine samples using high-pressure liquid chromatography in all PCOS and control subjects. Serum androgens i.e. testosterone, free-testosterone, androstendione (ASD), dihydrotestosterone (DHT) and DHEAS as well as serum estrogens (estradiol, estrone) were measured in PCOS group.
Results
There were no signifcant differences in BPA concentration between PCOS and controls (6.8 ± 1.1 vs 6.7 ± 1.3 μg/lcreatinine). In the PCOS group, no significant correlation has been detected between BPA and testosterone, free-testosterone, DHT, ASD and estradiol (all $P>0.05$), respectively. However, we found a significant negative correlation between BPA and DHEAS ($r=-0.59$, $P=0.0065$) and a slight but significant negative correlation between BPA and serum estrone ($r=-0.27$, $P=0.038$).
Conclusion
We conclude that PCOS women do not differ in urinary BPA concentrations from healthy controls. In PCOS group urinary BPA negatively correlates with serum DHEAS and estrone indicating that BPA may interfere with steroidogenesis and may inhibit production of some steroid hormones.

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GP180

An estrogen receptor-dependent pathway is involved in fludioxonil-induced cancer growth and metastasis linked with epithelial mesenchymal transition in cellular and xenografted ovarian cancer models

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Fludioxonil is an antifungal agent used in agricultural applications that is present at measurable amounts in fruits and vegetables. In this study, the effects of fludioxonil on cancer cell viability, epithelial-mesenchymal transition (EMT) and metastasis were examined in BG-1 ovarian cancer cells with estrogen receptors (ERs). BG-1 cells were cultured with 0.1% DMSO (control), 17β-estradiol (E2; 1×10^{-9} M), or fludioxonil ($10^{-5}-10^{-8}$ M). MTT assay revealed that fludioxonil increased BG-1 cell viability 1.2–1.5 times compared to the control, while E2 markedly increased BG-1 cell viability by about 3.5 times. When the samples were co-treated with ICI 182,780 (10^{-8} M), an ER antagonist, fludioxonil-induced BG-1 cell viability was reversed to the level of the control. Protein levels of cyclin E, cyclin D1, snail and N-cadherin increased in response to fludioxonil as E2 did, but these increases were not observed when fludioxonil was administered with ICI 182,780. Moreover, the protein level of p21 and E-cadherin decreased in response to treatment with fludioxonil, but remained at the control level when cotreated with ICI 182,780. In xenografted mouse models transplanted with BG-1 cells, fludioxonil significantly increased the tumor mass formation by about 2.5 times as E2 did when compared to vehicle (0.1% DMSO) during the experimental period (80 days). Immunohistochemistry revealed that the protein level of proliferating cell nuclear antigen, snail and cathepsin D increased in response to fludioxonil as E2 did. These results imply that fludioxonil may have disruptive effects on ER expressing cancers by inducing alterations in the expression of cell cycle- and EMT-related genes via the ER dependent pathway.

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GP181

Metformin directly alters key glycolytic enzyme protein expression and mitochondrial function in the endometria of PCOS patients

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Polycystic ovary syndrome (PCOS) is a significant risk factor for the development and progression of type I endometrial cancer (EC). Currently, it is not known whether metformin has a direct effect on the endometria and further regulates glycolysis and mitochondrial function in PCOS patients with endometrial hyperplasia and carcinoma. Here we show that endometria from PCOS patients with endometrial hyperplasia and carcinoma have a distinct protein expression pattern of glycolytic enzymes, including HK2, PFK, PKM2, and LDHA as well as mitochondrial TFAM, which is necessary for energy production from oxidative phosphorylation. Using endometrial tissues from PCOS patients with hyperplasia, we evaluated the effects of metformin on the protein levels of key enzymes in glycolysis *in vitro*. In response to metformin treatment, HK2 expression was decreased, whereas PFK, PKM2, and LDHA expression was increased compared to controls. Interestingly, the expression of TFAM and cleaved caspase-3, a downstream target of cytochrome C, was increased after metformin treatment. It is known that type I EC is an estrogen-dependent disease and that endometrial hyperplasia predisposes for the development of EC. We found that while endometrial ERβ expression was no different between non-PCOS and PCOS patients, ERα expression was gradually increased in women with PCOS following the onset of endometrial hyperplasia and carcinoma. Moreover, we found that *in vitro* treatment with metformin leads to inhibition of ERα expression without

affecting ERβ expression. Overall, our data indicate that metformin integrates endometrial glycolytic metabolism with mitochondria-related cellular function by regulating key glycolytic enzyme protein expression in the endometrium. Our results also show that ERα is a molecular link between metformin action and estrogen-induced endometrial cell proliferation, and they shed further light on the anticancer mechanism of metformin in PCOS patients with EC.

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GP182

Elevated circulating levels of betatrophin are associated with polycystic ovary syndrome

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Context
Betatrophin is a newly identified hormone appreciated for its role as a potent inducer of beta cell proliferation in line with insulin resistance in mice. Polycystic ovary syndrome (PCOS) is an inflammatory-based metabolic disease associated with insulin resistance. However, no evidence was available whether betatrophin is involved in women with PCOS.
Objective
To ascertain whether betatrophin levels are altered in women with PCOS.
Setting
Secondary referral center.
Participants
A total of 164 women with PCOS and 164 age- and BMI- matched female controls without PCOS were recruited for this cross-sectional study.
Main outcome measures
Circulating betatrophin levels were measured using ELISA; metabolic and hormonal parameters were also determined.
Results
Circulating betatrophin levels were significantly elevated in women with PCOS compared with controls (367.09 ± 55.78 vs 295.65 ± 48.97 pg/ml, $P < 0.001$). Betatrophin levels were positively correlated with insulin resistance marker HOMA-IR, free-testosterone, hs-CRP, atherogenic lipid profiles and BMI in PCOS. In multivariate logistic regression analysis, the odds of subjects in the highest quartile (OR = 2.51, 95% CI = 1.31–4.81, $P = 0.006$) of betatrophin having PCOS were significantly increased compared with subjects the lowest quartile betatrophin. Multivariate regression analyses showed that HOMA-IR, hs-CRP and free-testosterone were independent factors influencing serum betatrophin levels.
Conclusion
Betatrophin levels were increased in women with PCOS and were associated with insulin resistance, hs-CRP and free-testosterone in these patients. Elevated betatrophin levels were found to increase the odds of having PCOS. The physiologic and pathologic significance of our findings remain to be further elucidated.

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GP183

Intima media thickness and brachial artery flow mediated dilatation in women with polycystic ovary syndrome and type 1 diabetes mellitus

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Polycystic ovary syndrome (PCOS) and type 1 diabetes (T1DM) are accompanied by increased risk of atherosclerosis. A higher prevalence of PCOS in T1DM patients has been reported. Brachial artery flow-mediated dilatation (FMD) and intima media thickness of common carotid artery (IMT) are used to detect an early endothelial dysfunction.
The aim of our study was to examine IMT and FMD in T1DM women with PCOS. We also estimated the relation of IMT and FMD to clinical and hormonal parameters in the studied population.
We studied 85 women (mean age 25.1 ± 4.3): 27 with T1DM (14 with PCOS + T1DM, 13 with T1DM/no-PCOS), 38 with PCOS and 20 healthy women (control group). IMT and FMD were assessed by ultrasonography. PCOS was diagnosed using the Rotterdam criteria. Clinical examination, lipid, hormonal profile and ultrasonographic evaluation of ovaries were performed for all women. In addition, concentrations of soluble E-selectin (sE-selectin) and intercellular adhesion cell molecule-1 (sICAM-1), as well as C-reactive protein (CRP) levels were assessed.
IMT and FMD did not differ between all studied groups. In patients with PCOS + T1DM, the median IMT value was 0.53 mm (IQR 0.44–0.54) and median FMD value was 12.66% (IQR 9.5–20.43). IMT was positively associated with BMI in the entire studied group and in patients with PCOS ($r = 0.357$, $P = 0.001$; $r = 0.342$, $P = 0.036$). IMT was also related to CRP, sE-selectin and sICAM-1 in the entire group ($r = 0.261$, $P = 0.044$; $r = 0.23$, $P = 0.033$; $r = 0.29$, $P = 0.007$). sE-selectin and sICAM-1 concentrations were higher in PCOS + T1DM than in PCOS group ($P = 0.002$, $P = 0.006$). In the T1DM group, we found FMD to be related to diabetes duration ($r = -0.42$, $P = 0.033$). In the T1DM + PCOS patients, IMT was related to serum triglycerides ($r = 0.613$, $P = 0.02$) and to HDL-cholesterol ($r = -0.524$, $P = 0.055$).
Our data suggest that early vascular changes in young T1DM patients are related to diabetes duration and additionally, in patients with PCOS + T1DM, to atherogenic lipid profile.

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GP184

Impaired DHEA sulfation defines androgen excess in women with polycystic ovarian syndrome (PCOS)

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Context
Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women of classic androgen synthesis. Recent work has highlighted that impaired DHEA sulfation results in enhanced androgen production. Here, we evaluated the relationship between DHEA and DHEAS and androgen excess and metabolic phenotype in PCOS.
Patients and methods
We compared 65 women with PCOS to 35 healthy women matched for age and body mass index (BMI). All subjects underwent measurement of fasting glucose and insulin for Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). Androgen status was assessed in serum and 24-h urine by mass spectrometry. Pearson product-moment correlation coefficient analysis, Fishers exact test and one-way ANOVA were used for statistical analysis.
Results
Women with PCOS showed evidence of impaired DHEA sulfation as indicated by a significantly higher DHEA/DHEAS ratio (median 6.9 (range 0.4–28.0) vs 1.8 (0.5–3.7) nmol/μmol in controls, $P < 0.0001$). For further analysis, we divided the PCOS patients according to whether their DHEA/DHEAS ratio was normal, i.e. similar to controls, (< 5 nmol/μmol, $n = 24$) or increased (≥ 5 nmol/μmol, $n = 41$). The two PCOS groups did not differ with regard to BMI or HOMA-IR. PCOS patients with an increased DHEA/DHEAS ratio had significantly increased excretion of both major androgen metabolites, androsterone and etiocholanolone, reflective of total androgen production (androsterone (median 2496 (IQR 1645–4350) μg/24 h vs 1214 (827–1815) μg/24 h in controls, $P = 0.0002$; etiocholanolone (2076 (1483–3005) μg/24 h vs 1133 (717.5–1910) μg/24 h in controls, $P = 0.0069$). By contrast, androgen production in PCOS patients with normal DHEA/DHEAS ratio did not differ significantly from controls.
Conclusion
The DHEA/DHEAS ratio is an independent and sensitive indicator of androgen excess in PCOS. Impaired DHEA sulfation is much more prevalent in PCOS than previously assumed, with two thirds of PCOS patients showing an increased DHEA/DHEAS ratio closely linked to total androgen production.

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GP185

Human Chorionic Gonadotropin supports Treg-mediated fetal protection in mice by modulating DC phenotype

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Introduction
Human Chorionic Gonadotropin (hCG) contributes to fetal tolerance by regulating innate and adaptive immune responses during pregnancy. Our previous results suggested a pregnancy protective effect of hCG through enhancement of regulatory T (Treg) cells and inhibition of dendritic cell (DC) maturation. Here, we aimed to investigate whether hCG contributes to Treg generation by modulating DC phenotype *in vitro* and *in vivo* in a murine model.
Methods
Bone marrow-derived DCs (BMDCs) from virgin CBA/J female mice were *in vitro* stimulated with LPS and IFN-γ to induce maturation. In parallel, BMDCs were cultured in the presence of various concentrations of urine-purified or recombinant hCG. After 24 and 48 h the BMDCs were analyzed for their maturation state and cytokine secretion pattern. Additionally, BMDCs were analyzed for their capability to induce the differentiation of naïve T cells into TH1, TH2 or Treg cells.
Moreover, hCG- and non hCG-treated stimulated BMDCs were adoptively transferred into abortion-prone mice to evaluate their *in vivo* function. On pregnancy day 12 the pregnancy outcome as well as the peripheral and local number of Treg cells was determined.
Results
BMDC stimulation resulted in a significant increase in the number of mature BMDCs and in secretion of TH1 and TH2 cytokines. Both hCG preparations significantly impaired the ability of BMDCs to mature but did not significantly influence cytokine secretion. As for their function, recombinant hCG-treated BMDCs had a reduced potential to induce TH1 or Th2 cells but could increase the number of Treg cells. *In vivo*, the transfer of hCG-treated BMDCs increased the number of peripheral and local Treg cells and protected fetuses from immunological abortion.
Conclusions
Our results reveal that hCG contributes to Treg-mediated fetal protection by modulating the phenotype of DCs.

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GP186

FSH increases the different LH- and hCG-dependent intracellular signalling and the downstream life/death signals in vitro

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Background
Luteinizing hormone (LH) and choriogonadotropin (hCG) are glycoprotein hormones regulating ovarian function and pregnancy. They were routinely used in assisted reproduction techniques (ART) assuming they are equivalent, due to their binding to a common receptor (LHCGR). However, differences between LH and hCG were demonstrated at molecular and physiological level.
Aim
The aim of this study is to evaluate how follicle-stimulating hormone (FSH) co-treatment, in the ART therapeutic dose-range, affects the different LH- and hCG-specific responses *in vitro*.
Methods
We evaluated phospho-CREB, -ERK1/2 and -AKT activation by Western blotting, gene expression by real-time PCR, cAMP, progesterone and estradiol production by ELISA, and cell viability by MTT assay in human granulosa-lutein cells (hGLC). LH and hCG dose-response experiments (0.1 pM–1.0 nM range) were performed, in the presence of 10 nM FSH.
Results
In the presence of FSH, hCG biopotency is about 5-fold increased, in cAMP activation. Moreover, different LH and hCG dose-response curves were observed, in terms of 50% effective doses (EC50s), hill-slopes and maximal levels (Mann–Whitney's *U*-test; $P<0.05$; $n=6$), suggesting hormone-specific receptor cooperativity and biopotency. Accordingly, the cAMP-dependent CREB phosphorylation and steroid production increased under hCG and FSH co-treatment. Surprisingly, the activation of the steroidogenic cAMP/PKA/CREB signalling cascade did not change upon LH treatment, in the presence of FSH. However, FSH increased the LH-dependent ERK1/2 and AKT phosphorylation, the expression of the *X-linked inhibitor of apoptosis* (*XIAP*) gene, and the cell viability (Mann–Whitney's *U*-test; $P<0.05$; $n=4$), resulting in anti-apoptotic effects.
Conclusions
FSH potentiates the LH-dependent anti-apoptotic and the hCG steroidogenic (and pro-apoptotic) potential *in vitro*. The different modulatory activity of FSH on LH and hCG action *in vitro* reflects their different physiological functions, consisting in proliferative effects exerted by LH during the follicular phase and before trophoblast development, and the high steroidogenic potential of hCG requested to sustain pregnancy.

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GP187

Testosterone supplementation and body composition: results from a meta-analysis of observational studies

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Background
The concept of testosterone (T) supplementation (TS) as a new anti-obesity medication in men with testosterone deficiency syndrome (TDS) is emerging.
Aim
To systematically review and meta-analyze available observational and register studies reporting data on body composition in studies on TS in TDS.
Methods
An extensive Medline Embase and Cochrane search was performed including the following words: 'testosterone', 'body composition'.
Main outcome measures
All observational studies comparing the effect of TS on body weight and other body composition and metabolic endpoints were considered.
Results
Out of 824 retrieved articles, 32 were included in the study enrolling 4513 patients. TS was associated with a time-dependent reduction of body weight and waist circumference (WC). The estimated weight loss and WC reduction at 24 months were −3.50 (−5.21; −1.80) kg and −6.23 (−7.94; −4.76) cm, respectively. TS was also associated with a significant reduction of fat (−0.62 (−1.06; −0.18); $P<0.01$) and with an increase of lean mass (0.62 (0.18; 1.05); $P<0.01$) as well as with a reduction of fasting glycemia and insulin resistance. In addition, an improvement of lipid profile (reduction of total cholesterol as well as of triglyceride levels and an improvement in HDL cholesterol levels) and in both systolic and diastolic blood pressure were observed.
Conclusions
Present data support the view of a positive effect of TS on body composition and on glucose and lipid metabolism. In addition, a significant effect on body weight loss was observed, which should be confirmed by a specifically designed RCT.

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GP188

Human 3β-hydroxysteroid dehydrogenase deficiency associated with a normal spermatic numeration despite a severe enzyme deficit, after an accomplished transition period

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Human 3β-hydroxysteroid dehydrogenase deficiency is a rare form of congenital adrenal hyperplasia resulting from HSD3B2 gene mutations, leading to steroidogenesis impairment in both adrenals and gonads. The transition period is important for a successful adult fertility, but information about fertility is lacking in this rare disease.
The patient presented with salt wasting at birth in Trousseau Hospital. Consanguinity was present, since the parents were first cousins. A micropenis and two intrascrotal testes were noted, a perineal hypospadias was later surgically corrected. Highly elevated 17OH-Pregnenolone contrasting with low 17OH-Progesterone and an HSD3B2 687del27 homozygous mutation (Moisan *et al*; *JCEM* 1999) were described: *in vitro* activity of this mutation in terms of DHEA/D4-Dione conversion was very low. Despite high ACTH levels in infancy, SDHEA levels remains controlled, without dexamethasone treatment use. Normal puberty was achieved at age 15. After transition from the pediatric department at age 19, the compliance was good and his hormonal profile remains normal with Hydrocortisone 30 mg/day and Fludrocortisone 100 µg/day: 17OHPregnenolone 2.2 nM (*N*: 1.5–10.8); SDHA 2.6 µM (*N*: 3–14); total testosterone 28 nM (*N*: 11–40); ACTH 21 pg/ml; renin 18.1 pg/ml (*N*: 5–30). Testicular echography found two scrotal testes of 21 ml without any evidence of testicular adrenal rest tumors. No malignancy was noted, as the testes remains in the scrotal position. Plasma inhibin B (139 pg/ml; *N*: 135–350) confirmed a normal Sertoli's function. Finally, his spermatic numeration was quite normal according to WHO 2010 criteria, with 57.6 million/ml spermatozoids, although typical forms were 21% and vitality was 41% ($N > 58\%$), which allowed sperm cryopreservation.
This case illustrates potential male fertility in a patient with severe HSD3B2 deficiency and the importance of transition, which allowed a long term hormonal control and therefore exocrine consequences, questioning the testicular role of the peripheral, non-mutated, testicular HSD3B1.

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Thyroid – Basic

GP189

A new paradigm of TSH receptor signaling in the trans-Golgi network

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Whereas G-protein coupled receptors (GPCRs) have been long believed to signal through cyclic AMP exclusively at cell surface, our group has previously shown that GPCRs not only signal at the cell surface but can also continue doing so once internalized together with their ligands, leading to persistent cAMP production. This phenomenon, which we originally described for the thyroid stimulating hormone receptor (TSHR) in thyroid cells, has been observed also for other GPCRs. However, the intracellular compartment(s) responsible for such persistent signaling and its consequences on downstream effectors were insufficiently characterized. The aim of this study was to follow by live-cell imaging the trafficking of internalized TSHRs and other involved signaling proteins as well as to understand the consequences of signaling by internalized TSHRs on the downstream activation of protein kinase A (PKA). PKA activity was measured in real-time in living thyroid cells using a fluorescence resonance energy transfer (FRET) sensor (AKAR2). Our results suggest that TSH co-internalizes with its receptor and that the internalized TSH/TSHR complexes traffic retrogradely to the trans-Golgi network (TGN). We provide evidence that TSH/TSHR complexes meet an intracellular pool of Gαs in the TGN and activate it there, as visualized in real-time using a nanobody that binds selectively to the active Gs protein. Acute Brefeldin A-induced Golgi collapse hinders the retrograde trafficking of TSH/TSHR complexes, leading to reduced cAMP production. Direct monitoring of PKA activation in the TGN with a localized AKAR2 sensor shows a delayed PKA activation after TSH stimulation (~10 min), which is compatible with the time required for TSH/TSHR complexes to reach the TGN. These data provide evidence that internalized TSH/TSHR complexes meet and activate G-proteins at the TGN, leading to a local activation of PKA. These findings suggest unexpected functions for receptor internalization, with major pathophysiological and pharmacological implications.

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GP190

Functional and morphological phenotypes in the mouse thyroid gland associated with thyroid-specific Mct8 deficiency

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Introduction
Mct8 is a thyroid hormone specific transporter located at the basolateral plasma membrane of thyrocytes. To investigate the significance of Mct8 to the thyroid gland while excluding peripheral effects observed in global knockout models, we used a Cre-LoxP thyroid-specific Mct8-deficient mouse model. Phenotypes of the angiofollicular unit encompassing the follicle and surrounding endothelial cells were investigated with respect to functional and morphological states.
Methods
Morphology of the thyroid follicles, endothelial cells and thyrocyte cell death were investigated using a computer-based cell biology toolbox. Indirect immunofluorescence of tissue cryo-sections and immunoblotting were used to analyse thyroglobulin status, along with expression and localisation of thyroglobulin-processing cathepsins.
Results
Morphological analysis demonstrates that the average thyroid follicle size in thyroid-specific Mct8-deficient mice is comparable to the $Cre^{-/-}$ control. Epithelial extension was less in thyroid-specific-Mct8 deficiency, but not significantly. Strikingly, cell death in the thyroid-specific Mct8-deficient mice was 8.5-fold greater than observed in the control. Cathepsin B expression appeared increased 1.7-fold in the thyroid-specific Mct8 knockout in comparison to the control. Cathepsin L is only localised to certain thyrocytes around the follicle in the thyroid-specific-Mct8 deficient model; in the control, Cathepsin L is present across all thyrocytes. Initial observations of the thyroglobulin status suggest that a greater percentage of the prohormone in the thyroid-specific Mct8 knockout is cross-linked than the control.
Conclusion
Thyroid-specific Mct8 deficiency does not appear to have a great effect on follicle size or epithelial extension. However, differences associated with cathepsin expression and localisation suggests that Mct8 may be connected to expression and localisation of cathepsins B and L via an unknown mechanism. The absence of thyrocyte survival factor cathepsin L from many follicle cells might be the underlying cause of the increased cell death rate in follicles of the thyroid-specific-Mct8 deficient model.
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GP191

Chemical chaperones rescue pathogenic MCT8 mutations

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Introduction
Monocarboxylate transporter 8 (MCT8) is a thyroid hormone-specific transmembrane transport protein. Inactivating mutations in MCT8 lead to severe mental retardation, the Allan-Herndon-Dudley syndrome. The severity of the Allan-Herndon-Dudley syndrome differs among MCT8 patients. Partial activity of MCT8 can be caused either by mutations affecting the transport mechanism (e.g. substrate interaction, conformational change) or by inefficient protein expression, membrane translocation or stability. The latter MCT8 mutants may be responsive to chemical chaperones which stabilize the protein or support membrane localization. We have previously shown that application of the chemical chaperone sodium phenylbutyrate rescues expression and transport activity of the pathogenic ΔPhe501 mutant *in vitro*.

Methods
Several mutations were introduced into human MCT8 by site directed mutagenesis and stably transfected into MDCK1 (Madin-Darby canine kidney) cells. The cells were treated with increasing concentrations of chaperones for two days. Western blotting and radioactive thyroid hormone-uptake experiments were performed to analyze chaperone effects.
Results
Here we will show new mutants (e.g. L434W) which are responsive to sodium phenylbutyrate. It increases protein expression and function of various pathogenic MCT8 mutations.
Conclusion
MCT8 mutations do not only affect the transport activity of the protein, but also its stability and localization at the cell surface. Sodium phenylbutyrate is a common drug used for the treatment of urea cycle defects and cystic fibrosis. The administration of chemical chaperones, which are safe for use in humans, could be a new tool for the therapy of MCT8 deficiency to improve the patient's quality of life.

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GP192

FoxE1 expression is regulated by Sox9 in thyroid follicular cells

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Sox9 is a transcription factor of the HMG box DNA binding family involved in chondrocyte differentiation, sexual determination and the development of endoderm-derived-organs. Preliminary results from our laboratory have shown that Sox9 is expressed in the thyroid gland and its regulation is under the control of TSH and TGFβ. In this work we studied the role of Sox9 in the thyroid cells differentiation and its relationship with the other thyroid transcription factors, mainly with FoxE1, an important transcription factor essential for the development and differentiation of the thyroid gland.
Sox9 and FoxE1 mRNA and protein levels were determined by RT-qPCR and Western-blot respectively. Co-transfections assays with FoxE1 promoter and Sox9 expression vector were performed in Hela cells to elucidate the role of Sox9 in the regulation of Foxe1 expression. The binding capacity of Sox9 to its DNA consensus sequence in the rat Foxe1 promoter was analyzed by Electrophoretic Mobility Shift Assays (EMSA). Sox9 was silenced in PCCl3 cells using specific siRNA.
By *in silico* analysis we have observed a Sox9 consensus DNA sequence within the FoxE1 promoter, to which recombinant Sox9 protein efficiently binds. Furthermore, we have demonstrated that Sox9 is functional as it was able to induce four fold the transcriptional activity of FoxE1 promoter. Finally, the inhibition of Sox9 led to a drastic decrease in the expression levels of FoxE1.
These results show that Sox9 is a transcription factor upstream of FoxE1 and involved in its regulation in differentiated thyroid follicular cells. Considering the important role of FoxE1 in the pathophysiology of the thyroid gland these results encourage to think that Sox9 could play an important role in the regulation of development and differentiation of the thyroid gland.

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GP193

Interconnection between cathepsin protein levels and thyroid hormone transporters in human thyroid epithelial cells

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Background
Thyroid hormone transporting proteins Mct8 and Mct10 have been detected at the plasma membrane of thyroid epithelial cells, whereas Lat2 was found predominantly at vesicular membranes. In this study we look into the effects of inhibiting thyroid hormone transporters on their subcellular localisation to better understand their fate and trafficking pathways in thyrocytes. Thus, a pharmacological intervention study with specific inhibitors of thyroid hormone transporters was conducted using a human thyroid epithelial cell line as a model.
Method
The localization of the thyroid hormone transporters Mct8, Mct10, and Lat2 was analyzed in human Nthy-ori 3-1 thyroid epithelial cells by indirect immunofluorescence, and the protein levels were determined by immunoblotting.
Results
Although Mct8 and Mct10 have been shown to be located at the basolateral plasma membrane domain of thyroid follicle cells *in situ*, our results of this *in vitro* study reveal their localization in vesicles. Lat2 was predominantly vesicular, both *in situ* and *in vitro*. In order to identify whether these vesicles belong to the secretory or the endocytic pathway, co-localization studies with Lamp2 as an endo-lysosomal marker were performed. The results suggest that Lat2 is present in vesicles other than late endosomes or lysosomes.
Conclusion
Nthy-ori 3-1 cells represent an *in vitro*-model suited to study the expression, localization, and trafficking of thyroid hormone transporters like Lat2, Mct8, and Mct10. Future studies will have to include other compartment-specific markers to identify the subcellular location of endogenous and over-expressed thyroid hormone transporters in thyrocytes.

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GP194

Circulating 3-T1AM and 3,5-T2 in critically ill patients: a cross-sectional observational study

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Introduction
Patients in need of an intensive care unit (ICU) treatment due to severe diseases often develop the non-thyroidal illness syndrome (NTI). These critically ill patients present with low thyroxine (T_4), low 3,3',5-triiodothyronine (T_3) and elevated reverse T_3 (rT_3) serum concentrations while TSH and 3,3'-diiodothyronine (3,3'-T2) concentrations remain unaffected. To further elucidate the underlying changes in thyroid hormone (TH) metabolism, additional TH metabolites of physiological and pathophysiological relevance were determined in sera of ICU patients.
Study design
In this cross-sectional observational study blood was drawn from 83 ICU patients who were followed up during their ICU stay. 25 developed sepsis and 10 patients did not survive ICU stay. The control group consists of 38 healthy and demographically matched individuals.
Methods
TH and their binding proteins were measured with commercial assays. 3,5-T2 and 3-T1AM were determined with published in-house immunoassays.
Results
Classical TH function tests documented a NTI constellation. Median 3-T1AM concentrations were 44% lower throughout the ICU stay compared to the healthy control ($P<0.0001$). 3-T1AM is not different in survivors vs. non-survivors or sepsis vs. non-sepsis patients. Median 3,5-T2 concentrations were 30% higher in critically ill patients compared to the control group ($P=0.01$). In addition, we also observed that non-survivors and ICU patients with diagnosed sepsis had higher 3,5-T2 concentrations compared to other ICU patients. 3-T1AM but not 3,5-T2 correlates with low T_3.
Conclusion
We found highest 3,5-T2 and low 3-T1AM values in most severely ill patients (non-survivors and sepsis patients). This data may indicate enhanced T_3 deiodination to 3,5-T2 concomitant with decreased 3,5-T2 elimination. The observation that 3-T1AM concentration does not change with severity of illness or is even declining with decreasing T_3, is compatible with our hypothesis that 3,5-T2 serves as substrate for a decarboxylase yielding 3-T1AM, whose activity is impaired in severe NTI on ICU.

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GP195

Accumulation of PD-1-positve and PD-L1-positve T and B lymphocytes in patients with Graves' disease

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Introduction
Programmed death-1 (PD-1) is one of the most important inhibitory co-receptors. Studies show that the PD-1/PD-L1 pathway regulates the induction and maintenance of peripheral tolerance and protects tissues from autoimmune attack in physiological conditions. Several studies have shown association of PD-1/PD-L1 pathway with several autoimmune diseases although, to date, no such studies have been performed for Graves' disease (GD).
Aims
The aim of this study was to describe the frequencies of T and B lymphocytes expressing PD-1 and PD-L1 molecules in patients with GD. The relationships between PD-1+ and PD-L1+ cells, and selected clinical parameters were also assessed.
Material and methods
The expression of PD-1 and PD-L1 was analyzed using flow cytometry on T and B lymphocytes collected from 45 adult patients with newly diagnosed, untreated GD. The control group consisted of 20 healthy subjects.
Results
We observed high expression of PD-1 and PD-L1 on analyzed lymphocytes subpopulations of GD patients. Among T cells, the expression of PD-1 on protein level was higher on CD4+ cells in GD patients (mean: $31.54 \pm 13.74\%$) than in healthy controls (mean: $5.35 \pm 1.54\%$, $P<0.001$). Moreover, higher frequencies of PD-1+/CD8+ cells and PD-1+/CD19+ cells in the study group than in healthy volunteers were observed (mean: $18.71 \pm 10.37\%$ vs $3.6 \pm 1.45\%$, $P=0.015$ and $12.07 \pm 4.34\%$ vs $1.67 \pm 0.84\%$, $P=0.017$, respectively). There was a positive correlation of PD-1 and PD-L1 expressions on CD19+B cells ($r=0.43$, $P=0.026$) in patients with GD, and a positive correlation of the frequencies of PD-1+/CD4+ cells and the serum concentration of anti-TPO antibodies ($r=0.61$, $P=0.014$). Interestingly, there was also a positive correlation between the frequencies of PD-1+/CD19+ cells and the serum concentration of anti-TR antibodies ($r=0.53$, $P=0.019$).
Conclusion
High expression of PD-1 and PD-L1 on T and B cells could represent the hallmark of immune system reaction to chronic antigenic exposition in patients with GD.

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GP196

Determination of thyroid hormones in small amount of mouse tissue sample using new isotope-dilution liquid chromatography-mass spectrometry method

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Thyroid hormones (THs) play a critical role in the regulation of growth and development in both animals and humans. They regulate metabolism primarily through actions in the brain, white fat, brown fat, skeletal muscle, liver and pancreas. Therefore, it is not surprising that since a long time scientists have been interested in measuring TH concentration in different tissues and to relate this value with possible dysfunctions. In general, TH levels are measured by immunoassay (IA)-based methods, however several analytical procedures using liquid chromatography–mass spectrometry (LC–MS) and tandem mass spectrometry (LC–MS/MS) have been developed recently for the quantification of thyroid hormones. These new techniques proved to be more accurate than the IA analysis, but most of them employed rat tissue for TH measurement and required more than 200 mg of sample. This quantity can be considered too high especially when preclinical studies are conducted using mice as test subjects, thus an analytical method that reduces the amount of sample is essential. In this study, we developed a procedure for the quantification of six THs; L-thyroxine (T4), 3,3′,5-triiodo-L-thyronine (T3), 3,3′,5′-triiodo-L-thyronine (rT3), 3,5-diiodo-L-thyronine (rT2), 3,3′-diiodo-L-thyronine (T2), 3-iodo-L-thyronine (T1) using isotope (^{13}C-T4, ^{13}C-T3, ^{13}C-rT3, ^{13}C-T2) dilution liquid chromatography–mass spectrometry. The major difference with previously described methods lies in the utilization of a nano-UPLC system in micro configuration. This approach lead to a reduction of column internal diameter, flow rate, and injected volume. The results of all these improvements brought a decrease in the amount of sample necessary for the analysis. The method was initially tested to quantify the TH level in liver and then it was extended to kidney, heart, and lung. The new procedure allowed us to measure TH concentration using between 21 and 92 mg of tissue sample. With this method we reduced substantially the amount of tissue necessary for analysis, with respect to analogue methods described in literature. We consider this procedure suitable for analysis of small quantity of samples and it opens the way for a more routine testing of mouse tissues by LC–MS technique.

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GP197

Evaluation of interrelations between resistin, adiponectin, PAI-1, intercellular adhesion molecule and thyroid function in autoimmune thyroid disease

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Introduction
Given the significant impact of thyroid function on body weight, energy metabolism and adipocytes physiology, our aim was to study the impact of subclinical thyroid dysfunction in plasmatic levels of adipokines and ICAM-1 (intercellular adhesion molecule 1).
Methods
We evaluated 98 patients with autoimmune thyroid disease divided into three groups: 30 who were euthyroid (TSH = 0.35–4.94 UI/ml), 35 with subclinical hypothyroidism (hypoSC, TSH >4.94 UI/ml) and 33 with subclinical hyperthyroidism (hiperSC, TSH <0.35 UI/ml). We evaluated BMI, serum concentration of FT_3, FT_4, TSH, C-reactive protein (CRP), adiponectin, resistin, PAI-1 (plasminogen activator inhibitor-1) and ICAM-1. The statistical analysis was performed using ANOVA, Student's *t*-test and Spearman's correlations.
Results
We observed no significant differences in age between euthyroid (50 ± 16 years), hypoSC (46 ± 17 years) and hiperSC (44 ± 13 years) groups, or gender (90.0%, 97.1% and 90.9% of the female gender respectively). The plasmatic levels of CRP were higher in individuals with hypoSC in comparison to individuals who were euthyroid (0.56 ± 0.55 vs 0.30 ± 0.24, $P<0.001$). The resistin levels were significantly higher in the hypoSC group compared with the euthyroid group (20.7 ± 22.6 vs 19.3 ± 9.0, $P<0.01$) and the hiperSC (20.7 ± 22.6 vs 12.7 ± 10.9 ng/ml, $P<0.01$). We observed higher levels of PAI-1 in the hypoSC group when compared with the euthyroid group (27.3 ± 25.1 vs 18.7 ± 11.8 ng/ml, $P<0.01$) and the hiperSC group (27.3 ± 25.1 vs 19.9 ± 17.4 ng/ml, $P<0.01$). The patients with hypoSC had lower levels of adiponectin in comparison to patients with hiperSC (21.0 ± 13.3 vs 28.3 ± 14.7 ng/ml, $P<0.01$). The PAI-1 levels were negatively correlated with FT3 levels in the hypoSC group ($r=-0.42$, $P<0.05$) and in the hiperSC group ($r=-0.36$, $P<0.05$). The levels of adiponectin had a significant correlation with the FT3 levels in the hiperSC group ($r=-0.35$, $P<0.05$) and with TSH in the euthyroid group ($r=0.61$, $P<0.001$). ICAM-1 levels were positively correlated with resistin in hypoSC group ($r=0.38$, $P=0.03$).
Conclusions
In this study, we found significantly higher levels of resistin and PAI-1 in subclinical hypothyroidism. The interrelations between thyroid function, adipokines and ICAM-1 may contribute to the metabolic and cardiovascular complications in autoimmune thyroid disease.

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GP198

Differences in gene–gene interactions in Graves' disease patients stratified by the age of diagnosis

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Background
The genetic predisposition of Graves' disease (GD) was proved by the identification of genes with substantial, non-interactive effects on the disease process. It is known, however, that genetic interactions significantly increase the likelihood of immune-tolerance-related complex diseases like allergic asthma and rheumatoid arthritis. In the present study we analyzed the effects of interactions of multiple loci on the genetic predisposition to GD patients.
Material and methods
A total of 709 patients with GD and 1216 healthy control persons were included in the study. The patients were stratified according to age at the time of the GD onset. Further, association analyses were performed for genes with a known influence on the development of GD – *HLADRB1, PTPN22, CTLA4* and *TSHR*. The interactions among polymorphisms were analyzed using the multiple logistic regression and multifactor dimensionality reduction (MDR) methods.
Results
GD patients stratified by the age of onset differed in allele frequencies of the *HLADRB1*03* and *1858T* polymorphisms of the *PTPN22* gene (OR = 1.7, $P = 0.003$; OR = 1.49, $P = 0.01$ respectively).
We tested the genetic interactions of four SNPs in a pairwise fashion with regard to the disease risk. The interactions between the *HLADRB1/PTPN22 and HLADRB1/CTLA4* genes in young patients were found by the usage of multiple logistic regression. The coexistence of *HLADRB1* with *CTLA4* and *HLADRB1* with *PTPN22* showed interactions on more than additive levels (OR = 3.64, $P = 0.002$; OR = 4.20, $P < 0.001$ respectively), suggesting that interactions between these pairs of genes contribute to the development of GD. The MDR analysis confirmed these interactions.
Conclusion
In contrast with a single gene effect, we observed that interactions between the *HLADRB1/PTPN22* and *HLADRB1/CTLA4* genes provided a better match for determining the risk of young patients for GD onset.

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Thyroid–Translational & Clinical

GP199

Does maternal thyroid autoimmunity predict adverse pregnancy outcomes?

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Background
Previous studies of association between maternal thyroid autoimmunity and adverse pregnancy outcomes have produced inconsistent results.
Objective
To examine whether thyroid autoimmunity detected at first trimester screening is predictive of a range of adverse obstetric and fetal outcomes.
Patients and methods
We studied 438 women with singleton pregnancies who underwent first trimester screening test between June and July 2014. Women were elegible if fetal gestational age was 10–14 weeks from ultrasound crown-rump length measurement. We evaluated the association between thyroid autoimmunity (positive TPO and/or Tiroglobulin (TG) antibodies] with thyroid function (TSH, free T_4), adverse obstetric outcomes (pregnancy loss after 20 weeks, pre-eclampsia, cesarean section, preterm birth) and adverse neonatal outcomes (birth weight, small size for gestational age (SGA), metabolic complications and neonatal death).
Results
33 women (7.5%) were excluded because of previous thyroid disease. 72 women showed thyroid autoimmunity (TPO-TG-positive group, 17.8%). TSH was significantly higher in TPO-TG-positive group (median (lower and upper cuartiles) 1.87 (1.27–2.45) vs 1.41 (0.93–1.94) mcU/ml, $P < 0.01$). TSH exceed the 97.5 percentile for our specific late-first trimester limit (3.62 mcU/ml) in 12.5% of TPO-TG-positive group and in 2.1% in women with negative thyroid autoimmunity ($P < 0.01$). In 8.6% of the TPO-TG-positive women, thyroxine treatment was initiated at the end of the first trimester (vs 1.1% in the negative group $P < 0.01$). Adverse pregnancy outcomes occurred in 61 women (17.1%), there were not differences between TPO-TG-positive and negative group. There were no differences in cesarean section neither prematurity. Maternal thyroid autoimmunity did not predict SGA, metabolic complications or neonatal death.
Conclusions
Thyroid autoimmunity provides higher risk for mild abnormalities in thyroid function but does not predict adverse pregnancy outcomes in our cohort.

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GP200

Betatrophin level in Hashimoto thyreoiditis

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Aim
Clinical studies in Hashimoto thyroditis (HT) confirm, that even a minor thyroid dysfunction is related to significant changes in body mass. Betatrophin, also known as TD26/RIFL/lipasin/ANGPTL8/C19orf80, is a novel protein predominantly expressed in human liver and adipose tissue. Stimulators of betatrophin, such as thyroid hormones are usually relevant to energy expenditure or thermogenesis. The mechanisms of action of betatrophin are still unknown. In the present study we aimed to find out the relation between HT, obesity and betatrophin level.
Material and methods
The group studied consisted of 133 patients with HT in euthyreosis and 42 healthy individuals. All the patients underwent body mass analysis with the use of a medical analyzer INBODY 220. Serum concentrations of TSH and anti-TSH receptor antibodies (TRAb) were measured using RIA and IgG4, anti-peroxidase antibodies (TPOAb), TNFα, TGF-β1, betatrophin and leptin were measured by commercial ELISA.
Results
The patients with HT had higher level of betatrophin ($P = 0.008$) and TNFα ($P = 0.01$) than had the controls. Observed betatrophin levels are positively correlated with age ($P = 0.001$; $P = 0.03$), body mass ($P = 0.001$; $P = 0.03$), body mass index (BMI) ($P = 0.000$; $P = 0.000$), Waist-Hip Ratio (WHR) ($P = 0.01$; $P = 0.001$) and fat mass ($P = 0.000$; $P = 0.001$) in HT and controls, respectively. In the HT group betatrophin levels correlated significantly with TPOAb ($P = 0.005$; $R = 0.39$). The patients with elevated IgG4 had significantly lower level of TPOAb ($P = 0.001$), betatrophin ($P = 0.01$), BMI ($P = 0.02$), fat mass ($P = 0.04$) and WHR ($P = 0.001$) than the non-IgG4-HT individuals.
Conclusions
Significantly higher betatrophin level in the patients with HT, especially with high level of TPOAb, even in euthyreosis may be cause the increase in fat mass.

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GP201

The importance of maternal thyroid for the placental function

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Introduction
Maternal thyroid hormone during early pregnancy is important for proper fetal growth and development. Thyroid hormone receptors are widely expressed in placental tissue. Interestingly, thyroid dysfunction and suboptimal placental function have both been associated with pregnancy complications including preeclampsia, premature delivery and fetal growth restriction. First, we studied the association of the maternal thyroid and placental function and second, we investigated whether the placental function changes have an effect in the association of the maternal thyroid with pregnancy complications.

Methods
Maternal thyroid-stimulating hormone (TSH)/free thyroxine (FT4) at intake (median 13.2 weeks, 95% range 9.6–17.6 weeks) were measured in 3556 pregnant women from the Generation R cohort. Placental function in the 2nd and 3rd trimester was estimated by vascular resistance measurement with Doppler ultrasound. For that purpose umbilical artery pulsatility index (UMPI) and uterine artery resistance index (UTRI) were calculated. As the placental vascular resistance normally drops during gestation, we examined the change in values between the two times points which was defined as delta UMPI and delta UTRI. A mediation analysis was performed in order to investigate whether the placental function has a role in the association of thyroid with preeclampsia, premature delivery and fetal growth restriction.
Results
There was a negative linear association of TSH and FT4 with the delta UMPI ($P=0.03$; $P=0.005$ respectively). There was a positive linear association of FT4 with the delta UTRI ($P=0.03$) whereas there was no association for TSH. Placental function showed a partial mediating role with second trimester UTRI in the associations of maternal thyroid with preeclampsia and birth weight ($P=0.04$; $P=0.001$ respectively).
Conclusion
Maternal thyroid hormones are associated with placental function. Low FT4 levels were associated with differential changes in the physiological decrease in placental vascular resistance: a large decrease in the umbilical compartment but a smaller decrease in the uterine compartment. 2nd trimester UTRI showed a limited mediating role of placental function in the association of maternal thyroid with the adverse outcomes.

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GP202

Does mitotane influence free thyroid hormones levels? A possible explanation *in vivo* and *in vitro*

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Mitotane (o.p'DDD, Lysodren) is used to treat adrenortical carcinoma and Cushing syndromes. It is catabolised into o.p'DDA and o.p'DDE. It is lowly protein-bound but its tropism for lipids is high. It has multiple side effects on the digestive gut increasing alkaline phosphatases and cholesterol. Patients treated with mitotane have been described as having decreased FT4 levels without any signs of hypothyroidism. We wanted to know whether this is due to an analytical interference in the FT4 assay or a true disruption in the thyroid axis and FT4 metabolism.
We retrospectively investigate the sera of 31 patients (22 adrenortical carcinoma, nine Cushing syndromes) assaying o.p'DDD and o.p'DDE (liquid chromatography); TSH, FT4, FT3, albumin, cholesterol, triglycerides (Cobas Roche); TBG (AdviaCentaur Siemens); rT3 (RIA, IDS). Statistical analysis was performed using Staview software (Spearman correlation ρ, P significant if <0.005).
In vitro, the addition of increasing amounts of o.p'DDD (1–40 mg/l) and o.p'DDE (0.5–10 mg/l) in serum had no significant influence on FT4, FT3 and TSH serum assay. *In vivo*, we confirmed that FT4 were slightly decreased under mitotane although not significantly (-0.16, $P=0.24$) while TSH and FT3 were normal. o.p'DDD levels were negatively correlated with rT3 levels (-0.36, $P=0.013$) and positively correlated with TBG levels ($+0.43$, $P=0.0016$). FT4 levels were not influenced by albumin or lipids.
Our results show that o.p'DDD and o.p'DDE has no influence on FT4, FT3, and TSH assay in serum. The lack of correlation between TSH and FT4 levels is not in favour of a decreased pituitary production of TSH. Mitotane may increase TBG, thus decreasing FT4 levels but in a moderate way. The increase in rT3 levels while FT3 levels are unchanged suggests that mitotane may induce desiodases. Our results point out that the hepatic actions of mitotane may interfere with thyroid hormones physiology.

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GP203

Repeating FNA in AUS/FLUS – is it necessary?

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Background
The review of the Bethesda System Classification has brought some challenge to the clinical role of category III lesions. Repeating fine-needle aspiration (FNA) is time-consuming, painful, brings additional cost and sometimes does not change the clinical decision. Our aim was to prove if there is true benefit in repeating FNA.
Methods
Retrospective review of 4549 thyroid FNAs between January 2012 and June 2015, from which 671 classified as AUS/FLUS. SPSS was applied.
Results
14.8% FNAs were initially classified as AUS/FLUS and selected for analysis. 64.8% repeated FNA. AUS/FLUS rate on second FNA was 40%. Mean time between FNAs was 3.1 months. In 195 cases there was follow-up histology. Time between FNAs was longer in second FNA revealing carcinoma. Risk of malignancy in AUS/FLUS FNAs versus rate of malignancy on operated patients were as follows: global risk – 8.6 vs 29.7%; after a single AUS/FLUS diagnosis – 11.5 vs 24.1%; with two successive AUS/FLUS diagnosis – 16.7 vs 29.2% and for patients with a benign cytologic interpretation following the initial AUS/FLUS diagnosis −2.6 vs 23.1%. Rate of malignancy of lobectomy vs total thyroidectomy was 27 vs 33.8%. Rate of reintervention was 87.1%.
Conclusion
The authors applied the rate of malignancy after a single diagnosis of AUS/FLUS (11.5%) to all patients who had to repeat FNA (335). The hypothesis of going directly to surgery instead of second FNA is in the same confidence interval, arguing against the role of repeating FNA.

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GP204

Selenium supplementation and autoantibody titers in Graves' disease

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Background
Selenium (Se), a trace mineral with anti-oxidative properties, has been proposed to be potentially beneficial in patients with Graves' disease (GD), especially those with active Graves' ophthalmopathy (GO).
Methods
Trials evaluating the efficacy of Se among non-pregnant adult GD patients with active GO, versus either placebo or an alternative drug, and on top of standard therapy, were included. A literature search was performed by two independent authors with eligible studies undergoing a validity screen. Data extraction of selected studies was performed using a data extraction form, with subsequent statistical analysis using RevMan 5.1 software. Results were presented as mean differences, standard errors, and 95% confidence intervals, and graphically presented as forest plots. Estimates were calculated using the inverse variance method for continuous variables and pooled using the fixed effects model. I^2 and χ^2 tests were used to assess heterogeneity.
Results
Fourteen studies were initially retrieved, but only two trials were ultimately included in the analysis. Both had good methodological quality and totalled 197 GD patients with active, non-severe GO. The only common outcomes of interest were changes in TRAB and TPOAB titers. We found no statistically significant difference in both TRAB (95% CI, -1.38 (-3.19, 0.44), $P=0.14$) and TPOAB (95% CI, 36.66 (-32.56, 105.88), $P=0.3$) titers on follow-up among patients given Se as compared to placebo. No significant heterogeneity was observed in either analysis (TRAB, $I^2=36\%$; TPOAB, $I^2=0\%$). However, our study was limited by the small number of studies, a small sample size, and lack of other synthesizable outcomes.
Conclusion
This is the first meta-analysis on the efficacy of Se in GD patients with active, non-severe GO. We found no statistically significant differences in both TRAB and TPOAB titers between Se and placebo groups. We recommend larger studies to further validate these findings.

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GP205

One in four patients with adequately treated primary hypothyroidism continue to be symptomatic and persisting symptoms related to ongoing thyroid auto-immunity

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Background
A significant percentage of patients with adequately replaced primary hypothyroidism (PH) continue to be symptomatic. Some of these persisting symptoms maybe attributed to non-restoration of neurocognitive functions and psychological well-being.
Objectives
To estimate the prevalence of persisting hypothyroid symptoms in patients with PH on biochemically adequate replacement therapy. To correlate persistent symptoms with thyroid hormone levels, psychological distress scores and anti-thyroid peroxidase (TPO) antibody levels.
Methodology
Consequent adult patients (18–60 years), with PH, on replacement therapy and having achieved biochemical euthyroidism were enrolled in the study after informed consent. They were assessed for ongoing symptoms of hypothyroidism and psychological distress using three validated questionnaires i.e. Thyroid Symptom Questionnaire (TQ18), General Health Questionnaire (GHQ) and Hospital Anxiety and Depression (HAD) inventory. Serum was sampled on the same day for Free T4, Free T3, thyroid-stimulating hormone (TSH) assessments and for anti-TPO antibody titers.
Results
One hundred and seventeen patients (F: 102, M: 15, mean age 41years) diagnosed with PH were recruited. TQ18 scores revealed that 32 (27.3%) patients continued to be symptomatic despite biochemical euthyroidism. FT3, FT4 and TSH levels failed to reveal any significant correlation (*P*-0.18, *P*-0.96, *P*-0.54 respectively) with TQ18 scores whereas TPO antibodies titres were significantly correlated with TQ18 scores (*P*-0.008). HAD scores suggested that 27 (23%) patients had anxiety and 32 (27.3%) patients were depressed. Anti-TPO antibody titers and FT4 values had significant correlation with anxiety (*P*-0.008 & *P*-0.01) while depression was correlated only with elevated antibody titres only (*P*-0.02).
Conclusions
One in four patients with adequately replaced PH continue to be symptomatic. Symptom scores were significantly correlated with higher thyroid antibody titres but not with thyroid hormone levels. Psychological distress scores were correlated with lower FT4 levels and with higher antibody titres.

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GP206

FREND™ Thyroid Duo: a new way of helping patients with subclinical thyroid dysfunction

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Introduction
Subclinical thyroid dysfunction is defined as an abnormal serum thyroid-stimulating hormone (TSH) level and free thyroxine (FT4) and triiodothyronin (T3) levels within their reference ranges. The prevalence of subclinical thyroid dysfunction has increased, especially in women older than 60 years. There is good evidence that subclinical hypothyroidism is associated with progression to overt disease, so screening is recommended for high-risk populations. FREND™ Thyroid Duo, a microfluidic immunoassay, was developed to provide a convenient quantitative method for both TSH and FT4 in a single test.
Objective
To evaluate the analytical performance a FREND™ Thyroid Duo immunoassay on FREND™ system.
Method
The analytical performance studies (sensitivity, precision, linearity, interference and accuracy) were performed according to the CLSI protocols (EP17, EP05, EP06, EP07 and EP09). For the method comparison, serum TSH and free T4 were assayed by FREND™ and Architect i1000 (Abbott Diagnostics, Abbott Park, IL, USA).
Results
The FREND™ Thyroid Duo demonstrated acceptable imprecision of %CV (<10%) in low, intermediate, and high level samples for both analytes. The linearity of the assay was found to be acceptable in the range of 0.06–25 mIU/l for TSH and 0.4–6 ng/dl for FT4. Method comparisons between Abbott Architect's assays and NanoEnTek's FREND Thyroid Duo assay were made and no significant deviation from linearity was found. No significant interference was observed for both analytes from bilirubin, Intra-lipid and total protein up to concentrations of 20 mg/dl, 3 g/dl, and 12 g/dl respectively.
Conclusion
The NanoEnTek's FREND™ Thyroid Duo assay represents a rapid, accurate and convenient mean of measuring TSH and FT4 quantities in human serum on FREND™ system. The subclinical thyroid dysfunction may be screened or monitored in a clinic or physician's office using this microfluidic 2-in-1 thyroid assay with ease and comfort.

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GP207

Predictive factors of outcomes in radioiodine treatment for Graves' disease

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Introduction
Radioiodine (^{131}I, RAI) is a safe and effective option for the treatment of Graves' disease (GD). However, approximately 20% of RAI treated patients will have persistent disease or will relapse after the first treatment. Our aim was to identify the factors influencing the outcomes in RAI treatment for GD.
Methods
We analysed 143 DG patients (116 women) treated with RAI between October 2002 and April 2014 and ≥12 months of follow-up. Patients were assessed before (thyroid ultrasonography, thyroid scintigraphy, thyroid-stimulating hormone, free T4, free T3, and thyrotropin receptor antibodies (TRAbs)) RAI, and after 3, 6 and 12 months (thyroid-stimulating hormone, free T4) after RAI. Patients stopped antithyroid drugs 7 days before RAI. Successful treatment was defined as euthyroidism or hypothyroidism, 12 months after RAI treatment and no need for antithyroid drugs or additional RAI treatments.
Results
Therapeutic success was achieved in 80.4% of DG patients. Hypothyroidism prevalence increased during the study course; 43.2, 72.4, and 87% of patients had hypothyroidism at 3, 6, and 12 months, respectively. Univariate analysis showed TRAbs, functioning thyroid mass, and administered activity of RAI were significantly higher in patients with unsuccessful RAI treatment (48.2 U/l vs 20.0 U/l; 77.8 g vs 48.1 g; 517 vs 398 MBq, respectively). However, multiple logistic regression analyses demonstrated that only functioning thyroid mass was inversely associated with RAI success (odds ratio [OR] = 0.89, CI = 0.83–0.96, $P = 0.004$), particularly for estimated thyroid masses ≥60 g (sensitivity = 78%, specificity = 82%, likelihood ratio = 4.4, $P < 0.001$).
Previous treatment with methimazole, absence of thyroid nodules (≥1 cm), and scintigraphic homogeneous radiotracer uptake were associated with hypothyroidism development. Multivariate logistic regression confirmed previous treatment with methimazole and higher risk for hypothyroidism development (OR = 10.3, CI = 0.02–0.56, $P = 0.009$).
Conclusion
RAI was successful in most (80%) patients. Higher thyroid masses were associated with lower success rates. Patients previously treated with methimazole have higher probability of developing hypothyroidism after RAI treatment.

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GP208

Thyroid hormone profile after the single dose of iodine-containing contrast agent administration during coronary angiography-prospectice study

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Introduction
Previous studies suggest close relationship between thyroid morphology and the danger of thyroid hormones (THs) disturbances after high single dose of iodine-containing contrast agent. The aim of the study was to assess the prognostic risk factors which influence on THs after the cardiac catheterization at patient with coronary artery disease (CAD).
Methods
One hundred twenty patient (F/M = 40/80, 59 ± 11 years old) without recognized previous thyroid dysfunction and CAD were enrolled between March and October 2015 into the study group I ($N = 70$) with acute coronary syndrome (ACS) and II group ($N = 50$) with stable angina pectoris, matching to the age. Thyroid function serum parameters (TSH, fT_3, fT_4), serum concentration of thyroid antibodies (TPO-Ab, Tg-Ab) and thyroid ultrasound were performed before conventional angiography. Hormone status was also evaluated 48 h and 50 days after catheterization.
Results
At the admission, the subclinical hypothyroidism was recognize at five (4%) patients, low T_3 syndrome in two percents, thyroid antibodies at 8% and thyroid gland nodules at 44 (37%) participants. Two days after angiography the significant decrease of fT_3 occurred (mean differences −0.32 pg/ml, $P < 0.01$) and it was more significant in the group II (time × group interaction $P < 0.01$). After adjusting for thyroid morphology and thyroid antibodies the differences between groups was still significant ($P = 0.04$), but not after adjusting for the peak value of hs troponin T and hs CRP ($P = 0.23$). The concentration of fT3 normalized after 50 days in the whole group.
The TSH serum concentration was stable after 2 and 50 days after catheterization.
Conclusion
The iodine-containing contrast agent administration during coronary angiography is safe in the aspect of the thyroid function. It was not thyroid morphology but the presence of ACS which influenced THs levels.

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Thyroid – Translational & Clinical

GP209

Higher thyrotropin can be used as an additional risk factor in prediction of malignancy in euthyroid thyroid nodules evaluated by cytology based on Bethesda system

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Introduction
Recently, it has been suggested that thyrotropin (TSH) concentration can be used as a marker for prediction of thyroid malignancy. However, the association between the cytology results and TSH levels is not clear. In this study, we aimed to investigate the relationship between TSH levels and Bethesda categories and determine the role of TSH levels in prediction of malignancy in patients with different Bethesda categories.
Methods
The data of 1433 euthyroid patients with 3206 thyroid nodules who underwent thyroidectomy were screened retrospectively. The preoperative cytology results, thyroid function tests, thyroid autoantibodies and presence of histopathological Hashimoto's thyroiditis (HT) were recorded.
Results
Of the 1433 patients, 585 (40.8%) had malignant and 848 (59.2%) had benign histopathology. Malignant group had smaller nodule size, elevated TSH levels, a higher rate of presence of HT compared to benign group ($P < 0.001$, all). Cytology results of 3206 nodules were as follows; 832 nondiagnostic (ND), 1666 benign, 392 atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), 68 follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), 133 suspicious for malignancy (SM), and 115 malignant. Both SM and malignant cytology groups had significantly higher TSH levels than other 4 Bethesda categories ($P < 0.05$, all). Benign cytology group had significantly lower TSH levels compared to other cytology groups ($P < 0.05$, all). TSH was significantly lower in ND cytology group compared to AUS/FLUS, SM, and malignant cytology groups ($P < 0.001$, all). Patients with malignant final histopathology in ND and AUS/FLUS cytology groups had significantly higher TSH levels compared to patients with benign final histopathology ($P < 0.05$, all). As Bethesda category proceeded towards cytologies with higher estimated risk of malignancy, TSH levels tended to increase gradually.
Conclusion
In addition to cytology, TSH levels can be used as a supplementary marker in prediction of malignancy in certain Bethesda categories.

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GP210

The expression of co-stimulatory receptor SLAMF-1 in lymphocytes from patients with autoimmune thyroiditis

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Introduction
Signalling lymphocytic activation molecule SLAMF1 (CD150) is a modulatory receptor expressed in most immune cells. Different data indicate that CD150 is involved in T cell cytokine production, NK cell and CD8 T cell mediated cytotoxicity, and T regulatory (Treg) cell activity. Patients with autoimmune thyroid disease (AITD) show defects in their immune-regulatory mechanisms. Herein we assessed the expression and function CD150 in lymphocytes subpopulations from patients with AITD.
Patients and methods
Peripheral blood samples from 17 patients with Graves' disease (GD), 11 Hashimoto's thyroiditis (HT), and 21 healthy subjects were studied. Thyroid tissue samples were also analysed in five patients and expression of CD150 was assessed by flow cytometry and immunohistochemistry. In addition, the functional role of CD150 in CD4 + CD25 + Treg cells was assessed by a carboxyfluorescein proliferative assay.
Results
An increased expression of SLAMF1 by peripheral blood CD4 + T cells and Th17 cells was found in AITD patients compared to controls. In contrast, a decreased expression of SLAMF1 was observed in Treg cells from these patients. The SLAMF1 expression was diminished in thyroid mononuclear cells from AITD patients in comparison with peripheral blood CD4 + T cells. Finally, *in vitro* functional assays showed that exogenous SLAMF1 agonist increased activity in Treg cells from healthy controls but not in AITD patients.
Conclusion
The altered pattern of expression and the functional alteration of SLAMF1 found in patients with AITD suggests that SLAMF1 could be involved in the pathogenesis of AITD.

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GP211

Long-term outcome in levothyroxine treated individuals with Subclinical Hypothyroidism and concomitant Heart Disease

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Introduction
Subclinical hypothyroidism (SCH) is a common condition and can lead to impaired systolic and diastolic cardiac function. However, controversy remains over the potential benefits of levothyroxine substitution in patients with SCH and concomitant heart disease. We aimed to examine the effects of levothyroxine treatment on all-cause mortality in patients diagnosed with SCH and heart disease.
Methods
Primary care patients aged 18 years and older with established heart disease (ischemic heart disease, heart failure or cardiac arrhythmia) that underwent thyroid function tests in 2000–2009 were enrolled upon diagnosis of SCH. Exclusion criteria included a history of thyroid dysfunction, thyroid-related medication or medication affecting thyroid function. Patients were stratified according to cashed prescriptions of levothyroxine in a run-in period of 6 months. Risk of all-cause mortality was estimated as incidence rate ratio (IRR) by use of time-dependent Poisson regression models adjusted for age, gender and comorbidity, with patients not receiving levothyroxine as reference.
Results
The total study cohort comprised 814 patients with concomitant SCH and heart disease (mean age 74.1 (s.d. $\pm$13.5) years, 65% female). Within the run-in period of the first 6 months 44 (5.4%) patients were prescribed levothyroxine. During a median follow-up time of 5.1 years (IQR 8.7–2.8), 442 (54.3%) patients died. Incidence rates for all-cause mortality were 9.7 and 8.0 per 100 person-years among untreated and levothyroxine-treated patients, respectively. No significantly increased risk of all-cause mortality was found in patients substituted with levothyroxine (adjusted IRR 1.06 (95% CI: 0.69-1.65)).
Conclusion
Levothyroxine substitution in patients with subclinical hypothyroidism and concomitant heart disease is not associated with a significant change in the risk of all-cause mortality in a real-world cohort study.

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GP212

Acute icteric hepatitis as a presentation of Graves' thyrotoxicosis

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Introduction
Graves' thyrotoxicosis has been known to affect other organ systems in the body including the liver. However, severe hepatitis in this clinical context is quite rare.
Case report
We report a 55-year-old man who presented with marked weight loss and jaundice. In addition, he had a diffuse goitre with fine tremors in the hands. Laboratory work-up revealed thyrotoxicosis with FT_4 of 87.9 pmol/l and TSH of $<$0.01 mIU/l. He had abnormal liver function with total bilirubin 258.3 µmol/l, Direct Bilirubin 217 µmol/l, indirect bilirubin 41.2 µmol/l, ALP 306 U/l and ALT at 54 U/l. Serological tests excluded viral hepatitis. Ultrasound of the thyroid and hepatobiliary system together with MRCP were normal. In view of the hepatitis, he was given a potassium iodide solution and dexamethasone (10 mg daily) to prevent the peripheral conversion of T_4 to T_3. The jaundice and liver function test improved within a few days. Carbimazole 20 mg daily was slowly commenced with the resulting drop of FT_4 to 25 pmol/l. However the ALP increased to 359 mmo/l requiring the reduction of carbimazole dose down to 10 mg daily. Subsequent FT_4 came down to 15 pmol/l and he successfully underwent an RAI therapy 2 months later, which was uneventful.
Discussion
Acute icteric hepatitis occurs in $<$1% of Graves' thyrotoxicosis, posing a management dilemma. This has to do with the close association between liver enzyme abnormalities and oral antithyroid medications. Propylthiouracil and carbimazole, may cause elevation in aminotransferase levels (28%) usually 6 weeks to 2 months after administration. In our patient the elevated aminotransferase level preceded the administration of the drug which lead to rapid aggravation of the hepatocyte damage.
In conclusion, derangement of liver enzymes associated with Graves' thyrotoxicosis even in fulminant cases tends to be transient and most patients recover with no long-term sequeale.

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GP213

Autoimmune thyroid disease related to Helicobacter pylori contamination

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Introduction
Strong association between pathogenesis of autoimmunity and bacterial infection particularly Helicobacter pylori (H.pylori) had been observed in numerous studies. Nevertheless the possible role of H.pylori in progression of autoimmune thyroid disease is still discussed.
The aim of the study was to reveal the relation between Hashimoto thyroiditis (HT) and presence of H.pylori as well as to analyze the impact of eradication therapy on level of the autoantibodies against thyroid peroxidase (anti-TPO).
Methods
One hundred forty six patients (112 females, 34 males) with HT were prospectively included in this study. Control group consist of 90 volunteers without history of thyroid disease. Urea breath test had been used to detect H.pylori in all subjects. In H.pylori-positive patients the 14 days eradication therapy – clarithromycin 500 mg, pantoprazole 40 mg, amoxicillin 1 g twice a day had been prescribed. The anti-TPO level had been measured using ELISA kits on baseline, 15th and 30th days. The results were analysed using two-sided Fisher's exact test and the respective odds ratio (OR) was calculated.
Results
The rate of H.pylori evaluation was 70% in HT patients compared with 53% in control group (OR $=$ 2.02, 95% CI 1.2–3.3; $P=0.01$). The successful HP-eradication rate was 86%. We revealed significant reduction of anti-TPO up to 62% ($P<$ 0.001) on 30th day in successfully treated patients. Notable reduction in the severity of tissue inflammation on ultrasound pictures had been observed under H.pylori-eradication therapy.
Conclusion
The sustained relationship between Hashimoto thyroiditis and presence of H.pylori had been revealed. Encouraging data of HP-eradication influence on anti-TPO level suggests the need for further observations and possible optimization of autoimmune thyroiditis diagnostic and treatment protocol.

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GP214

Evaluation of quality of life in euthyroid patients with high autoantibody titers

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Introduction
Thyroid dysfunction affects quality of life (QoL) in untreated patients. However, patients with high thyroid autoantibodies complain about symptoms that resemble thyroid dysfunction even if they are euthyroid. The aim of this study was to evaluate QoL in euthyroid patients with elevated thyroid autoantibodies.
Methods
Patients who admitted to Endocrinology clinic with symptoms of thyroid dysfunction and no other disease were included in the study. Thyroid function tests and thyroid autoantibodies (anti-thyroglobulin and anti-thyroid peroxidase) were studied. Patients with normal thyroid functions but high autoantibody titers ($n=100$) were included as the patient group. Healthy individuals with normal thyroid functions and normal autoantibody ($n=100$) titers were included as the control group. Short Form-36 (SF-36) questionnaire was used to assess and compare QoL between the groups. Beck Depression and Anxiety Inventories

were used to determine whether the effect of thyroid autoantibody positivity on patients' QoL is affected by the presence of depression and anxiety.
Results
Physical functioning ($P=0.004$), role physical (<0.001), role emotional (<0.001), social functioning (0.017), mental health (<0.001), vitality (<0.001), physical (<0.001) and mental (<0.001) component scores were significantly lower in patients compared to controls. Beck Depression ($P<0.001$) and Anxiety ($P<0.001$) Inventory scores were significantly higher in the patient group. Only bodily pain and general health were similar between the groups. In the patient group, all SF-36 domains were negatively correlated with both Beck Depression and Beck Anxiety scores.
Conclusion
This study revealed that QoL in euthyroid patients with high autoantibody titers was lower compared to healthy controls, and also negatively affected with depression and anxiety. Both physical and mental components of QoL are affected. Thyroid autoantibodies may therefore affect QoL and well-being independent of thyroid function tests.

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GP215

Assessing thyroid function and immunogenicity in patients undergoing chronic treatment with methadone

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Introduction
The aim of the study was to assess the function and immunogenicity of thyroid gland of patients undergoing chronic treatment with the opiate agonist Methadone.
Material and methods
Cross-sectional, observational study included patients from 18 to 40 years of age undergoing chronic treatment with Methadone for at least 6 months. A total of 176 participants took part in the study. 140 patients were from five clinical programs in Bulgaria and 36 clinically healthy people from the same age and without a history of thyroid disorder were selected as a control group. Patients' group was subdivided into different groups by dose of methadone, time of exposition and duration of heroin abuse before starting the methadone treatment by using the 25, 50, and 75 percentile of each value. We investigated thyroid function by measuring levels of fT_3, fT_4 and TSH in the serum of our participants. Also immunogenicity of thyroid gland was investigated by assessing levels of anti-Tpo-antibody and anti-Tg- antibody.
Results
Mean daily dose of Methadone was $98.9/\pm41$/mg. Mean duration of treatment was $33.91/\pm24.57$/months and the mean duration of heroin abuse prior starting the treatment with Methadone was $6.61/\pm4$/years. The patients' and the control group were identical by the factors sex, age and BMI. We found statistically significant higher levels of free T_4 in the patients' group. Also statistically significant differences were found in some of the groups compared with controls when analyzing factors duration of treatment with Methadone, daily dose and duration of heroin abuse. There were no statistically significant differences regarding levels of free T_3 and TSH. We did not found differences in immunogenicity between the groups.
Conclusions
Chronic Methadone treatment is associated with isolated higher levels of fT_4 without changing levels of TSH, fT_3 or immunogenicity of thyroid gland.

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GP216

Endocrine toxicities of immune checkpoint inhibitors: a single centre experience

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Introduction
Immune checkpoint inhibitors (ICI) are a new drug generation used for advanced neoplasias. They are monoclonal antibodies which enhance the immune system to combat cancer cells. As a result, immunologic tolerance can be altered and autoimmunity triggered. Toxicities associated to ICIs have been named immune-related adverse events (irAE). 'Time to resolution' of endocrine irAEs have not been well described as this term has not been defined in clinical trials. The aim of this study was to describe the frequency and characteristics of endocrine irAEs in the patients treated with ICIs at our centre.
Methods
Between 2010 and 2015, 91 patients have been treated with anti CTLA-4, PD1 and PD-L1mAbs for advanced neoplasias (melanoma, lung cancer and Hodgkin's Lymphoma). This report is based on the retrospective review of the records of 81 patients considered suitable for inclusion. For thyroidopathies, we defined "time to resolution" as the time it took to normalize TSH levels.
RESULTS
Seven patients (8.6%) presented endocrine irAEs. Five patients (6.2%) developed painless thyroiditis, 1 (1.2%) Hashimoto's thyroiditis and 1 (1.2%) hypophisitis. Endocrinopathies presented after a median of 9 weeks (2–11) once treatment started, and the patients received a median number of doses of 4.5. Thyroiditis where all secondary to antiPD1mAbs. All patients presented with the classic triphasic presentation with a median of 7 weeks of hyperfunction and a mean time to resolution of 20 weeks. Three of five patients developed permanent hypothyroidism. The patient with hypophysitis presented with asthenia, intense headache and blurred vision 11 weeks after starting treatment with an antiCTLA4mAb. Corticotroph and thyrotroph axes where affected and have not recovered 6 months after the event. Five more patients (6.2%) showed a transitory decrease in TSH with normal T_4 and T_3 levels which could correspond to Sick Euthyroid Syndromes or short, subclinical thyroiditis.
Conclusions
Endocrinopathies due to the use of ICIs are common and generally mild. In our series, thyroiditis was the most frequent irAE. Clinical presentation and duration of ICIs-induced thyroiditis is similar to sporadic cases, although there could possibly a higher tendency to develop permanent hypothyroidism. Hypophisitis is an unfrequent but serious irAE. Endocrinologists must be aware of this emerging cause of autoimmune endocrinopathies.

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GP217

Evaluation of the interrelations between thyroid function, insulin resistance, lipid profile, C-reactive protein and homocysteine in patients with autoimmune thyroiditis

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Introduction
In patients with autoimmune thyroiditis, thyroid function appears to be related to increased cardiovascular risk. It was our objective to evaluate the relationship between TSH, insulin resistance, lipid profile, C-reactive protein (CRP) and homocysteine in patients with autoimmune thyroiditis (AIT).
Methods
We analyzed the lipid profile, the CRP, anti-thyroid antibodies, homocysteine, folic acid, vitamin B12 levels and the insulin resistance indexes such as HOMA-IR, QUICKI (Quantitative Insulin Sensitivity Check Index), HISI (Hepatic Insulin Sensitivity Index), WBISI (Whole-Body ISI) and IGI (Insulinogenic Index), in 171 patients with AIT and TSH <2.00 μUI/ml and in 71 patients with AIT and TSH >2.00 μUI/ml. All patients had normal levels of FT_3 and FT_4. The statistical analysis was done with the Student's *t*-test and Pearson correlation. The results are in mean $\pm$ DP. We considered a two-tailed *P*-value of <0.05 significant.
Results
We found significantly higher levels of insulin at 120 min of OGTT in the patients with TSH >2.00 μUI/ml (65.9 ± 57.8 vs 84.1 ± 65.4 μUI/ml; $P=0.02$). The levels of homocysteine were also significantly higher in the group with TSH >2.00 μUI/ml (10.8 ± 12.6 vs 8.3 ± 3.3 μmol/l; $P=0.04$). We found the IGI (0.036 ± 0.378 vs 0.252 ± 0.310; $P=0.02$) and WBISI (6.323 ± 7.335 vs 6.112 ± 4.019; $P=0.003$) indexes to be significantly higher in the TSH >2.00 μUI/ml group. In the group with TSH <2.00 μUI/ml there were positive correlations between IGI and the triglyceride levels ($r=0.256$; $P=0.004$) and the anti-TPO levels ($r=0.137$; $P=0.03$). In the same group we found negative correlations between WBISI and CRP ($r=-0.199$; $P=0.02$) and positive correlations between WBISI and TSH ($r=0.44$; $P=0.01$). In the group with TSH >2.00 μUI/ml we found positive correlations between the FT_4 levels and the BMI ($r=0.413$; $P<0.001$). In the same group the levels of LDL were positively

correlated with TSH ($r=0.245$; $P=0.04$), and negatively with FT_3 ($r=-0.265$; $P=0.02$). There was also a positive correlation between the Lp(a) and FT_4 levels ($r=0.259$; $P=0.04$).
Conclusion
In patients with AIT, the relationship between thyroid function, lipid profile, homocysteine and the insulin resistance indexes, may contribute to an increased cardiovascular risk.

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GP218

Relationship between immunoexpression of IL17A, CD68 positivity and lymphocyte infiltration degree in Hashimoto's thyroiditis patients

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Introduction
Th17 cells and their hallmark cytokine IL-17A were reported to be involved in the development of autoimmune orchitis and encephalomyelitis by impairing the integrity of the blood–testis and blood–brain barrier integrity and by inducing local inflammation. However, the role of IL17A in autoimmune thyroid disease is still debatable.
The aim of our study was to estimate immunoexpression of IL-17A in the thyroid tissue of patients with Hashimoto's thyroiditis (HT) and Graves' disease (GD) compared to control group.
Materials and methods
35 adult patients presenting 18 cases of HT, seven of GD, and ten cases of ordinary colloidal goiter without autoimmune component undergoing thyroidectomy were enrolled in this study. Immunostaining was performed using an anti-IL17A antibody; macrophages were visualized by CD68 immunohistochemistry. Results were expressed in a semiquantitative manner.
Results
The highest expression level of IL17A in the follicular epithelial cells was observed in HT patients, furthermore, in HT and GD patients it was significantly higher than that in control group ($P<0.001$; $P=0.007$, respectively). CD68-positive macrophages of both intra- and extrafollicular localization were observed in all tissue samples. The largest number of CD68-positive cells within follicular lumen was found in HT patients ($P=0.001$). CD68 positivity observed in GD patients was higher compared to nodular goiter, but the difference was not significant ($P=0.064$). A strong positive correlation was found between the degree of inflammatory cell infiltration and the number of CD68-positive macrophages in HT patients ($r=0.912$, $P=0.0001$). In addition, HT patients demonstrated a moderate positive correlation between CD68 and IL17A immunopositivity ($r=0.631$, $P=0.005$).
Conclusion
Overexpression of IL17A in the follicular epithelial cells associated with the presence of intrafollicular macrophages and high inflammatory infiltration degree in HT patients may indicate the involvement of IL17 in thyroid follicular barrier impairment.

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Thyroid Cancer

GP219

Prognostic factors for tumor invasiveness in papillary thyroid microcarcinomas

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Introduction
Papillary thyroid microcarcinomas (PTMC) are usually considered low-risk tumors with favorable prognosis. However, a small percentage behaves aggressively and controversies exist for various prognostic factors. The aim of this study was to evaluate demographic and tumor specific characteristics related to PTMC invasiveness.
Patients – methods
This is a retrospective study of 510 thyroidectomized patients with PTMC who were treated in two Endocrine Departments of Athens, between 1995 and 2015. All data were obtained from the patients' medical records. Most of the patients underwent thyroidectomy for multinodular goiter (70.5%) and the rest for a single nodule (29.5%). Demographic and tumor specific characteristics were evaluated.
Results
Patients' mean age was 46.4 ± 12.9 years. Women were more frequently affected (84.5%) than men. Pathology of the tumors revealed classic papillary subtype in 55.4% of the patients, follicular variant in 35.4%, tall cell variant in 2.7%, columnar variant in 0.2% and combinations less frequently. Regarding tumor size, the median diameter was 8 mm (0.01–15). Patients were divided in three subgroups regarding maximum tumor size as follows: 0–5 mm (47%), 6–10 mm (46.6%) και 11–15 mm (6.4%). Multifocality was observed in 34.9% of the patients, while 3.4% had PTMC in more than three foci. The median diameter of the sum of all foci was 8 mm (range 1–43 mm). Thyroid capsule invasion was present in 25% of the patients, lymph node invasion in 8.7%, muscle or fat tissue invasion in 6.4% and vessel invasion in 1.4%. Multiple regression analysis revealed that PTMC variants, was the only independent predictive factor for invasiveness.
Conclusions
Tumor subtype seems to be the most powerful prognostic factor for PTMCs aggressiveness, as it is expressed by invasion of thyroid capsule or surrounding tissues.

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GP220

Genomic alterations of anaplastic thyroid carcinoma detected by targeted massive parallel sequencing of a BRAFV600E mutation-prevalent area

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Background
Anaplastic thyroid carcinoma (ATC) is the most aggressive type of thyroid cancer and has no effective therapy. Due to its dismal prognosis, it is vital to understand the genetic alterations of ATC and identify effective molecular targets. We performed targeted next-generation sequencing to investigate the mutational profile of ATC using a massive parallel sequencing approach.
Methods
DNA from formalin-fixed, paraffin-embedded archival samples of 11 ATCs and normal matched pairs were used. We identified 45 genetic alterations by targeted exome sequencing. They were validated by mass spectrometric genotyping and direct Sanger sequencing.
Results
The most commonly mutated gene was BRAF identified in ten samples (91%); all showed the V600E point mutation. A KRAS point mutation was observed in the one sample (9%) without the BRAF V600E mutation. All 11 ATCs harboured BRAF or RAS mutations, reflecting the possibility that differentiated thyroid carcinomas progress to ATCs after the accumulation of mutations. A loss of function mutation of TP53 was observed in eight samples (73%) and a PIK3CA mutation was observed in two samples (18%). We found 29 novel mutated genes that had not previously been associated with ATC. Of these, loss of function mutations of NF2, KMT2D and PKHD1 were repeatedly seen in three samples (27%), two samples (18%) and two samples (18%), respectively. Using direct Sanger sequencing, we also found two samples (18%) with a RASAL1 mutation. KMT2D and RASAL1 mutations were significantly associated with shorter ATC patient survival.
Conclusions
In this comprehensive analysis of ATCs using targeted massive parallel sequencing identified several novel mutations of ATCs, such as loss of function mutations of NF2 or KMT2D. Future studies are needed to confirm the role of these novel mutations as independent drivers for ATC development.

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GP221

Predictive value of SPECT/CT after radioiodine therapy in differentiated thyroid cancer

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Purpose
SPECT/CT has numerous advantages over planar and traditional SPECT images. The aim of this study was to evaluate the role of SPECT/CT after radioiodine treatment of patients with differentiated thyroid cancer (DTC) in early risk classification and in prediction of late prognosis.
Methods
One hundred and eighty-one consecutive patients with DTC were investigated after their first radioiodine treatment. The risk for recurrence based on ATA 2009 classification was low, intermediate and high in 67, 93 and 21 cases, respectively. ETA classification showed low risk in 86, high risk in 95 patients. Planar image from the neck, whole body scan and SPECT/CT from the neck and chest were carried out in all patients 4–6 days after oral administration of 1100–3700 MBq radioiodine.
Results
SPECT/CT was positive in 25.9% of patients, detecting lymph node metastases in 42, lung and bone involvement in 8 and 3 patients, respectively, resulting in the early reclassification of 57 cases (31%). No evidence of disease was found in 140 cases at 9–12 months after radioiodine treatment and 144 patients at the end of follow-up (median 55 months). The sensitivity, specificity and diagnostic accuracy of risk classification systems to predict the persistence or relapse of the tumor at one year were the followings: ATA: 94, 46, 55%; ETA: 88, 57, 63%; SPECT/CT: 76, 85, 83%. The risk for late recurrence was reevaluated based on the 1-year results. The 1-year risk prediction had high diagnostic value at the end of follow-up: sensitivity: 97, specificity: 96, accuracy: 96%.
Conclusions
SPECT/CT after radioiodine treatment is useful in the early classification of patients and influences the therapeutic plan. Risk stratification based on SPECT/CT has lower sensitivity and higher specificity and diagnostic accuracy than ATA and ETA classification. Reevaluation of patients for risk of relapse is required at 1-year follow-up.

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GP222

Clinical outcome of thyroid nodules characterised as follicular neoplasm or suspicious for a follicular neoplasm (The Bethesda System for Reporting Thyroid Cytopathology) after fine-needle aspiration

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Introduction
Follicular neoplasm (FN) or suspicious for a follicular neoplasm category is established by The Bethesda System for Reporting Thyroid Cytopathology because of the necessity to identify a nodule that might be a follicular carcinoma and triage it for surgical lobectomy. Estimated risk of malignancy for this category is 15–30%.
Description of methods
We conducted a retrospective study that included all patients with a follicular neoplasm result after thyroid fine-needle aspiration (FNA) between 2010 and 2014. The following variables were considered: age, necessity of surgery and type of procedure (total or partial thyroidectomy), malignancy incidence rate.
Results
We studied 97 patients (85.6% female; mean age 53 ± 15 years). Thyroidectomy was performed in 62.9% of all patients. Lobectomy was the selected procedure in 32.8% of cases. 67.2% of patients underwent total thyroidectomy. The incidence of malignancy was 16.4% of patients who underwent surgery (13.2% of the total sample). Of those that proved to be malignant two Hurthle cell carcinomas, one papillary carcinoma, one follicular carcinoma and two medullary carcinomas were found. In 4 cases incidental papillary microcarcinoma were discovered after surgery. 19.6% of benign lesions were follicular adenomas.
Conclusions
Follicular neoplasm or suspicious for a follicular neoplasm category is a useful tool for classifying those thyroid FNA that may be suspicious for follicular carcinoma and may help selecting patients that should undergo surgery. The incidence of malignancy detected in our series is consistent with the incidence expected by the Bethesda System for Reporting Thyroid Cytopathology.

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GP223

Macro, but not micrometastases, detected by OSNA technique are related with more aggressive papillary thyroid cancer features

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Introduction
Classically, risk stratification in papillary thyroid carcinoma (PTC) assigned the same magnitude of risk to all patients with regional lymph node involvement (N1 disease). However, specific lymph node characteristics (such as size, number, extension, etc.) will allow individualizing treatment and follow-up. One-Step Nucleic Acid Amplification (OSNA) measures the number of copies of mRNA of cytokeratin 19 (CK19) as a marker of lymph node metastasis. Thus, copy numbers between 250 and 5000 were considered micrometastases (mM1), and more than 5000 copies were designated as macrometastases (MM1).
Objective
To analyze the influence of OSNA lymph node metastasis classification in the histological characteristics of PTC in patients submitted to lymph node dissection (LND).
Material and methods
LND from 40 patients (28 female, mean age 49 ± 15 years old) were evaluated. Lymph node metastases were detected using OSNA. Metastases characteristics include total tumoral load (TTL), TTL per total lymph node weight (TTL/TLNW), and mM1 versus MM1. According to the metastases status tumor related variables were studied.
Results
A total of 513 lymph nodes were found, with a mean (S.D.) of 12.8 (9.5) per patient. Thirty LND were considered positive for metastases (75%). There were no significant differences in tumor histological variables and TTL or TTL/TLMW. According to mM1 versus MM1 status, there were 10 (25%) patients with no lymph node involvement, 11 (27.5%) with only mM1, and 19 (47.5%) with at least one MM1. Only this last group was significantly related with primary tumor size ($P = 0.04$), vascular invasion ($P = 0.03$), extrathyroidal extension ($P = 0.04$) and positive margin ($P = 0.04$).
Conclusion
Lymph node macrometastases detected by OSNA are related with more aggressive PTC. OSNA could be a useful technique to improve lymph node metastases characterization.

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GP224

A cancer of undetermined significance – incidental thyroid carcinoma

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Introduction
Incidental thyroid carcinoma (ITC) in patients operated on for a benign disease is frequent. ITC characteristics in patients operated for malign disease, but not sampled by fine needle aspiration (FNA) or seen in ultrasonography, is unknown. We aimed to compare ITC with nonincidental ITC (NITC) in this study.
Material and method
Retrospective analyses of 918 individual patients who were operated for benign and malign thyroid disease in our hospital between December 2006 and September 2014 and had a final histologic diagnosis of thyroid carcinoma were enrolled in this study. All patients underwent ultrasonographic examination and FNA biopsy was performed for all nodules > 1 cm and nodules ≤ 1 cm with at least one of the suspicious ultrasonographic findings as irregular margins, hypoechoism, increased internal vascularity and presence of microcalcifications.

The lesions in thyroidectomy specimens that did not represent the FNA or ultrasonographic nodule target were classified as ITC. The lesions that match with FNA results or ultrasonographic features were classified as NITC. Characteristics of ITC and NITC were compared in this study.
Results
There were 1231 cancer foci in histopathology specimens. Among all these cancer foci, 687 were detected incidentally while 635 were detected non-incidentally. Mean age was 51.6 ± 11.01 in ITC group and 48.1 ± 13.1 in NITC group ($P < 0.001$). Mean size was 12 mm (1–90 mm) in NITC group while it was 3 mm (0.1–25 mm) in ITC group and differed significantly between the groups ($P < 0.001$). Frequency of capsular invasion (37%/7.9%), extrathyroidal extension (16.2%/4.1%), non-complete resection (11.9%/2%) and lymph node metastasis (9.1%/2.6%) were significantly higher in the NITC group ($P < 0.001$).
Conclusion
ITC is often encountered in older patients and frequently determined in early stages that can relieve the clinicians.

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GP225

Relationship between autoimmune thyroiditis and papillary thyroid cancer

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Introduction
Coexistence of autoimmune thyroiditis (AIT) and papillary thyroid cancer (PTC) has been well documented, but causality is still a matter of debate. Pathogenetic links between PTC and AIT try to explain two theories: 1) PTC is induced or facilitated by AIT, 2) AIT is a response to PTC. It is believed that PTC associated to AIT has a better prognosis.
Aims
To find out: 1) the incidence of AIT in PTC patients, 2) the course of PTC associated to AIT, 3) relationship between these diseases.
Methods
Histological and laboratory results of 1251 differentiated thyroid cancer (DTC) patients were reviewed. 90% of them were PTC patients. Diagnosis of AIT was based on histological finding and/or high antiTPO level ($\geq$ 3-times above upper reference range limit).
Results
The incidence of AIT in DTC/PTC patients was 41% (four-times higher compared to general population). PTC patients with coexisting AIT compared to that without AIT had better prognostic indicators (TNM), e.g. significantly higher incidence of micro- and small cancers (T1) and lower incidence of distant metastases. These illusory favourable findings were caused by the fact, that 65% of AIT patients were followed-up for this disease and PTC developed and was revealed during this period. When we compared prognostic indicators of PTC patients without AIT with those of PTC patients where AIT was revealed only after operation, no significant difference were found out. AIT therefore does not improve the clinical course of PTC patients.
Conclusions
We detected a high incidence of AIT in PTC patients. These data support the hypothesis that AIT is a predisposing factor in the development of PTC. Clinicians should pay particular attention to thyroid nodules in AIT. AIT does not represent a protective factor against spreading of PTC. At first sight better prognosis of PTC with coexisting AIT is not caused by immunological mechanisms, but by follow-up of AIT patients and therefore timely diagnosis of PTC.

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GP226

Systemic epidermal growth factor receptor-targeted gene delivery using the theranostic sodium iodide symporter (NIS) gene in an advanced orthotopic tumor model

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The well characterized sodium iodide symporter (NIS) in its dual function as reporter and therapy gene displays an outstanding opportunity to target different cancer types allowing non-invasive imaging of functional NIS expression and therapeutic radionuclide application. We recently reported induction of tumor-selective accumulation and therapeutic efficacy of radioiodide after systemic non-viral epidermal growth factor receptor (EGFR)-targeted NIS gene delivery in a subcutaneous hepatocellular cancer (HuH7) xenograft tumor model.
As a next step towards clinical application, we investigated tumor specificity and transduction efficiency of EGFR-targeted polyplexes based on linear polyethylenimine (LPEI), polyethylene glycol (PEG), and the synthetic peptide GE11 as an epidermal growth factor receptor (EGFR)-specific ligand (LPEI-PEG-GE11) as systemic NIS gene delivery vehicles in an advanced orthotopic tumor model. HuH7 cells were injected directly into the liver leading to the development of orthotopic liver tumors, representing a clinically more relevant model, as it reflects the clinical situation more adequately including the tumor microenvironment. *In vitro* experiments with LPEI-PEG-GE11/NIS polyplexes had already demonstrated high levels of EGFR-specific transduction efficacy in HuH7 cells. Mice with orthotopic HuH7 liver carcinomas showed high tumoral levels of functional NIS protein expression 24 h after intravenous injection of LPEI-PEG-GE11/NIS as shown by ^{124}I-PET/^{18}F-TFB imaging and *ex vivo* biodistribution. In contrast, injection of control vectors (LPEI-PEG-Cys/NIS) did not result in specific iodide uptake.
In conclusion, our preclinical data confirm the enormous potential of EGFR-targeted synthetic polymers for systemic NIS gene delivery in an advanced orthotopic tumor model and open the exciting prospect of NIS-mediated radionuclide therapy in advanced disease.

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GP227

Is ultrasensitive Tg measurement capable of substituting for Tg measurement after rhTSH stimulation in evaluation of effectiveness of radioiodine ablation in patients with differentiated thyroid cancer

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Introduction
Undetectable concentration of Tg after rhTSH stimulation (Tg/rhTSH) is one of the most important criteria in evaluating the effectiveness of radioiodine ablation in patients with differentiated thyroid cancer (DTC) treated with 131I.
Aim
To evaluate the possibility of using L-T4 suppression treatment (Tg/L-T4) measurements by the ultrasensitive method TRACE (immunofluorescence method) with the KRYPTOR analyzer instead of the Tg/rhTSH measurements with the chemiluminescent immunoassay (CLIA).
Material
The study was performed on 34 consecutive DTC patients after surgery and adjuvant treatment with 131I, referred for evaluation of ablation effectiveness 9 months after 131I treatment.
Method
Tg measurement was performed in patients during L-T4 treatment at two time points: before administration of rhTSH and 5 days after the first injection, using both tests: Tg detection with CLIA (analytical sensitivity 0.2 ng/ml and functional sensitivity of 0.9 ng/ml) and Tg by TRACE (analytical sensitivity of 0.09 ng/ml and functional sensitivity 0.15 ng/ml).
Results
Tg/L-T4 concentration in all patients was < 1.0 ng/ml in the CLIA assay, and in the range of < 0.09 ng/ml – 0.354 ng/ml in the TRACE assay. After rhTSH stimulation, Tg concentration of < 1.0 ng/ml (excellent treatment response) as measured by CLIA was found in 30/34 patients. In four patients, however, Tg/rhTSH was in the range of 1.0–10.0 ng/ml (1.02, 1.83, 2.2, 9.24 ng/ml – indeterminate response). In the latter group Tg/L-T4 by TRACE was 0.09 ng/ml; 0.1141 ng/ml; 0.1629 ng/ml; 0.09 ng/ml.
Conclusions
1 None of the four cases with indeterminate response to ablation showed elevated Tg/L-T4 concentrations according to the ultrasensitive TRACE assay.
2 Results in our trial group do not entitle us to recommend determinations of Tg/L-T4 with the TRACE method instead of the Tg/rhTSH in assessing the ablation efficacy.
3 It is necessary to validate the method on a larger group of patients.

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GP228

Genetic heterogeneity of thyroid cancer

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There are growing evidences suggesting the existence of intra-tumor heterogeneity within the same patient, leading to a different genetic pattern between primary tumour and metastases.
We report a paradigmatic example of genetic heterogeneity in thyroid cancer (TC). A 42 years old female patient was submitted, for a follicular TC, to total thyroidectomy and lymphadenectomy followed by radioiodine residue ablation in late 1999. In 2000 and 2001 diagnostic total body scans (TBS) were negative, thyroglobulin (Tg) and anti-thyroglobulin antibodies (TgAb) under TSH stimulation were negative, and patient was considered cured until April 2005 when Tg levels began to progressively increase. Between July 2006 and February 2008 the patient was submitted to four additional radioiodine treatments for lung metastases (total dose 27 750 MBq), with Tg levels ranging 30–40 ng/ml and negative TgAb neg. Since then, Tg and TgAb levels continued to increase and in November 2014 the patient was submitted to the surgical removal of a vertebral metastasis. At the molecular analysis, this bone metastasis was shown to harbour a C228T TERT mutation, while both the primary tumor and the lymph-node metastases were negative for the mutation. Possible explanation to this interesting finding are: 1) TERT mutation could have been acquired as a secondary event and transmitted to a subset of tumor cells at the primary site (sub-clonal distribution), 2) TERT mutation could have been acquired at the metastatic site, 3) the primary tumor could have been polyclonal. The present case clearly demonstrate that thyroid cancer can be genetically heterogeneous. This finding is highly relevant because clinicians must consider that the genetic pattern found in the primary tumor, that in some cases have oriented the clinical and therapeutic decisions, may evolve during tumor progression, in particular in the regional or distant metastases, also due to the selection pressure of treatment.

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GP229

ALK alterations in thyroid cancer

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Background
Thyroid cancer is the most frequent endocrine malignancy, with >7000 cases diagnosed in central Europe every year. Recently, ALK/EML4 translocations have been reported in single cases in anaplastic thyroid cancer (ATC). Little is known about the frequency of ALK alterations in poorly differentiated thyroid cancer (PTC). Our aim was to investigate the frequency of ALK alterations in patients with advanced thyroid carcinomas.
Material and methods
Formalin-fixed and paraffin embedded (FFPE) samples of 60 ATC and 55 PTC were analyzed. Five samples of goiters served as controls. FFPE samples were investigated immunohistochemically with different antibodies against ALK (clone D5F3, Cell Signaling Technology, and clone 5A4, Leica Biosystems). Stainings were analyzed quantitatively using a grid ocular, with an arbitrarily cut-off level of 10%. Additionally, fluorescence *in situ* (FISH) analysis was performed on tissue microarrays using Vysis ALK Break apart FISH probe (Abbott Laboratories), with a cut-off level of 15%.
Results
Of all investigated thyroid cancers, 10% of ATC and 27% of PTC showed immunohistochemically a light to moderate nuclear staining for ALK. All five controls were negative for ALK. FISH analysis showed single breaks without reaching the cut-off level for ALK/EML4 translocations.
Discussion
The occurrence of ALK/EML4 translocations is a rare event in ATC and PTC, with no verifiable case in our series. However, in contrast to the reported ALK-stainings, which were cytoplasmatic, we found a nuclear positivity in 10% of ATC and 27% of PTC, which has been not described in thyroid cancers so far. According to the recently described RANBP2-ALK translocation in epitheloid inflammatory myofibroblastic sarcoma, which show a nuclear ALK expression in immunohistochemical staining, further studies are necessary to clarify the significance of nuclear ALK stainings in thyroid carcinoma, and a possible different break event of the ALK gene.

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GP230

Analysis of germline VEGF-A SNPs allows the identification of a subgroup of ATA low-intermediate risk DTC (differentiated thyroid cancer) patients with poor probability to develop recurrences

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Introduction
Constitution of new blood vessels is crucial for cancer self-maintenance and progression. Neo-angiogenesis may be affected from hereditary traits, namely the presence of SNPs (single nucleotide polymorphisms) of genes involved in its regulation. VEGF-A represents the main regulator of angiogenesis. Germline SNPs of the VEGF-A gene have been associated to outcome of several cancers, but no data exist about differentiated thyroid cancer (DTC).
Patients and methods
Multicenter retrospective study. Blood samples were obtained from consecutive DTC-patients afferent to included centers (Federico II University, "*INT Pasc*ale" Institute, "*Cardarelli*" Hospital, Second University of Naples). Four VEGF-A SNPs (rs2010963, rs699947, rs833061, rs3025039) were chosen basing on their probable functional impact and genotyped using TaqMan protocol (Applied biosystems StepOnePlus). Clinico-pathological data at diagnosis and prognostic outcome were retrieved. The genotypes were analyzed as a three-group categorical variable (reference model) and according to the dominant and recessive model. Linkage disequilibrium (LD) was analyzed using HAPLOVIEW. Primary endpoint was rate of recurrent disease.
Results
Overall, 249 patients were included. Allele frequencies were consistent with data from the National Center for Biotechnology Information Databank. Genotype frequencies were in Hardy–Weinberg equilibrium ($P>0.05$). Outcome analysis was restricted to 226 patients classified as low-intermediate risk of recurrence according to ATA (America Thyroid Association) system, having a median follow-up of 4 years. Homozygous minor allele genotypes of rs699947 and rs833061 SNPs (A/A and C/C, respectively) were associated with a significantly lower rate of recurrent disease ($P=0.035$ and 0.031, respectively). rs699947 and rs833061 SNPs were in LD ($D'=1$). The combination of the genotypes A/A of rs699947 and C/C of rs833061 had PPV of non-recurrent disease of 97.3% (95%CI 85.84–99.93).
Conclusions
Analysis of germline VEGF-A SNPs refines risk stratification of DTC by identifying a subgroup of ATA low-intermediate patients with excellent prognosis.

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GP231

Antiproliferative actions of $1,25(OH)_2D_3$ in differentiated thyroid carcinoma are dependent on Sirtuin1 activity

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Antiproliferative actions of $1,25(OH)_2D_3$ (1,25D), the active form of Vitamin D, are reported in various types of cancer, whereas little is known about the

underlying molecular mechanism. Interestingly, in non thyroid-cancer cells, stimulation with 1,25D has been shown to affect cell proliferation in a Sirtuin 1 (Sirt1) dependent manner. Sirtuin histon deacetylases are key factors in cell metabolism recently found to be overexpressed in different carcinomas. The aim of the present study was to investigate the relevance of Sirt1 and the existence of a 1,25D-Sirt1 pathway in differentiated thyroid carcinoma (DTC). Sirt1 gene expression was analyzed in human DTC ($n=13$) and goiter tissue ($n=11$) by quantitative real-time PCR with CT-value defined as $2^{-[CTSirt1-CTGAPDH]} \times 10^6$. Furthermore, cells of papillary thyroid cancer cell line BCPAP were cultivated at 5×10^5 cell test approaches and incubated with or without ($=$Co) the following stimuli: 1,25D, Sirt1 inhibitor Ex-527 (Ex) or Ex$+$1,25D. After 96h, cell proliferation was measured by Neubauer counting chamber and Sirt1 gene expression was analyzed. In order to investigate the influence of 1,25D action on Sirt1 activity, stimulation with 1,25D$+$Ex was compared to stimulation with 1,25D alone. DTC showed enhanced Sirt1 expression in comparison to goiter tissue (DTC vs. goiter, 1.9×10^4 vs 7.7×10^3 $2^{-[CTSirt1-CTGAPDH]} \times 10^6$ p_c: 4×10^{-2}). Moreover, in cell culture 1,25D inhibited DTC proliferation (mean cell count: 1,25D vs Co$=5.6\times10^5$ vs 1.2×10^6 cells/ml, p_c: 6×10^{-4}). Interestingly, addition of Ex to 1,25D reduced the cell suppressive effect of 1,25D (Ex$+$1,25D vs 1,25D$=9.5\times10^5$ vs 5.6×10^5 cells/ml, p_c: 6×10^{-4}). However, none of the stimuli affect Sirt1 gene expression. This study indicates Sirt1 to be over-expressed in DTC. Furthermore, antiproliferative actions of 1,25D on papillary thyroid cancer cells appear to be dependent on Sirt1 activity, indicating the existence of a 1,25D regulated Sirt1 signal transduction in thyroid cancer cells.

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GP232

Does serum Galectin-3 add value in thyroid cancer diagnosis?

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Background
The role of circulating Galectin-3 as a potential biomarker of malignancy in thyroid disease remains inconclusive. In a previous pilot study we reported a significant difference between serum Gal-3 levels in papillary thyroid carcinoma (PTC) patients and those with benign pathology, but no association with tumor aggressiveness.
Aim
We measured serum Gal-3 levels in a larger series of patients submitted to thyroidectomy, in order to assess its value as possible biomarker in PTC.
Patients and methods
We retrospectively investigated serum Gal-3 in 190 patients, aged 49.09$\pm$13.55 years, 151 women (79.5%) and 39 men (20.5%). Patients, who gave their informed written consent, were divided in two groups, based on the pathology report: benign disease ($N=88$) and PTC ($N=102$). The thyroid cancer group was analyzed according to pathological stage, histological subtype, multifocality, invasion and tumor size. Sera were collected before surgery. Gal-3 was measured by Elisa, using a monoclonal antibody specific for human Gal-3 (R&D Systems). The study was approved by Ethics Committee of the Institute.
Results
According to the pathology tumor stage (T1-T4), the thyroid cancer patients were divided in four subgroups: PTC1 ($N=35$), PTC2 ($N=21$), PTC3 ($N=41$) and PTC4 ($N=5$). We found no significant difference in serum Gal-3 levels between cancer and non-cancer patients (9.98$\pm$2.66 ng/ml vs 8.11$\pm$2.81 ng/ml, $P=$NS), or between different PTC stages (PTC1:8.01$\pm$2.39 ng/ml vs PTC2:7.66$\pm$2.26 ng/ml vs PTC3: 8.36$\pm$2.95 ng/ml vs PTC4:9.57$\pm$2.78 ng/ml, $P=$NS for all comparisons). Serum Gal-3 did not discriminate between unifocal vs multifocal PTC or invasive vs non-invasive tumors. There was no correlation between serum Gal-3 and tumor size ($r=0.05$).
Conclusion
The analysis of a large series of patients with tumor thyroid disease, using a highly specific Gal-3 antibody, revealed no difference in serum Gal-3 between cancer and non-cancer patients and no correlation with tumor aggressiveness, suggesting no benefit in its use as a diagnostic test in thyroid cancer.

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GP233

Malignancy risk and false negative rate of fine needle aspiration cytology in thyroid nodules equal or greater than 4 cm

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Background
We aimed to evaluate malignancy rate in thyroid nodules $\geq$4 cm and determine false negativity of fine needle aspiration biopsy (FNAB) in these nodules.
Methods
Patients who underwent thyroidectomy between January 2007 and December 2014 in our institution were reviewed. Demographical and clinical data and preoperative ultrasonography (US) findings were obtained from the medical records. The nodules in these patients were grouped as $\geq$4 cm and $<$4 cm according to US measurements. Nodules $<$4 cm were further divided into 1–3.9 cm and $<$1 cm. US features and malignancy rates were compared. Histopathologically malignant nodules with preoperative benign cytology were defined to have false negative FNAB.
Results
Data of 5561 nodules in 2463 patients were analyzed. There were 1008 nodules $\geq$4 cm, 4013 nodules 1–3.9 cm and 540 nodules $<$1 cm. Histopathologically, 8.5, 10.2 and 25.6% of nodules $\geq$4 cm, 1–3.9 cm and $<$1 cm were malignant, respectively ($P<0.001$). There was no significant difference between the 1–3.9 cm and $\geq$4 cm nodules with respect to malignancy ($P=0.108$). Preoperative US features were similar in histopathologically benign and malignant nodules $\geq$4 cm, except higher prevalence of hypoechoic appearance in malignant ones ($P=0.02$). False negativity rates were 4.7% (32/683) in $\geq$4 cm, 2.2% (45/2093) in 1–3.9 cm and 4.8% (10/206) in $<$1 cm nodules. $<$1 cm and $\geq$4 cm nodules had similar false negativity ($P=0.93$), while 1–3.9 cm nodules had statistically lower false negativity than both groups ($P=0.03$ and $P<0.001$, respectively).
Conclusion
Malignancy rate in thyroid nodules $\geq$4 cm is similar with nodules 1–3.9 cm. Although false negativity of FNAB was significantly higher in $\geq$4 cm than 1–3.9 cm nodules, the rate was 4.7% which we think not high enough to recommend routine surgery when cytology was benign.

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GP234

TROP-2 is a novel reliable marker for immunohistochemical diagnosis of papillary thyroid carcinoma

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Introduction
Immunohistochemistry (ihc) in thyroid pathology is often recruited for differentiating between challenging benign and malignant tumors. There is no single antibody that can render definitive diagnosis. Most of the recently identified ihc markers have never been assimilated into daily clinical practice due to their low reproducibility and other associated limitations. Trop-2 ihc was recently reported as a useful tool for identifying papillary thyroid carcinoma (ptc) in fine-needle aspirate and tissue microarray samples. We aimed to validate trop-2 utility in the differential diagnosis of thyroid tumors on whole slide sections using automated digital image analysis.
Materials and methods
Trop-2 immunostaining was performed on a wide range of thyroid tumors ($n=226$) and controls ($n=207$).
Results
Normal thyroid, nodular goiter, hashimoto's thyroiditis, graves' disease, follicular adenoma, follicular carcinoma, and medullary carcinoma samples were negative for trop-2 ihc. The majority of ptc specimens (94/114, 82.5%) were positive for trop-2; however, the pattern of staining differed significantly between the histopathological variants. All papillary microcarcinomas (mptc), ptc classic variant (ptc cv), and tall cell variant (ptc tcv) were trop-2-positive with mainly diffuse staining. In contrast, less than half of ptc follicular variant specimens were positive for trop-2, with only focal immunoreactivity. Trop-2 could identify ptc cv with high diagnostic performance (sensitivity 98.1%, specificity 97.5%,

area under curve 98%). Roc curve analysis found that >10% of trop-2-positive cells in a tumor support a diagnosis of ptc. Trop-2 h-score was significantly associated with ptc variant and presence of capsular invasion in encapsulated ptc fv ($P<0.001$). None of the baseline (age, gender) and clinical (tumor size, nodal disease, tnm stage) parameters were associated with trop-2 expression.
Conclusion
Trop-2 membranous staining is a very sensitive and specific marker for ptc cv, ptc tcv, and mptc – with high overall specificity for ptc.

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GP235

Thyroid nodules: a highly specific molecular and cytological combined predictor of malignancy

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Thyroid nodules are very common and benign in most cases. Thus, malignancy detection avoiding overtreatment is a challenge. Nodule evaluation mainly supports on US and fine needle aspiration cytology (FNAC). The Bethesda classification (BC) for reporting thyroid cytopathology is now currently used for the interpretation of results but it does not enable classifying 30% of samples.
The objective was to identify, by transcriptome analysis, a molecular signature to improve the accuracy of preoperative diagnosis of nodules. We built a combined Bethesda-Molecular predictor that takes into account the prevalence of the disease.
Methods
In this prospective study, 722 patients with a solid thyroid nodule more than one centimetre diameter underwent FNAC. The molecular test, a transcriptomic array of 20 genes selected from a previous study, was performed on FNA material in operated patients. The optimal set of genes was identified using a logistic regression model to discriminate malignant and non-malignant nodules and was constituted of 7 genes. The performances of a combined predictor (molecular test in addition to BC) were compared to that of BC alone using the area under the ROC curve (AUC) for different levels of malignancy prevalence.
Results
Among the 225 operated nodules, 128 underwent the molecular test. In these patients, with a prevalence of malignancy of 36%, the combined predictor presented a 95% specificity and a 76% sensitivity. The AUC was 93.5%; significantly higher than the AUC of BC alone ($P=0.004$). In a general population of unselected nodules with an estimated prevalence of malignancy of 7%, the specificity of the test would be optimal (100%), but sensitivity would be lower (47.8%).
Conclusion
This very specific molecular test improves the detection of thyroid cancer in addition to standard cytological analysis and may be particularly useful in case of indeterminate result at cytological analysis.

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GP236

Utility of ultrasound shear wave elastography for diagnosis of malignant thyroid nodules: evaluation of maximum and standard deviation elasticity values

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Background
Shear wave elastography (SWE) is an emerging technique that can be used to evaluate malignancy in many organs. The aim of this study was to address the role of elasticity indices as a possible predictive marker for detecting papillary thyroid carcinoma (PTC) and quantitative assessment of SWE for differential diagnosis of benign and malignant thyroid nodules.
Methods
One hundred and nineteen patients with thyroid nodules undergoing SWE before ultrasound (US)-fine needle aspiration (FNA) were analyzed. The SWE elasticity indices of mean (E_{Mean}), minimum (E_{Min}), maximum (E_{Max}) and its standard deviation (E_{SD}) of nodules were measured.
Results
Among a total of 105 nodules, 14 were PTC and 91 were benign. E_{Mean} ($P=0.005$), E_{Min} ($P=0.034$), E_{Max} ($P<0.001$), and E_{SD} ($P<0.001$) were significantly higher in PTCs than in benign nodules. The cut-off values with high accuracy of E_{Max} and E_{SD} for predicting PTCs were 45.9 kPa, achieved 57.1% sensitivity and 88.1% specificity, and 5.0 kPa, achieved 71.4% sensitivity and 88.1% specificity, respectively. No thresholds produced high sensitivity without lowering specificity appreciably, and *vice versa*.
Conclusions
Although the quantitative assessment of SWE was significantly higher in PTCs than benign nodules, the precision results do not suggest a definitive role for SWE in identifying or excluding thyroid malignancy.

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GP237

The origin of patients with inherited medullary thyroid cancer, who are carriers of the rare exon 8 mutation (G533C) of the RET gene in Greece

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Introduction
Mutations in the *ret* gene are responsible for the transmission of inherited medullary thyroid cancer (MTC). In recent years a high prevalence of the 'rare' exon 8 mutation (G533C) has been found in patients with inherited MTC in Greece. The aim of this study was to record with more detail the place of origin of these families in the country.
Design
We analysed the details of 44 patients belonging to 22 families who were carriers of the *ret* G533C mutation. Data concerning their place of origin as well as that of their ancestors were collected. Patients were distributed in four age groups (G1-4) according to age at diagnosis.
Results
The age at diagnosis was 21.0 ± 2.9 (youngest age group G1, $n=4$), 37.7 ± 5.5(G2, $n=30$), 54.1 ± 4.4 (G3, $n=8$), 72.5 ± 0.7 (G4, oldest, $n=2$) years. The patients belonged to 22 families, 15 of which were index cases diagnosed in our centre. Twelve belonged to G2, two to G3 and one in G4. 'Hot spots' for the origin of these families were recognized. Nine families originated from central/western Greece in an area around Lake Trichonis, and Fokis, nine originated from Peloponese (Lakonia (mount Parnon region) and Arcadia), three from the Attika region (two from Pireaus) and four families from Asia Minor, all of them without any recognised familial relationship. No phenotype or outcome differences were found between the families from the various regions.
Conclusions
The majority of the *ret* gene exon8 (G533C) carriers originate from Central/Western Greece and Peloponese. Increased awareness for inherited disease is required for patients with apparently sporadic MTC originating from these areas, as the age at presentation is usually delayed (25–70 years).

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GP238

Correlation between basal and stimulated thyroglobulin in differentiated thyroid carcinoma of intermediate and high risk

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Thyroglobulin (Tg) is a highly sensitive tumor marker of differentiated thyroid cancer (DTC). To optimize the sensitivity, guidelines recommend Tg measurement after stimulation with recombinant TSH (rh-TSH) 6–12 months after radio remnant ablation (RRA). Based on recent evidence in Literature, it is possible to avoid the measurement of Tg after stimulation with rh-TSH (S-Tg) in presence of undetectable values of basal Tg (B-Tg) if high functional sensitivity (0.1 ng/ml) method is used. However, most patients enrolled in the available studies are affected by low-risk DTC, while there are less evidence in intermediate and high risk patients.

A retrospective analysis on 113 intermediate or high risk DTC patients has been performed. Risk stratification has been evaluated on the basis of 2009 ATA guidelines but our data were also considered on the basis of new ATA guidelines (2015). Patients were tested for B-Tg and S-Tg. All patients with undetectable B-Tg showed S-Tg <1 ng/ml (sensitivity: 100%). B-Tg cut-off showing best sensitivity and specificity (100% and 99% respectively) in predicting S-Tg <2 ng/ml was 0.22 ng/ml while in predicting S-Tg <1 ng/ml was 0.09 ng/ml (sensibility 100%, specificity 86%).

The cut-off appeared independent from the variables analyzed (pT, N, M, aggressive variants). Moreover, the cut-off appeared independent from Tg values during thyroid hormone withdrawal at the moment of radio remnant ablation.
We conclude that undetectable B-Tg values can predict the biochemical remission of DTC alternatively to S-Tg if high sensitivity assay is used, also in patients with intermediate or high risk DTC.

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Eposter Presentations

Adrenal cortex (to include Cushing's)

EP1

Establishment and characterization of immortalized porcine 11β HSD1-hepatocytes

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Glucocorticoid, known as cortisol, is a steroid hormone essential to the maintenance of homeostasis, and is released in response to stress and low blood glucose concentration. It is converted from cortisone by 11β hydroxysteroid dehydrogenase type 1 (11β HSD1). The liver plays a major organ in metabolism, has numerous functions, mostly consists of hepatocytes, and is a principal target of cortisol. In murine model, it was observed that too much cortisol or overexpression of 11β HSD1 induced obesity and the insulin resistance that accompanies metabolic syndrome. In our previous study, 11β HSD1-transgenic (TG) fibroblasts were established and then the porcine model was generated by SCNT using those fibroblasts. Hepatocytes overexpressing 11β HSD1 isolated from liver of this porcine model, and *in vitro* cultured. However, primary hepatocytes showed short life span and low proliferation rate. To overcome these problems, SV40 large T antigen, oncogene, was transduced into primary 11β HSD1-TG hepatocytes and those cells were immortalized. Immortalized 11β HSD1-TG hepatocytes shows restored morphology, more rapid proliferation rate, and more expression of 11β HSD1 than primary ones. Immortalized 11β HSD1-TG hepatocytes increase the expression of gluconeogenic genes including G6Pase and PEPCK by cortisone treatment. These immortalized cells maybe be useful for studying traits and potential pharmarcotherapeutic drugs for metabolic disorders induced by overexpression of 11β HSD1 in hepatocytes.

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EP2

Effect of heterophilic antibody interference in ACTH immunoassay to Subclinical Cushing's Syndrome screening: A pilot study

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Heterophilic antibodies are well-known interferent factors affecting most immunoassays. However, they have been poorly evaluated in routine clinical practice. Definition of Subclinical Cushing's Syndrome (SCs) has been arbitrary and prevalence has shown significant variations related with the diversity of the diagnostic tests. In most of the guidelines a low or suppressed corticothropin (ACTH) level has been suggested as an important predictor of SCs. Here, we sought to investigate the burden of heterophilic antibody interference in ACTH immunoassays in SCs screening.

We designed a pilot study including all referred individuals ($n=72$) with incidentally discovered adrenal adenomas between June 2015 and January 2016. We identified seven individuals having disproportionally elevated ACTH levels (>15 pg/ml) despite non-suppressed 1 mg DST(>2.5 μg/dl). In four of the subjects, polyethylene glycol precipitation (PEG) showed decreased recovery suggesting a high molecular weight interfering substance.

Interference in immunoassays is a well-known but usually underestimated problem, leading to discordant results and unnecessary, time consuming, expensive additional tests. A simple method using PEG precipitation of ACTH samples could distinguish individuals with suppressed ACTH levels.

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EP3

Pro-coagulant imbalance in patients with Cushing disease detected by thrombin generation assay is associated with increased levels of neutrophil extracellular trap-related factors

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Patients with Cushing disease (CD) are at increased risk of venous thromboembolism (VTE). It was surmised, but not conclusively shown that the risk is related to plasma hypercoagulability secondary to the effect of glucocorticoids. This study aimed at investigating the thrombin-forming potential of patients with CD in the presence of a functioning protein C system by adding its main physiological activator, thrombomodulin. Under these experimental conditions, which mimic closely the *in vivo* situation, we observed significantly enhanced thrombin-generation in patients with CD, as shown by the modification of thrombin generation parameters (i.e., shortened lag-time and time-to-peak, increased thrombin-peak and endogenous-thrombin-potential (ETP)). Moreover, the ETP ratio (with/without thrombomodulin), recognized as an index of hypercoagulability, was increased in patients as compared to controls, indicating that patients with CD are resistant to the anticoagulant action of thrombomodulin. We attempted to explain such hypercoagulability by measuring both pro- and anticoagulants factors and some other non-coagulation parameters (i.e., neutrophil extracellular traps (NET), recently associated with the risk of VTE and/or increased procoagulant imbalance. We show that the hypercoagulability detected by thrombin-generation in patients with CD is associated with increased levels of factor VIII and NET-related variables. Whether this plasma hypercoagulability can entirely explain the occurrence of VTE (first event or recurrence) in patients with CD should be investigated by ad hoc clinical trials. However, until these studies will be available the evidence for the hypercoagulability supports the concept that patients with CD are candidates for antithrombotic prophylaxis.

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EP4

Missed opportunities for appropriate diagnosis and management of profound hyponatraemia – Audit of District General Hospital experience

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Population and methodology

Patients with profound hyponatraemia (serum Na $\leq$125 mmol/l) admitted 1 November 2014 to 30 April 2015 were identified using hospital admission registry, laboratory's database and qualitative data from the patients' electronic records. Discharge summaries and death certificates were reviewed.

Objectives

This is a retrospective audit set to asses: i) whether initial investigations of hyponatraemia were performed in accordance to published European guidelines. ii) incidence of profound hyponatraemia among acutely ill iii) sodium level on discharge and crude mortality.

Results

201 patients (59% females) with serum sodium of $\leq$125 were admitted during the audit period. Serum Na ranged between 125 and 105 mmol/l, with 10% having Na (114. Incident increased with age (37% were $>$80 years).

Overall incidence of profound hyponatraemia in patients presenting to A&E department for the audit period was 2.51%.

In hospital mortality including 6 weeks post-discharge was 19% (38 patients).

When deceased patients were excluded, only 32 out of remaining 163 patients (20%) had complete initial investigations. These were completed within 24 hours of presentation in nine out of 32 patients (28%), 24–72 h in 10 (31%), and $>$72 h in 13 (41%). Of the 131 patients (80%) who did not have essential investigations, only 40 (31%) had recorded cause of hyponatraemia.

Discharge Na ranged between 120 and 146 with trend of improvement (average $\Delta+7.87\%$).

For deceased patients Na level ranged between 113 and 125, with varied registered cause of death.

Conclusion
Significant profound/severe hyponatraemia is common in acutely ill patients with increased incidence in elderly and associated with high crude mortality. Current practice lag well behind the desired standard of appropriate management. Three strategies were proposed to improve management; i) Electronic pop up alert, ii) readily available checklist, and iii) Incorporation of diagnosis in patients' records.

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EP5

Paradoxical worsening of lipid metabolism after successful treatment of primary aldosteronism

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Primary aldosteronism (PA) describes the most frequent cause of secondary arterial hypertension. Aldosterone itself represents a BP-independent cardiovascular risk factor associated with increased rates of morbidity and mortality. Recently a worsening of lipid metabolism after treatment has been described.
Objective
Our aim was to analyse changes in lipid parameters according to treatment outcome in PA patients. Data of 215 consecutive PA patients with unilateral aldosterone-producing adenoma (APA, $n=144$) or bilateral idiopathic adrenal hyperplasia (IHA, $n=71$) were extracted from the database of the German Conn's Registry.
To assess the metabolic outcome, they were investigated before, one year and three years after treatment by adrenalectomy (ADX) or by MR-antagonist (MRA).
Results
One year after initiation of treatment potassium had been normalized in all patients. High-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) changed inversely. HDL-C was significantly lower in patients with APA (53.00 (45.3; 67) vs 52.00 (44; 65) mg/dl, $P=0.046$) and IHA (52.00 (42; 66) vs 48.00 (39; 62) mg/dl, $P=0.004$) after treatment. TG were significantly higher in both subgroups at follow-up (APA 103.5 (69.3; 148.0) vs 111.0 (78.3; 166.5) mg/dl, $P=0.000$; IHA 111.0 (82; 150) vs 129.0 (85; 195) mg/dl, $P=0.020$), whereas BMI remained unchanged and fasting plasma glucose (FPG) even improved in follow-up patients with APA (99.0 (90; 109) vs 95.0 (88; 104) mg/dl, $P=0.004$). Changes in the HDL-C-to-TG ratio at one year follow-up correlated with decrease of GFR ($\beta=0.184$, $P=0.024$) in multivariate analysis but not with change in potassium, urea or urine albumin-to-creatinine ratio (ACR). After two more years there was a slight further decline in GFR ($P=0.012$), whereas HDL-C remained stable.
Conclusion
Our results show that treatment of PA is associated with a worsening of lipid parameters despite improved glucose parameters and stable BMI. This paradoxical effect could be explained by renal dysfunction following ADX or MRA treatment caused by a decrease in glomerular hyperfiltration. In view of stable low-density lipoprotein cholesterol, reduced albuminuria, FPG and blood pressure, however, a higher risk for atherosclerosis in patients with PA after treatment seems unlikely.

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EP6

Bilateral adrenalectomy is a safe long-term procedure

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The aim of this retrospective study was to compare the long-term evolution of adrenal insufficiency (AI) due to bilateral adrenal surgery (S) or medical cause (M).
Seventy AI patients (mean age 41 ± 16 years; 60% female, similar in both groups) were followed during a mean 6-year period (2–16); 38 were AI after bilateral adrenalectomy (60% Cushing), 32 AI of medical origin (62% polyglandular autoimmune syndrome). BMI, blood pressure (BP), fasting blood glucose (FBG), cholesterol, triglycerides (TG), metabolic therapy, cardiovascular events, AI episodes, hospital admissions, and death were recorded at the beginning of replacement therapy (T1) and at last news (T2).
At T1, prevalences of overweight/obesity, hypertension, type 2 diabetes (T2D and mean TG level were higher in S compared to M group ($P<0.01$). At T2, the prevalence of overweigh/obesity, hypertension and T2D were similar in both group (20–34%) but TG level remained higher in S group ($P=0.01$).
Between T1 and T2, 0% S patients developed hypertension and its prevalence decreased significantly ($P<0.003$) from 58% (T1) to 34% (T2) while other metabolic disorders prevalences remained the same. In M group, 22% developed hypertension, 21% T2D and 21% dyslipidemia while the prevalence of overweight increased significantly ($P<0.005$). A significantly higher weight gain in M vs. S groups ($P=0.0006$) and a greater FBG decrease in S vs. M groups ($P<0.0001$). Eight patients died (1 S). Cardiovascular events were more frequent in S (10%) vs. M (3%) groups. Acute AI (median/patient S: 0 (0–1); M 1 (0–5)) and hospital admissions (S: 1 (0–6); M: 2 (0–5)) did not differ between the 2 groups.
Conclusion
Compared to baseline, bilateral adrenalectomy appeared safe in the long-term and enabled significant improvement of hypertension and other metabolic disorders. Overtime, adrenal insufficiency, whatever surgical or medical origin were complicated with a metabolic syndrome in 20–30% of cases.

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EP7

Radiological formula for differentiating between secreting and non secreting adrenal adenomas

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Introduction
Purpose of this study is to find a radiological score and to correlate radiological characteristics of adrenal adenomas and functional parameters to predict subclinical glucocorticoid secretion.
Methods and materials
This retrospective study included 55 patients with adenomas, investigated through CT with adrenal protocol assessing diameters, HU values of the unenhanced and contrast enhanced phases (enhanced–E, and 15 min delayed enhanced–D). Patients underwent dexamethasone overnight suppression test 1 mg (DST). Post-DST cortisol >50 nmol/l identified subclinical cortisol secretion.
We identified 28 subjects with typical non secreting adenomas (NSA), nine with typical secreting adenoma (SA), 11 with atypical NSA and seven with atypical SA.
Results
The post-DST cortisol value was significantly and positively related to mass diameters. At univariate analyses only the two diameters were significantly related to post-DST cortisol ($P<0.001$), while at the stepwise multivariate analysis the minimum diameter first entered the procedure ($P<0.001$) and E also added a significant ($P=0.027$) contribution to the relationship (overall $r^2=0.334$; $P<0.001$). The correlation coefficients showed that, while the minimum diameter alone accounted for 26.8% of the variability of post-DST cortisol, the accounted variability of post-DST cortisol increased to 33.4% after the addition of E. The radiological score to discriminate SAs versus NSAs resulted in $0.2034\times$ minimum diameter $+0.0378\times$E.
Diagnostic accuracy in differentiating SAs from NSAs was 86.0%, sensitivity 90.9% and specificity 71.8%, considering SA in patients having a score >7.21 and NSA if <7.16.
Conclusion
This study confirms the relation between adenoma's size and glucocorticoid secretion. It also shows that, using the predictive radiological score, a more evident nodular pattern and a greater vascularity of the lesion corresponds to a greater functional activity.

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EP8

Serum but not salivary cortisol levels are influenced by daily glycemic oscillations in type 2 diabetes

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Diurnal salivary and plasma cortisol variations are considered valid expression of circadian cortisol rhythmicity. The aim of this study was to assess the reliability of salivary and plasma cortisol evaluating if glycemia and glycemic oscillations may interfere with their concentration.
Methods
Forty-seven type 2 diabetic patients and 31 controls were studied for glycemic profile and diurnal salivary and plasma cortisol variations on two contemporary samples taken at 0800 and 2300 h (Late Night, LN). Glucose variability was evaluated in diabetic patients by considering the standard deviation of blood glucose (BGSD) readings, by calculating the mean amplitude of glycemic excursions (MAGEs) and continuous overlapping net glycemic action (CONGA).
Results
A significant correlation between LN serum cortisol and morning fasting glycemia ($r=0.78$; $P=0.004$) was observed in T2DM group but not in the control group ($r=0.09$; $P=0.74$). While LN serum cortisol significantly correlated with CONGA in diabetic patients ($r=0.50$; $P<0.001$), LN salivary cortisol did not correlate with any indices of glucose variability. Moreover, a highly significant correlation between LN salivary and LN serum cortisol concentrations was found in control group ($r=0.80$; $P<0.001$) but not in diabetic patients ($r=0.07$; $P=0.62$).
Conclusions
This study shows for the first time that late night salivary cortisol may give more information than late night plasma cortisol on the dynamic of adrenal function of type 2 diabetic patients, as it is not significantly influenced by glycemic variations.

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EP9

The use of [131I] 6β-iodomethyl-norcholesterol scintigraphy in evaluation of adrenal tumors

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Adrenal cortex scintigraphy has been used as early as in the 1970s, however, in recent years, it has been a rarely performed and unappreciated examination. In fact, this examination does not provide a perfect view on morphology of adrenal glands, however it provides an assessment of the examined tumor's function. The aim of this work is to present our experience with adrenal cortex scintigraphy in assessment of adrenal tumors.
We present a series of 50 Iodomethyl-norcholesterol (NP-59) scintigraphies. The indications for examination were: subclinical hypercortisolemia in patients with bilateral adrenal tumors (32 cases), primary hyperaldosteronism (eight cases), uncertainty in assessment of cortex function ('border results' of hormonal investigations) (six cases) and assessment after the surgery of adrenal cancer (four cases). We used two different protocols, depending of assessed adrenal function (without dexametasone if hypercortisolemia was present, with dexamethasone in assessment of hyperaldosteronism).
Scintigraphy showed exclusive or predominant unilateral tracer uptake in 23 of 32 patients with hypercortisolemia. In all these patients after the adrenalectomy of the dominant gland, transient secondary adrenal insufficiency was observed, confirming the proper choice of the operating side. The scintigraphy in eight patients with primary hyperaldosteronism showed unilateral tracer uptake in four subjects. These patients have already been operated with clinical and biochemical benefits. The other four patients (tumors without uptake) are treated pharmacologically with good results. In six patients with 'border results' of hormonal investigations there was no tracer uptake after the dexamethasone, so their tumors were classified as non-secreting and the further observation until now confirms this statement. Finally, in one of four patients after the adrenalectomy due to adrenal cancer scintigraphy revealed a very small fragment of adrenal tissue, missed in the operated area.
We concluded that adrenal scintigraphy can be a useful method for functional assessment of various adrenal tumors.

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EP10

Computerized tomography and magnetic resonance imaging features for differentiating functioning adrenal lesions from non-functioning adrenal lesions

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Aim
The aim of the present study was to evaluate the characteristic features of computerized tomography (CT) and magnetic resonance imaging (MRI) among functioning and non-functioning adrenal lesions.
Materials and methods
We retrospectively reviewed the medical records of patients with adrenal mass. CT or MRI findings were available in 89 functioning and 148 non-functioning adrenal lesions (NFAL). Of the patients with functioning adrenal mass, 34 were diagnosed as Cushing's syndrome, 32 as pheochromocytoma and 23 as primary hyperaldosteronism. Patients with functioning adrenal lesions were defined as group 1 and patients with NFAL were adopted as group 2.
Results
Patients in group 1 were younger, with a similar gender distribution. In patients with functioning adrenal mass, adenoma size, unenhanced and early arterial phase Hounsfield units (HU) were significantly higher compared to those with NFAL. Patients with pheochromocytoma had significantly larger lesions, higher unenhanced HU levels and lower washout values compared with NFAL, Cushing's syndrome and primary hyperaldosteronism. Mean early arterial phase HU was higher in all functioning groups compared to NFAL. The best predictive cut-off value of early arterial phase HU for detecting functioning adrenal mass was 27 with a specificity of 80% and sensitivity of 82.7% on ROC curve analysis ((AUC:0.85, (95% CI 0.75–0.95)). On T1- weighted images 44.4% of the patients with functioning adrenal lesions were hypointense, whereas 18.9% of the patients with NFAL had hypointense lesions (P:0.02). T2-weighted images or chemical shift sequence in phase and out phase images between functioning and non-functioning adrenal adenomas showed no difference.
Conclusion
Our study revealed that functioning adrenal lesions might be discriminated from NFAL using CT characteristics, and T1- weighted MRI images. Especially early arterial phase HU, which is elevated in all functioning adrenal mass forms, can be used effectively to distinguish functioning adrenal lesions from NFAL.

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EP11

ARMC5 mutation and Cushing syndrome due to bilateral macronodular adrenal hyperplasia – case report

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Introduction
Bilateral macronodular adrenal hyperplasia ACTH-independent (BMAH) represents less than 1% of the causes of Cushing's syndrome (CS). Studies have shown that mutations in the gene ARMC5 are a common cause of family BMAH and are associated with severe clinical disease and the development of meningiomas.
Case report
64-years-old man presented to our consult due to bilateral macronodular adrenal hyperplasia. He had diabetes mellitus, arterial hypertension, dyslipidemia and coronary heart disease. The physical exame showed excess weight (weight 81 kg, height 1.65 m, BMI 29.7 kg/m^2), bruising, facial rubeosis, skin atrophy and deposition of cervical dorsal fat. Laboratory work up revealed ACTH-independent CS: ACTH $<$ 1 ng/l (ref.v. $<$ 63.3), serum cortisol after 1 mg dexamethasone suppression test 27.6 µg/dl, urinary free cortisol (UFC) 520 µg/dl (ref.v. 36–137) and serum cortisol after low-dose dexamethasone test 24 µg/dl. He underwent research of ectopic adrenal hormone receptors with positive response (under β-blocker and angiotensin receptor antagonists) and partial (after discontinuation of these drugs) in the posture test and negative response to the others tests. The patient would be subjected to adrenalectomy, but due a complication during surgery, he performed just right adrenalectomy. Histological results confirm macronodular adrenal hyperplasia. Genetic study was preformed and a ARMC5 mutation in heterozygosity (c.1379T$>$C) was identified in adrenal and blood. Patient is currently with no evidence of CS: UFC 36.3 µg/dl, salivar cortisol 0.180 and 0.193 µg/dl (ref.v. $<$ 0.32) and ACTH $<$ 1 ng/l). Cerebral CT performed showed left posterior temporal calcified lesion, placing the hypothesis of meningioma.
Conclusion
Genotyping of ARMC5 gene has important clinical implications in counseling the patient and family: the presence of the mutation helps identify patients at risk of developing CS and other related injuries, allowing early diagnosis and treatment. There are cases described of CS remission after unilateral adrenalectomy, so we opted for medical surveillance of the patient.

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EP12

Nonfunctional adrenal incidentalomas and cardiometabolic risk

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Background
Incidentally discovered adrenal tumours have become a common clinical problem. The presence of an adrenal incidentalomas has been associated with an increase incidence of several cardiovascular risk factors. These abnormalities are more frequent in patients with clinical and subclinical hypercortisolism, nevertheless some studies have reported an association between nonfunctioning adrenal incidentalomas (NFAIs) with increased insulin resistance and cardiovascular risk.
Aim
The aim of the study was to identify features of cardiometabolic risk in patients with NFAIs.
Material and methods
Fifty-one patients with adrenal incidentaloma and negative screening testes to rule out catecholamine, mineralocorticoid and glucocorticoid overproduction were included in the study. Retrospective analysis based on clinical parameters and results of imaging and laboratory procedures was conducted. Features such as BMI, hypertension, abnormal parameters of glucose and lipid metabolism were assessed. Cardiovascular risk was estimated with SCORE (The European Systematic Coronary Risk Evaluation).
Results
We investigated 51 patients with NFAIs (67% were females) with mean age of 61 $\pm$ 10 years. The mean adrenal mass size was 21.5 $\pm$ 9.3 mm; 30% had bilateral incidentalomas.
Excessive body mass was observed in about 66% of patients: 38.3% were overweight and 27.7% obese. Hypertension was observed in 60% of patients. Type 2 diabetes was diagnosed in 29.4%, impaired fasting glucose in 27.5% cases and median HOMA-IR was 4.3. SCORE system classified as low risk 3.9% of patients, moderate risk 41.2%, high risk 15.7% and very high risk 39.2%. Among patients with low or moderate risk 56.5% had LDL-c levels above 115 mg/dl; 62.5% of patients with high risk had LDL-c higher than 100 mg/dl and all patients with very high risk had LDL-c over 70 mg/dl.
Conclusion
Patients with NFAIs have high cardiometabolic risk. Cardiovascular features should be screened during their initial workup and follow-up to identify those at risk and implement the appropriate interventions.

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EP13

Immunohistochemical characteristics of blood vessels in non-visualized and visualized on MRI pituitary adenomas in patients with Cushing's disease (pilot study)

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Introduction
Regardless of improvements in MRI, up to 20% of ACTH-secreting pituitary tumors are only identified at surgical exploration. The objective was to estimate whether there is any difference in blood vessels and the subsequent ability to uptake contrast agent in visualized micro-adenomas as compared to non-visualized on MRI ACTH-secreting pituitary tumors.
Materials and methods
Retrospective evaluation of ACTH-positive pituitary tumors from patients with Cushing's disease (n = 24) with either non-visualized pituitary tumor on MRI (n = 7) or pituitary tumor less then 10 mm (n = 17). Cushing's disease was confirmed by histological evaluation in all enrolled subjects. Selected tumors were treated immunohistochemically with antibodies to the following antigens: CD34 (clone QBEnd/10, RTU, Leica) or CD 31(clone 1A10, RTU, Leica), D2-40 (clone D2-40, RTU, Dako). A biotin-free Bond Polymer Refine Detection system (Leica) was used according to standard protocols with the automated system Bond max (Leica). The investigators were not aware of the diagnosis before performing the micro vessel counting. The representative field $\times$200 magnifications were chosen for each tumor. These fields were digitized as JPEG images using a digital camera system (Leica, DFC 490). Image-processing software (Leica Application suite V3). We calculated the density of micro vessels and measured the diameter of larger and smaller vessel.
Results
The density of blood vessels were not different in subject with visualized Me-112 (Q25-Q75 95-136) and non-visualized 117 (56-138) pituitary adenomas. However the shape and diameter of these vessels differ: the largest of visible vessels tend to be larger in patients with non-visualized pituitary adenomas 65 µm (41–93) vs 35 µm (25–66) P = 0.06; the diameter of medium vessels were significantly higher in subjects with non-visualized adenoma 16.0 µm (13.5–30.0) vs 12.5 µm (11.7–14.2) P = 0.028, the diameter of small vessels were not different 7.0 µm (5.0–9.5) vs 7.0 µm (6.0–9.3). In six cases, the vessels were slit-shaped and five of these cases were patients with visualized pituitary adenomas on MRI.
Conclusions
The larger diameter of blood vessels in subjects with non-visualized pituitary adenomas might influence the contrast agent uptake and its retention making the pituitary adenoma tissue less different from normal pituitary.

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EP14

Adrenal crisis and sick day episodes among CAH patients: preliminary report based on international CAH (I-CAH) registry

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Background

Congenital adrenal hyperplasia (CAH) is a rare condition that is associated with life long risk of adrenal crisis. Management of CAH demands a fine balance between excess glucocorticoid leading to adverse effects and too little glucocorticoid risking adrenal crises. Frequent occurrence of sick day episodes warrants dose adjustment and education regarding adrenal crisis. In a condition such as CAH it is difficult to collect sufficient data from small cohorts at a single center level to establish clinical significance. To address this issue we have used the I-CAH registry to investigate the frequency of sick day episodes and adrenal crisis.

Methodology

The I-CAH registry is a part of the I-DSD registry, which has national ethics approval as a pseudoanonymized registry in the UK for which patients provide consent for curation of routine clinical data. We have built a prospective longitudinal module in the registry and collected data on number and duration of sick day episodes, history of adrenal crisis and change in medications since last visit.

Results

Amongst the 2012 cases, in the I-DSD/CAH Registry**,** there were 504 records of CAH ($n=490$ 21-OHD and $n=14$ 11-β hydroxylase deficiency) and data were accessible in 389 ($n=377$ 21-OHD, $n=12$ 11-β hydroxylase deficiency). Data were entered from 13 countries. There were 163 adult patients (>18 years) and 226 children (<18 years). There were 52 patients with longitudinal data and the recorded number of sick day episodes was 36. Duration of Sick day episodes ranged between 1–10 days and mean duration of an episode was 2.5 days. There were no reported adrenal crises. Dose of medication was changed based on the sick day episodes.

Conclusion

The I-CAH registry provides a tool to look at adverse events in patients with CAH. Preliminary data suggest that patients experience frequent episodes where they evoke the sick day rules.

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EP15

Impact of the chemokine receptors CXCR4 and CXCR7 on metastatic potential and survival in adrenocortical carcinoma

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Background

The chemokine receptor CXCR4 and its associate receptor CXCR7, that modulates CXCR4 function, have been associated with tumor progression and metastasis in human cancers. In ACC, Ki67 index and ENSAT stage are the most important prognostic parameters.

Objective

To assess expression of CXCR4 and CXCR7 in adrenal cancer and correlate results with clinical outcome.

Methods

CR expression was assessed by immunohistochemistry in paraffin-embedded sections of 215 ACC tissues (174 primary tumors (PT), 18 local recurrences (LR), 23 metastases (M)). 47.4% ($n=102$) of patients had an initial R0 resection status. Data were correlated with metastatic status, tumor progress and survival.

Results

Staining for CXCR4 and CXCR7 was found in 85% and 82% of investigated tumors, respectively (h-score >1 in 48 and 50%). No differences were observed regarding CR staining between PT, LR and M. Patients with initial R0 resection status and a positive CXCR4 membrane staining tended to more frequently develop metastases at follow up (59 vs 41%; $P=0.075$). However, for the whole patient group, no significant correlation was observed between clinicopathological data and membrane staining of the CR, with neither of the CR being an independent factor of overall and progression-free survival. In contrast, strong cytoplasmic CXCR4 staining appeared to be associated with a better overall survival in multivariate analysis (130 vs 49 months, RR 0.55, $P=0.046$). Among the subgroup of cases with a low ENSAT stage (I and II), a strong CXCR7 membrane staining described a trend towards a better overall survival (77 vs 41 months; $P=0.077$).

Conclusion

Different from other malignancies, CXCR4 and CXCR7 membrane staining did not significantly influence prognosis in ACC. The observation of improved outcome in patients with strong cytoplasmic CXCR4 staining remains to be assessed in further studies.

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EP16

Adrenal function recovery after adrenalectomy in Cushing syndrome

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Background

First-line therapy of ACTH-independent Cushing's Syndrome (CS) is the resection of the underlying tumor in all cases. After surgical cure of CS, most patients develop transient secondary adrenal insufficiency with a variable time of recovery. Adrenal function testing can identify patients who may require glucocorticoid replacement.

Methods

We reviewed 61 patients diagnosed with ACTH-independent CS excluding 6 with adrenocortical carcinoma; 40 underwent unilateral adrenalectomy for adrenocortical adenoma or bilateral macronodular hyperplasia. Postoperatively, blood was sampled for plasma cortisol levels at 08:00AM; 4 hours and 24 hours after administration of 1 mg Synacthen depot im. Glucocorticoid replacement was started if basal plasma cortisol <5 μg/dl, or a stimulated plasma cortisol <20 μg/dl. Follow up was performed at 3, 6, 9 months and 1 year or more in selected cases, in order to see the duration of glucocorticoid replacement, morphological aspect of the contralateral adrenal and complications remission.

Results

Between 2005–2015, 55 patients were diagnosed with benign ACTH-independent CS in our clinical department, 7 men and 48 women, aged 52 ± 11.68 (range 26–76): 43 adenomas and 12 bilateral macronodular hyperplasia. Tumor size ranged from 16 to 140 mm (39 ± 20.2 mm). Subclinical Cushing (pathological dexamethasone test only) was diagnosed in 29 cases and overt Cushing in 26 cases. Mixed glucocorticoid and androgen secretion was found in four cases. From all cases, forty underwent unilateral adrenalectomy; six patients were excluded because of missing data. From the remaining 34 patients, 18 were with secondary adrenal insufficiency (15 with overt CS and 3 with subclinical CS), receiving replacement therapy 3–18 months after surgery. The decision of ceasing therapy was based on a stimulated cortisol $\geqq 20$ μg/dl. A longer period of substitution was required for those patients with atrophic contralateral adrenal at initial morphological evaluation.

Conclusion

Only about a half of the patients with CS develop postoperatively secondary adrenal insufficiency. The synacthen depot test is useful for the decision of starting or ceasing the replacement therapy.

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EP17

Psychopathology, memory and quality of life in Cushing's syndrome

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Introduction
Cushing's syndrome (CS) has been related to higher psychopathology. Psychopathology can be related to poor memory performance, and low quality of life. The aim of this study is to establish the relationship between the three parameters and with subjective symptom perception in CS.
Methods/design
Thirty six patients in remission of CS and 36 matched controls for age, sex and education years were included in the study. They completed SCL-90R, CushingQoL (only patients), Rey-Osterrieth Complex Figure, a symptom list ranging from 0 to 10 and performed blood tests.
Results
Patients showed more psychopathology in all the SCL-90R variables (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, global severity index, positive symptom distress index and positive symptom total) ($P<0.01$) and poorer long-term memory performance ($P=0.024$), compared to controls. They also reported more symptoms than controls ($P<0.001$). Psychopathology did not correlate with memory performance, quality of life or symptoms. The hostility subscale was positively correlated to blood cortisol levels ($r=0.459$, $P=0.005$).
Conclusion
CS patients after endocrine control show more psychopathology and memory impairment than healthy controls. These data show that despite normalization of hypercortisolism psychological morbidity persists.

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EP18

Carotid intima-media thickness as the cardiometabolic risk indicator in patients with nonfunctional adrenal mass and metabolic syndrome screening

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Objective
Nonfunctional adrenal masses are a risk indicator of increased cardiometabolic risk. Especially; increased thrombogenic ambient, insulin resistance, hepatosteatosis and abdominal obesity are determined in these patients with nonfunctional adrenal masses. Our purpose was to show the association of adrenal incidentalome and metabolic syndrome in consideration of the studies and to detect the increase in the carotid intima-media thickness which is regarded as the precessor of atherosclerosis.
Material and methods
Eighty one patients who applied to our clinic between 2014 and 2016 were diagnosed with adrenal mass and follow-ups were included in the study. During the first application from the patients, their height/weight, BMI, waist circumference and tension arterial were measured. Participants underwent hormonal evaluation and insulin rezistance with the HOMA-IR. A 1-mg DST test was conducted after evaluating basal cortisol measurements of the patients. After the existence of adrenal mass of the patients was verified with MRG, the patients were classified into two groups: the patients with mass size <3 cm (K_1) and the patients with mass size of at least 3 cm (K_2). Lastly, detailed echocardiography (tissue Doppler and diastolic dysfunction parameters) and carotid intima-media of the patients were measured using B-mode ultrasound. The control group ($n=33$) was created by choosing healthy volunteers who applied to our polyclinic. While choosing the control group, it was targeted that age, gender distribution, and BMI values of the control group would equal those of the patient group.
Findings
Within the scope of the study, mean mass size of the patients ($n=81$) with adrenal mass was determined to be 2.5 ± 1.2 cm. Mass size of 64.19% ($n=52$, K_1) of the patients was found as <3 cm, while mass size of the remainder (35.81%) ($n=29$, K_2) was calculated to be at least 3 cm. As a result of the analyses, five of the patients with adrenal mass were detected to have subclinical Cushing syndrome. The remaining 76 patients were accepted as nonfunctional. It was seen with regard to metabolic and biochemical parameters that plasma glucose ($P=0.01$), insulin ($P=0.00$) and triglyceride ($P=0.012$) values of NFAİ and SCS patients were significantly high compared to those of the control group. It was detected that measured heart rate ($P=0.00$), end-diastolic diameter (EDÇ) ($P=0.02$), end-systolic diameter (ESÇ) ($P=0.014$) and carotid intima-media thickness (CIMT)($P=0.00$) values of the patients with adrenal mass ($n=81$) were significantly higher than those of the healthy control group.
Result
We see the increased insulin resistance, increased risk of cardiovascular disease with the increase in the thickness of carotid intima-media and diastolic disfunction parameters, although the patients with adrenal incidentaloma are nonfunctional.

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EP19

Are adrenal incidentalomas components of metabolic syndrome?

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Introduction
The aim of the study was to asses frequency of the components of metabolic syndrome (MS) according to the criteria of the International Diabetes Federation (IDF) in patients with adrenal incidentaloma (AI) without hormonal activity.
Design
The study comprised of patients with AI without hormonal activity, confirmed in CT. The adrenal function was determined by measuring circadian rhythm of cortisol and/or dexametasone suppression test, aldosterone, plasma renin activity (PRA), DHEAS, androstenedione, metanephrines in urine. The physical examination of the patients included BMI, the waist circumference, blood pressure. The biochemical assays: OGTT, fasting insulin and lipids (total cholesterol, HDL, LDL, triglycerides). HOMA IR was also calculated. MS was diagnosed according to the IDF criteria.
Results
We examined 125 patients, mean age: 61.3 ± 8.8 years, 72 (42.4%) were men. Tumor mean size: 27.6 ± 15 mm. MS was diagnosed in 53 (42.4%) patients, 24 (19.2%) men. Abdominal obesity was diagnosed in 87 (69.6%) patients- 31 (24.8%) men. Total cholesterol was 218 ± 49.7 mg/dl, HDL 59 ± 21.1 mg/dl, LDL 134 ± 44.1 mg/dl, triglycerides 116 ± 60 mg/dl. 83 (66.6%) patients had dyslipidemia. In 99 (79.2%) patients hypertension was diagnosed, with the mean arterial systolic BP 131 ± 15 mmHg, and diastolic PB 80 ± 9 mmHg. Dysglycemia was observed in 62 (49.6%) patients aged: 62.9 ± 7.5 years- 30 (24%) men. IFG was recognized in 24 (19.2%); IGT in 34 (27.6%), diabetes in 16 (13%) patients. Mean HOMA IR was 2.3 ± 2.0 (mmol/l$\times$uU/ml); in 78.4% (99 patients) we diagnosed insulin resistance (HOMA IR >1).
Conclusions
(1) In patients with AI without hormonal activity according to the IDF criteria MS was diagnosed in 42.4%.
(2) Patients with AI without hormonal activity are a risk group of prediabetes and diabetes.

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EP20

Congenital adrenal hyperplasia– "natural history of the disease" – very late diagnosis in a series of patients

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Background
Classical congenital adrenal hyperplasia (CAH) is diagnosed mainly in newborns. While patients with salt wasting form cannot survive without timely diagnosis, those with simple virilizing or nonclassical may be diagnosed even in advanced age.
Aim
To present clinical, biochemical, radiological and genetic characteristics of series of CAH patients diagnosed in advanced adulthood.
Material and methods
Eight patients (F=5, M=3) with adult diagnosis of CAH were qualified to the analysis. CAH was diagnosed based on urine steroid profile made by GC/MS-SIM. Clinical data consisted of antropometric measurement, metabolic and hormonal assessment, adrenal CT/MR imaging, testicular ultrasound and semen analysis in men. Genetic analysis was made by direct sequencing of *CYP21A2* gene.
Results
Women's age at CAH diagnosis was 18–65 yrs (three were over 30), men's 32–52 yr. Women were seeking endocrine consultation because of primary amenorrhea, clinical hyperandrogenism, adrenal incidentaloma and clinical suspicion of hypercorstisolism. Men were admitted for a diagnostic work-up of adrenal incidentaloma, one with suspicion of ACTH- dependent Cushing's syndrome. 3/5 women and all men had partial cortisol deficiency. Beside one men, none presented in past with adrenal crisis. 4/5 females were *virgo*, 3-had primary amenorrhea, 4/5 had pronounced hirsutism, one presented with acne and 2 with *alopecia*. All men were complaining on slight libido decrease. All patients had short stature. BMI- among women was 20–40.6 kg/m^2, in men 33.6–33.7. All patients presented with insulin resistance, one man with diabetes. Mean testosterone level in females was 10.25 (1.97–27.9) nmol/l, androstendione-10.02 (4.4–14.1) ng/ml. All men were diagnosed with biochemical hypogonadotropic hypogonadism. In the oldest men TART's were found, while in others no abnormalities in testes were seen. Adrenal tumors or hypertrophy was found in all three men and in 3/5 women.
Conclusion
The diagnosis of classical CAH in advanced age is possible. Males with hypogonadotropic hypogonadism, adrenal tumors and short stature should be evaluated towards CAH. The assessment of cortisol reserve in manadatory in case of adrenal incidentaloma, elevated ACTH level and no clinical data for hypercortisolism.

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EP21

Long-term metabolic evolution of a cohort of patients treated for adrenal insufficiency

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The aim of this retrospective study was to compare the long-term metabolic evolution of a cohort of patients treated for adrenal insufficiency (AI), and the best biological parameters of a good balance.

Seventy patients with AI (mean age 41 years (±16); 60% female) were followed during a median 6-year period (2–16 years): 38 after bilateral adrenalectomy (60% Cushing) and 32 after AI of medical origin (62% polyglandular autoimmune syndrome). BMI, blood pressure (BP), fasting blood glucose (FBG), cholesterol, triglycerides, ionogram, plasma renin activity, ACTH before and 2 h after hydrocortisone intake, daily hydro- and fludro-cortisone were recorded at the beginning of replacement therapy (T1) and at last news (T2).
At T2 vs T1, the prevalence of overweight was 35% vs 17% ($P<0.02$), obesity 18% vs 22% (non significant; NS), hypertension 29% vs 31% (NS), dyslipidemia 26% vs 17% ($P=0.058$) and type 2 diabetes (T2D) 21% vs 8. Between T1 and T2, IMC ($P<0.02$) and FBG ($P<0.0001$) medians increased.
PRA levels were inversely correlated with T1 (p1=0.002) and T2 (p2=0.0001) natremia and positively correlated with kalemia (p1=0.07; p2=0.04) without any relation with fludrocortisone dose or BP. In contrast, fludrocortisone doses were positively correlated with T2 systolic BP ($P=0.03$) with a trend for natremia ($P=0.08$). T1 ACTH levels were significantly correlated with natremia ($P=0.004$). ACTH levels 2 h after hydrocortisone intake were not influenced by hydrocortisone doses. In contrast, hydrocortisone doses were correlated with diastolic BP (p1=0.02; p2=0.006), T2 FBG ($P=0.03$), with a trend for BMI (p1=0.09; p2=0.07). Hydrocortisone doses/kg of body weight were higher in case of T2D ($P<0.03$).
Conclusion: weight and T2D increased significantly during the follow-up, in relation with hydrocortisone dose. Both hydro and fludrocortisone doses control BP. Hormonal measurements (PRA, ACTH…) do not bring more than BP and ionogram to the quality of replacement therapy.

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EP22

Method-specific serum cortisol responses to the ACTH test: comparison of two generations of Roche automated immunoassays using polyclonal vs MABs

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Introduction
The plasma cortisol response to the ACTH test is known to vary significantly by assays. An automated cortisol immunoassays with increased specificity due to the shift from polyclonal to MABs, and standardized against mass spectrometry was recently introduced, with an expected decrease in cortisol concentrations by 20%. Cut-offs used in clinical practice for patient evaluation will thus have to be adjusted. We aimed to assess the normal cortisol response to ACTH stimulation measured by Elecsys Cortisol II.
Methods
An ACTH test (250 µg i.v. $ACTH_{1–24}$) was undertaken in 100 healthy volunteers (age, 18–70 years; 50 women) and 13 women on oral contraceptives. Serum cortisol was measured by two commercially available immunoassays: Elecsys Cortisol (polyclonal Ab)(Roche) and Elecsys Cortisol II (MAB). The estimated lower reference limit for the 30 min cortisol response to ACTH was derived from the 2.5th percentile of log-transformed concentrations.
Results
Cortisol concentrations measured by Elecsys Cortisol II were approximately 20% lower relative to Elecsys Cortisol. The 30 min cortisol response was normally distributed in males but not in females, with no significant gender difference at baseline nor post-ACTH ($P=0.1$). The lower reference limit for the 30 min cortisol response was method-specific; Elecsys Cortisol (range: 534–1013; lower reference limit: 572 nmol/l) and Elecsys Cortisol II (range: 399–817; lower reference limit: 432 nmol/l), and remained significantly elevated by both methods in women on oral contraceptives.
Conclusion
The cutoff defining a normal 30 min. cortisol response to the ACTH test is influenced significantly by assay employed as well as oestrogen treatment. New cutoffs should be introduced with the introduction of new generation immunoassays with higher specificity

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EP23

Ascending aorta dilatation in primary aldosteronism: a new deleterious consequence of aldosterone excess

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Introduction
Primary aldosteronism (PA) features a higher prevalence of cardiovascular events and renal complications as compared with essential hypertension. The effects of aldosterone excess on ascending aorta have never been investigated in human subjects.
Methods
From August 2014 to December 2015, we enrolled forty-seven consecutive PA outpatients who had not undergone surgery of the adrenal mass. Hypercortisolism and pheochromocytoma were excluded. All patients were ordered a trans-thoracic echocardiogram. Besides, an echocardiogram was requested to study forty-five consecutive hypertensive outpatients (at least on one antihypertensive drug) with an adrenal mass, after ruling out PA. They were considered essential hypertensive (EH) controls. Adrenal masses were studied in both groups with: 2-hour-upright-Aldosterone-to-Renin-Ratio (ARR) and, if positive, Captopril Challenge Test, the 1 mg dexamethasone suppression test, and 24-hour-acidified urinary metanephrines. We considered the presence of ascending aorta dilatation, which was defined as having an aortic root diameter higher than 37 mm and/or a tubular ascending aorta diameter superior to 36 mm.
Results
Forty-seven cases of PA and forty-five EH controls were assessed. In each group, the male-to-female ratio was 27/20 and 21/24, respectively. The groups did not differ in BMI, hypertensive cardiomyopathy, smoking history, adrenal morphology and creatinine. Ascending aorta dilatation was significantly higher in PA compared to EH controls, independently of age (36.2% vs 11.1%; odds-ratio = 4.614, 95% CI 1.33–15.97; $P = 0.007$). The difference was still significant when comparing males of either group (51.9% vs 19.0%; odds-ratio 4.577, 95% CI 1.22–17.22; $P = 0.034$), whereas in females significance was not achieved.
Conclusion
Ascending aorta dilatation is more prevalent in males with PA than in EH controls, while in females with PA it is a rarer manifestation.

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EP24

Identified mutations in CYP11B1 gene in two Tunisian patients with 11-beta hydroxylase deficiency

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Introduction
11β-Hydroxylase deficiency (11β-OHD), caused by CYP11B1 mutations, is characterized by hyporeninemic, hypokalemic hypertension and hyperandrogenism. We studied the mutations of CYP11B1 gene in two patients with classic 11β-OHD.
Observations
We present the first case of a 23 year old boy with preliminary diagnosis of 21 β-OHD diagnosed at the age of 10. The patient presented with hypertension and hypokalemia which were against the diagnosis of 21 β-OHD. The physical examination showed microgenitalia with no palpable gonads. The patient's karyotype was 46 XX. Cortisol level was normal. Deoxycorticosterone, corticosterone, DHEA and 17OH-progesterone were markedly elevated. The hypothesis of 11β-OHD deficiency was considered and confirmed by genetic exploration. A non-sense mutation 6379V of the *CYP11* gene was found. The patient was referred to an experienced surgeon for micropenis.
The second case is about a 9 year old girl who was diagnosed at birth with a disorder of sexual differentiation 46 XX, without signs of salt loss. The patient had a feminizing surgery at the age of 6 months and she was treated par hydrocortisone. When she was 6 year old, she presented with hyperandrogenism, male behavior, hypertension and severe hypokalemia. Deoxycorticosterone and 17OH-progesterone were markedly elevated. The hypothesis of 11β-OHD deficiency was considered and confirmed by genetic exploration. A non-sense mutation p.G379V of the *CYP11B1* gene was found.
Conclusions
Our cases show the importance of the early etiologic investigation in children with disorder of sexual differentiation. Medical and psychological management are necessary to improve the prognosis of these patients.

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EP25

Low positive predictive value of midnight salivary cortisol measurement to detect hypercortisolism in type 2 diabetes

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Background
Hypercortisolism is prevalent in type 2 diabetes (T2D), but analytical and functional uncertainties prevail. Measurement of salivary cortisol is considered an expedient screening method for hypercortisolism, but its usefulness in the context of T2D is uncertain.
Aim
To compare late night salivary cortisol (LNSC) with the 1 mg overnight dexamethasone suppression test (DST), which was considered 'reference standard', in T2D.
Patients and methods
382 unselected and recently diagnosed T2D patients underwent assessment of LNSC and DST, and the test outcome was related to age, gender, BMI and Hemoglobin A1C levels. We used the following cut-off values: LNSC $\leq$3.6 nmol/l and DST $\leq$50 nmol/l.
Results
The mean $\pm$ S.E.M. levels of LNSC and DST were 7.3 $\pm$ 0.25 nmol/l and 28.7 $\pm$ 1.4 nmol/l, respectively. Hypercortisolim was present in 85.6% based on LNSC values and 22% based on DST. LNSC, as compared to DST, had the following test characteristics: sensitivity: 84.5% (95%CI: 75.0–91.5%), specificity: 14.1% (95%CI: 10.4–18.6%), positive predictive value: 21.7% (95%CI: 17.4–26.6%), negative predictive value: 76.4% (95%CI: 63.0–86.8%) and overall accuracy 29.6% (95%CI: 25.0–34.4%). LNSC and DST values were not associated with Hemoglobin A1C, BMI and age in this diabetes cohort.
Conclusion
The LNSC is characterized by very low specificity and poor positive predictive value as compared to the DST, resulting in an overall low accuracy. Further methodological and clinical studies are needed to substantiate the relevance of cortisol status in T2D.

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EP26

Glucocorticoid axis in patients with primary aldosteronism

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Introduction
Primary aldosteronism is associated with increased prevalence of cardiometabolic complications. The mechanisms are not fully elucidated, but an association with autonomous cortisol secretion could increase vascular and metabolic risk.

Aims
To assess glucocorticoid axis in patients with primary aldosteronism as compared to patients with ACTH-independent Cushing syndrome and control hypertensive patients without gluco or mineralocorticoid excess.
Patients and methods
Twenty two patients (10M/12F, aged 43.9±11.2 years) with primary aldosteronism- PA (14 adrenal tumors, 8 uni/bilateral adrenal hyperplasia), 13 patients (2M/11F, aged 43.8±13.3 years) with ACTH-independent Cushing syndrome and 42 control hypertensive patients (16M/26F, aged 35.8±14.5 years) were retrospectively reviewed. Plasma aldosterone and plasma direct renin were measured by chemiluminescence (method's sensitivity 2.2 ng/dl for aldosterone and 0.27 ng/dl for renin, respectively); serum cortisol and ACTH were measured by electrochemiluminescence.
Results
BMI, maximum systolic blood pressure, fasting glycaemia and total cholesterol were similar in the three groups. Serum potassium levels in patients with PA (2.6±0.5 mmol/l) were significantly lower than in patients with ACTH independent Cushing syndrome (4.3±0.9 mmol/l, $P<0.0001$) and in control patients (4.4±0.4 mmol/l, $P<0.0001$). Midnight (11 p.m.) serum cortisol in PA patients (4.9±3.1 μg/dl) was significantly lower than in patients with ACTH-independent Cushing syndrome (10.4±3 μg/dl, $P=0.007$), and similar with control patients (3.2±2.7 μg/dl, $P=0.17$). Median serum 8 a.m. cortisol after 1 mg low-dose dexamethasone suppression test (LDDST) in PA patients (1.34 μg/dl) was significantly lower than in patients with ACTH-independent Cushing syndrome (12.3 μg/dl, $P<0.0001$), but significantly higher than in control patients (0.84 μg/dl, $P=0.001$). ACTH levels were similar in PA patients and in control group. One operated patient with PA developed postoperative adrenal insufficiency and required glucocorticoid replacement therapy.
Conclusion
Mild cortisol excess may co-exist in primary aldosteronism patients, reflected by higher cortisol levels after overnight low-dose dexamethasone test.

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EP27

Bilateral adrenalectomy in Cushing's syndrome: evaluation of quality of life compared to other treatment options

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Context
Bilateral adrenalectomy (BADX) has become an important treatment option of Cushing's syndrome (CS), especially when other treatments have failed. Long-term outcome is not well known.
Objective
To evaluate long-term quality of life (QoL) of patients who underwent BADX for CS compared to other therapeutic options.
Methods
Fourty five patients with all cause CS were identified: 23 patients had BADX and 22 underwent one or more of the following treatments: transphenoidal surgery, medical therapy or radiotherapy. Medical records were retrospectively reviewed and entered into a database. Each patient had to fill three questionnaires to evaluate their QoL: Short Form-36 Health Survey (SF-36) and Cushing QoL questionnaire which are rated over 100 (defined as the best QoL), and Beck depression inventory, the lower limit for depression symptoms being established at 17.
Results
34 (75.6%) patients had ACTH dependent CS and 11 (24.4%) had ACTH independent CS. Women prevailed (77.8%). The mean age of the patients was 51.3±16.4 years in BADX group and 48.4±16.3 in the other treatment group. Patients who underwent BADX had an impaired QoL in each questionnaire. In the SF-36, both physical and mental scores were altered, respectively at 52.4±20.9 and 53.6±22.9 compared to the other treatment group (69.4±22.5 and 63.3±20.2). The most altered dimension was vitality: 35.4±22.7 vs 51.4±19.2 ($P<0.05$). Cushing QoL questionnaire was also altered: 49±23.2 vs 59.7±20.1. Beck depression inventory indicates that BADX group has still persistent symptoms of depression, with a score of 17.9±12.7, which is not the case in the other group (11.7±9.6).
Conclusions
Despite clinical remission, patients who underwent BADX have an impaired QoL compared to patients who experienced another therapeutic option for CS. This could be the consequence of a longer exposure to hypercortisolism. Further investigations are needed to understand the causes.

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EP28

Adenoma size could be an important predictor of Subclinical Cushing's Syndrome

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Subclinical Cushing's syndrome (SCs) is used to refer to an adrenal incidentaloma with subtle autonomous cortisol secretion and without typical signs and symptoms of hypercortisolism. Diagnostic criteria are uncertain and arbitrary. In this study we aimed to investigate the power of adenoma size as an independent predictor of SCs.
Dokuz Eylul University Adrenal Tumours Study Group database includes 596 patients by January 2016. Briefly, there are 332 subjects with non functioning adrenal adenomas and 141 subjects (adrenal Cushing Syndrome was excluded) with alterations in 1 mg dexamethasone suppression tests (1 mg DST). We stratified the individuals according to the 1 mg DST results. Group A ($n=310$, 1 mg DST <1.8 μg/dl), Group B ($n=68$, 1.8 <1 mg DST<3 μg/dl), Group C ($n=46$, 3<1 mg DST<5 μg/dl) and Group D ($n=26$, 1 mg DST > 5 μg/dl). Adenoma size showed a strong relation with 1 mg DST results. Median size was 20, 25, 33 and 31 mm in Group A to D, respectively. The ROC curve analysis showed that the cut-off of the adenoma diameter with the best diagnostic accuracy for detecting individuals with a non-suppressed 1 mg DST level (>3 μg/dl) was 25 mm (sensitivity, 80%; specificity, 74%; AUC: 0.808, $P<0.001$). We also evaluated prospective hormonal data in 110 individuals and demonstrated that 1 mg DST results were substantially stable among individuals.
The limitation of SCs screening to the individuals with larger adenomas would decrease medical costs and further time consuming procedures.

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EP29

Long term folow-up of patients with adrenal incidentalomas and subclinical hypercortisolism: a single center experience

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It has been more than 70 years since the first adrenal incidentalomas (AI) were described. Most of these tumors are non-secreting, and are found in 4–7% of adult population. Patients with subclinical hypercortisolism (or autonomous cortisol secretion) (SH) are observed in 1–29% of patients with AIs. Evidence suggests that this condition may be associated with higher prevalence of diabetes, obesity, hypertension and osteoporosis.
Between 1999 and 2015, 857 patients with AI were evaluated in Department for Obesity, Reproductive and Metabolic Diseases, Clinic for Endocrinology, Clinical Centre of Serbia. Seventy-two patients were diagnosed with SH based on two out of three criteria: 1 mg overnight dexamethasone cortisol >83 nmol/l, low basal ACTH (below 14 ng/l) and lack of diurnal cortisol rhythm (midnight cortisol >150 nmol/l). Fifty-nine women and thirteen men, mean age 58.37±8.25 years and mean BMI 28.91±5.19 kg/m^2. Thirty-seven (51.38%) patients had bilateral tumors and thirty-five (48.61%) had unilateral tumors, mean tumor size was 37.91±10.88 mm and mean follow-up was 5.02±2.98 years. At admission fifty-nine patients (81.94%) had hypertension, 20 (27.7%) had glucose intolerance, 18 (25%) had diabetes and 20 (27.75%) had osteoporosis, 14 patients (19.44%) already suffered cardiovascular events (nine had myocardial infarction and one had a stroke). During the follow-up period one patient (1.38%) had a stroke, one (1.38%) developed diabetes, five (6.94%) developed glucose intolerance and one (1.38%) patient decreased bone mineral density to osteoporotic levels. Three patients underwent surgery due to tumor growth. Pathohistology showed cortical adenoma.
During the average follow-up of 5 years of 72 patients with SH and AI, 1.38% have had a new cardiovascular event, but nearly 7% developed glucose intolerance which is important when deciding about the optimal management and follow-up strategies.

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EP30

Do lipid profile predict subclinical Cushing's Syndrome in patients with adrenal incidentalomas?

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Introduction
Adrenal Incidentalomas (AIs) have been associated with an increased risk of metabolic syndrome and dyslipidemia, though evidence regarding the latter is limited and, sometimes conflicting. Lipid abnormalities in patients with AIs have been described to be associated with subclinical hypercortisolism. Our aim was to test if lipid profile in patients with adrenal incidentalomas may predict subclinical Cushing's Syndrome (sCS).
Material and methods
Ninety-four patients ($n=94$) with adrenal incidentalomas (AIs) were included in a prospective cohort study. All patients were followed up for three years and alternations of their hormonal and lipid profiles were recorded. IBM SPSS Statistics v20 were used.
Results
The 94 patients (25 men and 69 women) of our cohort harbored 111 AIs. There were no differences between patients with sCS and those without, with respect to their baseline lipid profile and blood pressure (systolic and diastolic). Non-HDL concentrations decreased over time (Repeated Measures ANOVA, $P=0.013$), despite patients' Body Mass Index (BMI) remaining unchanged. Logistic regression revealed that the only predictor of sCS is the size of adrenal incidentalomas, as calculated by computed tomography (CT).
Conclusion
The current study demonstrated that lipid profile at baseline or during follow up cannot predict sCS in patients with adrenal incidentalomas. The improvement of patients' lipid profile during follow up is probably due to better medical management.

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EP31

Primary aldosteronism – results from the first Portuguese multicentre study

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Primary Aldosteronism (PA) is the most prevalent cause of secondary hypertension. The aim of this work was to characterize the diagnostic workup, treatment and follow-up of confirmed PA.
The adrenal tumour study group of the Portuguese Society of Endocrinology undertook the first retrospective multicentre study of Portuguese PA patients. Data was gathered from nine Portuguese Endocrinology centres (three in the north, one in the centre and five in the south). The data was analysed with SPSS 21.
Sixty-three cases were selected with a mean age of diagnosis of 52.1 ± 13.1 years; 9.9 years after the diagnosis of hypertension. At presentation 32.8% of patients had hipokalemia and 22.9% resistant hypertension (52% with ≥ 3 drugs). Baseline laboratory investigation showed a mean serum aldosterone of 33.4 ng/dl, plasmatic renin activity (PRA) of 0.2 ng/ml per h with a aldosterone/PRA of 97.1. Confirmatory testing was performed with saline infusion in 91.7% (aldosterone >10 ng/dl in 84.4%) and captopril in 23.7% (positive in 85.7%).
Imaging showed adenomas in 87.3% (mean size: 1.7 cm), hyperplasia in 3.2% and bilateral cases in 13.6%. Arterial venous sampling (AVS) was conclusive in 1 case (11%). Iodocholesterol scintigraphy was done in 22% with unilateral fixation in 64% and no fixation in 29% (nodule size 1.5–1.8 cm). Iodocholesterol and CT agreed in 50%.
Patients were treated with laparoscopic adrenalectomy in 58.3% and aldosterone antagonists in 41.7% (median spirolactone dose of 62.5 mg/d). The surgical treated group had a bigger tumour size (1.8 vs 1.5 cm, $P=0.022$), less duration of hypertension (8 vs 14 years, $P=0.002$) and higher prevalence of anti-hypertensive treatment at presentation (100 vs 75% $P=0.009$). During follow-up (median 2.5 years), there was a trend towards more hypertension cure in the surgical treated group (92.6% vs 70.6%, $P=0.089$).
This is the first Portuguese PA multicentre study. It shows that PA remains an under-diagnosed condition with a significant delay in diagnosis. Surgical treated patients had a more aggressive disease and showed a trend towards better hypertension control.

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Adrenal pigmentation in PPNAD is a result of melanin deposition and associated with upregulation of the melanocortin 1 receptor

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Primary pigmented nodular adrenal disease (PPNAD) is a form of bilateral adrenocortical hyperplasia characterised by small to normal sized adrenal glands containing multiple small cortical pigmented nodules. It may occur independently, but 90% of cases are a manifestation of the Carney complex. Most cases of PPNAD are diagnosed before age 30, and are the result of a germline mutation in PRKAR1A or PDE11A, leading to upregulation of cAMP signalling. It is a cause of ACTH-independent Cushing's syndrome. The cause of the black/brown pigmentation in PPNAD has not been definitively established, although some authors have ascribed it to lipofuscin, a product of lysosomal breakdown.
Paraffin-embedded bilateral adrenalectomy specimens from five paediatric patients with PPNAD were subjected to a series of histological and immunohistochemical staining techniques. Haematoxylin and eosin staining revealed intracellular deposits of a brown pigment that was removed by permanganate bleaching. The pigment was negative on Ziehl-Neelsen staining, and strongly positive with the PERLS and Masson-Fontana stains. Immunohistochemistry showed strong staining within the nodules for the melanosome marker HMB-45. These findings identify the pigment as melanin. The adrenal nodules in all five cases immunostained strongly positive for the melanocortin-1 receptor (MC1R), and for 11β-hydroxylase, the final enzyme in the steroidogenic pathway leading to cortisol production.
We suggest that the autonomously activated cAMP signaling pathway associated with PPNAD leads to upregulation of the MC1R, induction of steroidogenic enzymes, and generation of melanin within melanosomes. We hypothesise that the mechanism for hyperpigmentation in Carney complex skin lesions has a similar aetiology.

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Androgen producing adenoma in a patient with non-diagnosed congenital adrenal hyperplasia

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Androgen secreting adrenal tumor is a rare cause of androgen excess in women. There are only few case-reports of androgen producing adenoma in a patient with congenital adrenal hyperplasia.
Our patient, 61 year old woman was referred to our department for progressive hirsutism and androgenic alopecia. She did not mention neither excessive facial hair growth nor balding until age of 59 when rapidly progressive balding and overt hirsutism started. She has had three childbirths and three abortions in the past.

Laboratory evaluation showed markedly elevated levels of androgens and other adrenal steroids (testosterone 9.1 nmol/l ((upper limit 3,0), DHEA androstendion 82.67 nmol/l (upper limit 6,30), DHEA: 7.30; S_DHEA: 4,78 (mol/l (upper limit 3,70) and 17-OH progesteron: 228.00 nmol/l (upper limit 4,50)). ACTH as well as urinary free cortisol were normal. Physiological pattern of diurnal variability of cortisol secretion was preserved. In overnight low-dose dexamethason suppression test partial supressibility of elevated androgens was preserved.
Gynecological investigation did not show any pathology in her ovaries. On CT there were enlargement (tumors) of her adrenals (40×30×30 mm in the right gland and 30×25×20 mm in the left). We have performed scintigraphy with ^{131}I-6β-iodomethyl-19-norcholesterol which showed enhanced accumulation of the substance in the right adrenal gland. Laparoscopic adrenalectomy of the right adrenal was performed. Histology proved cortical adenoma 40×30×20 mm with diffuse hyperplasia of the surrounding adrenal tissue.
There was a significant decrease in testosterone postoperatively (1.66 nmol/l) as well as of androstendion (6.21) and DHEAS (0.39). On the contrary 17-OHP remained elevated (129.26) and ACTH raised up to 229 ng/l. Genetic test for suspected congenital adrenal hyperplasia (21 OH def.) revealed compound heterozygosity for CAH. Treatment with corticosteroids, to supress the androgen overproduction from the left adrenal was commenced.
Conclusion
Androgen secreting adenoma is a rare cause of hyperandrogenism. In the presented case adenoma had developed in a patient with, so far undiagnosed, congenital adrenal hyperplasia.

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Menstrual function in women with cushing's disease (CD)

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Background
Menstrual abnormalities (MA) can be the first sign of the disease.
Aim
To assess the structure of MA before and after treatment of CD.
Material and methods
Twenty-eight women with CD 39 (31.8;43.5) y.o., were investigated initially and 3.5 (2;5.5) years after treatment. Patients were subdivided into three groups: with normal cycles (NC; 26–30 days), oligomenorrhea (31–120 days), amenorrhea (>120 days).
Results
Before treatment of CD, NC had 3 (10.7%), oligomenorrhea 8 (28.6%), amenorrhea 17 (60.7%). UFC were higher in women with MA than in women with NC (993±629 and 536±159 nmol/24 h, $P=0.05$). 1) 17 women with previous amenorrhea. Remission was achieved in 11: NC restored in 2 (18.2%), oligomenorrhea – 4 (36.4%), amenorrhea – 5 (45.4). Persistence of CD in 6: NC restored in 2 (33.3%), 4 (66.7%) have amenorrhea. 2) three women with initially NC. Remission in 2: 1 NC, 1 amenorrhea. One woman with persistence of CD now has oligomenorrhea. 3) eight women with oligomenorhea initially. In remission-6: NC 1 (16.7%), oligomenorrhea 4 (66.6%), amenorrhea 1 (16.7%). Two have persistence of CD: 1 amenorrhea, 1 oligomenorrhea.
In overall after treatment of CD, NC had 6 (21.4%), oligomenorrhea 10 (35.7%), amenorrhea 12 (42.8%). In 19 with remission, NC have 4 (21.1%), oligomenorrhea 8 (42.1%), amenorrhea 7 (36.8%). In nine with persistence, NC have 2 (22.2%), oligomenorrhea 2 (22.2%), amenorrhea – 5 (55.6%). There were no any differences between those with remission and persistence of CD. Patients with remission and amenorrhea were significantly older and had less weight loss after treatment of CD, than patients with remission and NC. Patients with persistence of CD had no any differences between groups. Pituitary insufficiency did not correlate with MA. Spontaneous pregnancy occurred in two patients with remission of CD and oligomenorrhea.
Conclusion
MA are common both before and after treatment of CD. Women with remission and women with persistence of CD have not any differences in frequencies of MA.

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The effect of stress, diet and analytical methods on the levels of corticoid metabolites

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Introduction
A precisely measured corticoid level is important for decision-making in daily clinical practice. These levels can be influenced in the pre-analytical phase, when the effect of stress, timing, and diet can be important.
The aim of this study was to elucidate optimal conditions for blood sampling as well as the choice of analytical methods, which they will be used in measuring of corticoids.
Methods
By studying ten women, we focused on the influences of the stress of cannulation and a large lunchtime meal on cortisol, cortisone, aldosterone and corticosterone levels. We further compared results of cortisol measurements from RIA and LC-MS/MS.
Results
Stress from cannulation caused increase of cortisol, cortisone and corticosterone already, when the cannula was being inserted. This indicates that this increase is stimulated by fear of the blood drawing rather, than just by the needle insertion itself. The effect of stress on corticosterone disappeared after an hour, while effect on other corticoids was still apparent.
Concerning the lunchtime meal, we found an increase in all measured corticoids between 11 and 12 o'clock. After the food, there were marked decreases in cortisone and aldosterone, while declining levels of cortisol and corticosterone had rather plateaus.
We compared cortisol in 90 plasma samples measured by a commercial RIA kit and the LC-MS/MS method. Results from both methods showed a strong correlation ($r=0.85$).
Conclusion
When measuring corticoid metabolites, the chosen analytical method, eliminating stress factors, and precisely timed blood sampling considering the daily rhythm and food intake are critical.
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Adrenocortical carcinoma: single center experience

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Introduction
Adrenocortical carcinoma (ACC) is a rare endocrine malignancy, with an incidence in the literature of 0.5 to 2 cases per million population per year. The most important prognostic factors are stage of cancer at the time of diagnosis and success of the first surgery. However, advanced age, tumor size, functionality, high Ki-67 index (>10%), necrosis, and high mitotic activity are among poor prognostic factors.
Patients and method
Fifteen patients diagnosed with adrenocortical carcinoma, were included in present study. The patients' data were collected by scanning their electronic records. Age, sex, surgery procedure, resection margin, treatment and prognosis were analyzed.
Results
Ten of 15 patients included in our study were men (66.7%). Descriptive characteristics of the patients and the tumors are provided. R0 resection rate could be achieved in fewer than 50% of the patients. Eight patients were not given postoperative adjuvant therapy. While mitotane was administered to 6 patients, combined systemic chemotherapy was given to 2 patients. Two patients underwent adjuvant radiotherapy. Overall survival rates, median survival time and progression free survival time are provided. Nine patients died during follow-ups. In our study, the rate of development of metastases in patients with complete

surgical resection was significantly lower than in patients without R0 resection ($P<0.05$). There was no statistically significant difference in median survival time, rate of locoregional recurrence and metastases among patients who underwent open or laparoscopic surgery. Mitotane, systemic chemotherapy and radiotherapy had no statistically significant positive effect on survival.

Conclusion

Complete surgical resection of tumoral tissue is the most important factor for long-term survival, but, even if R0 resection is achieved high recurrence rate is seen. Therefore, it is often a need for additional postoperative adjuvant treatment modalities, but the efficacy of them is limited.

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CYP11B2 polymorphism affects the aldosterone – renin ratio?

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Introduction

Nowadays is believed that primary aldosteronism (PA) is the most frequent cause of secondary hypertension and reaches 10% of whole hypertensive population. The activity of the mineralocorticoid hormone may be change by polymorphism of aldosterone synthase gene (CYP11B2) e.g. in promoter -344T/C region. Aim of this study was to find differences in baseline plasma aldosterone concentration (PAC), plasma renin activity (PRA), aldosterone – renin ratio (ARR) and plasma aldosterone concentration post saline infusion suppression test (SIST) in genetic model of CYP11B2 -344T/C (TT, TC, CC).

Material and methods

The study group consist 151 patients who were diagnosed because of a suspicion of primary aldosteronism. Normality data distribution was checked by Shapiro – Wilk test. The significance of differences between the groups was evaluated through Student's *t*-test. The differences in frequencies between categorical data were tested for statistical significance with χ^2 tests.

Results

There were no significant differences in distribution of these alleles in comparison with distribution described in European population in "1000 Genome" Study. The statistical significance was demonstrated between homozygotes (TT and CC) only in ARR. In TT genetic model ARR was markedly higher than was in CC genetic model ($P=0.048$ CI 95%). Finally, 18 (11.9%) patients were diagnosed with PA, 11 (13.25% of all TC) with TC allele, six with TT (20% of all TT) and only one with CC (2.6% of all CC).

Conclusion

Genetic model consisting thymine instead cytosine in -344 region of promotor CYP11B2 suggest predisposition to primary aldosteronism which is expressed mainly by impairment of ARR. TT genetic model in comparison with CC model significantly raises ARR but changes in PAC and PRA almost remains unnoticeable. This suggest TT genetic model as factor slightly decreases PRA and simultaneously slightly increases PAC what giving quotient PAC and PRA markedly elevated.

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Moderate/severe Hypovolemic Hyponatremia with urinary sodium loss secondary to Hypoaldosteronism: analysis of 28 cases

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Introduction

Hypoaldosteronism (HA), a cause of hypovolemic hyponatremia (HN) with urinary(U) sodium(Na) loss, is often underdiagnosed. We studied 28 patients with an episode of HA-induced moderate/severe hyponatremia.

Methods

Retrospective 2012–2015. In all patients, Nadir(N) serum(S) Na <130 mmol/l (corrected for total proteins and glycemia), low internal yugular venous pressure, low ocular pressure. Addison's Disease ruled (ACTH, cortisol and/or Synacthen test). UNa >25 mmol/l, U osmolality(Osm) $>$ Plasma(P) Osm, Transtubular Potassium Gradient (TTKG) <5. Group I (GrI) (10/28) had risk factors for aldosterone deficit (heparin, ARBs, ACEi, aliskiren, NSAIDs, and/or tacrolimus), Group II (GrII) (2/28) risk factors for mineralocorticoid resistance (obstructive uropathy, urinary infection, renal transplant, NSAIDs, trimetroprim, and/or spironolactone), Group III (GrIII) (16/28): both. Na, Potassium (K) values in mmol/l, Osm mOsm/kg. *t*-test, X^2, Spearman's Rho, Kruskal-Wallis, Mann–Whitney *U*. Results given as Mean (S.D.) unless stated otherwise.

Results

12/28 females, age: 71.36 (15.55). 78.6% had either chronic renal disease (12/28), diabetes (13/28) or both (3/28). NSNa: 121.82 (5.19) with SK of 5.08 (0.63). Values at diagnosis (D): SNa: 126.07 (5.62), SK: 4.93 (0.62). UNa:73.03 (38.66), TTKG:3.6(0.85), POsm:277.78 (12.47), UOsm:392.53(167.75), In mg/dl: SUrea 50.78 (25.23) SCreatinine:1.12 (0.56), uricemia:5.26 (1.45). NSNa GrI:123.9 (3.18), GrII:121.2 (2.83), 83), GrIII:120.63(6.12). Corresponding SK GrI:4.85 (0.62), GrII:4.65 (0.49). GrIII:5.27 (0.62). GrII aldosteronemia-345.5 pg/ml (20.51)- was higher than in GrI:103 (60.3) or GrIII:117.85 (88.4). Median reninemia tended to be lower in GrI: 7 pg/ml (3.5–11.5) than GrII + III: 21 (5–67), $P=0.08$. Patients with both high renin(>25) and low aldosterone(<100), all in GrIII, had significantly lower NSNa:113.33(4.04) than the rest:123.19(4.2), $P=0.033$. Heparin(11/28), trimpetroprim (8/28), or both (6/28) were precipitating factors in 46.4% patients, and associated with significantly lower DSNa:123.7 (5.82) vs128.13 (4.69) $P=0.038$, and lower DPOsm:271.23 (11.45) vs 283.47 (10.63), $P=0.007$.

Conclusion

Hypoaldosteronism can induce marked hyponatremia. Most patients had risk factors for both inhibition of aldosterone secretion and mineralocorticoid resistance. Heparin and/or trimetroprim use was associated with lower SNa and SOsm levels.

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The classical form of congenital adrenal hyperplasia-clinical characteristics and genetic analysis

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Classical form of congenital adrenal hyperplasia (CAH) is associated with the impairment of enzymes involved in process of adrenal steroidogenesis. More than 90% of CAH cases are connected with mutations in the 21-hydroxylase gene *CYP21A2* in the HLA class III area on the short arm of chromosome 6p21.3. CAH is characterized by a strong correlation between the genotype and the phenotype. Mutations in the *CYP21A2* gene can cause different degrees of loss of 21-hydroxylase enzyme activity resulting in various clinical characteristics.

Fifty patients (31 females and 19 males) with classical form of CAH were involved in the study (43 with salt wasting form and seven with simple virilization). Patients anthropometric, hormonal and metabolic data were assessed. In females history of reconstructive gynecologic surgery and fertility aspects were also assessed. In 31 patients genetic analysis using MLPA with use of probemix SALSA MLPA P050 CAH from MRCHolland was performed.

The average height in group of females was 155,36 cm and 179 cm in males respectively. Median woman's BMI was 28.18, while in case of man-24.26. The average concentration of serum fasting glucose was 4.97 mmol/l and of total cholesterol 4.96 mmol/l. The average age of menarche was 14 years, but almost all women had different menstrual abnormalities. Seventeen females underwent reconstructive gynecologic surgery. Fourteen different types of genetic changes were found in thirty one patients, who had genetic testing. In six patients were found changes only in one allele and in one female patient no changes in both alleles of *CYP21A2* gene.

Genetic defects are well correlated with the phenotypes of classical form of CAH. Further studies are required to search for new genetic disorders which may be responsible for development of CAH.

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Analysis of 176 cases of adrenal incidentaloma investigated in a single clinical center, what are we doing?

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Introduction
Patients referred for adrenal incidentalomas (AI) are increasing. Current guidelines are controversial on diagnosis and length of follow-up.
Objectives
Analyze clinical, radiologic and hormonal characteristics of patients with AI. Evaluate the number and usefulness of tests needed for diagnosis, clinical outcome and follow up.
Material and methods
Observational, retrospective study in patients with AI in our endocrinology department from 1993–2014, including oncologic patients. Those with hormonal hyperproduction symptoms were excluded.
Results
One hundred and seventy six patients (111F/65M) were included. Medium age: 59.68 ± 12.54 (31–84) years. Radiologic study: Medium radiologic tests per patients was 4.14 ± 2.69 (1–14) during a medium follow up: 3.65 ± 3.75 (0–18) years. Initial radiological diagnosis: 13% undetermined lesions, 69% adenoma, 6% hyperplasia, 3% mielolipoma, 2% malignant and 1% pheochromocytoma. 84% were <4 cm and 29% were bilateral. Functional study included: 1 mg dexamethasone suppression test (1 mg DST), basal ACTH, UFC and urinary catecholamine. Medium follow up: 3.75 ± 3.5 (0–17)years. 75% patients had at least one altered test; 1mgDST was altered in 80 patients (47.3%), only 33 patients (19%) met criteria for subclinical Cushing syndrome (SCS). Functional diagnosis: 64% (107) nonfunctioning, 19% (33) SCS, 4% (8) pheochromocytomas, 3% (5) clinical adrenal Cushing(CAC), 1 ACTH-dependent Cushing. Malignancy: Metastases were diagnosed in six patients, all with previous cancer history. No adrenal corticocarcinoma (ACC) was diagnosed. Outcomes: seven patients developed SCS, no patients with SCS developed CAC. Four tumors had significant growth: two were metastases. No patients developed malignant transformation to ACC.
Conclusions
The majority of AI are small, benign, non-functioning and remained stable even in patients with long follow up. Most of them were well defined with the first radiologic test. In our serie SCS is the most frequent hormonal alteration, but transformation in CAC was not found. Low incidence of malignant transformation in non-oncologic patients and the lack of hyperfunction development should make us reconsider our practice to avoid prolonged follow up and unnecessary testing.

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The role of DHEAS in diagnosis of subclinical hypercortisolism in patients with adrenal incidentalomas

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At present there are no unified diagnostic criteria for subclinical hypercortisolism (SH) in patients with adrenal incidentalomas (AI). Recently it has been proposed that an age and gender specific DHEAS ratio (calculated by dividing DHEAS by the lower limit of the respective reference range) has a significant diagnostic value in detection of SH.
The aim was to evaluate the value of DHEAS as a diagnostic tool for SH. Retrospectively we evaluated 140 AI patients admitted to Department for obesity, reproductive and metabolic diseases, Clinic for endocrinology, diabetes and metabolic diseases, Clinical centre of Serbia. SH was diagnosed if a patient had at least two out of three criteria: 1mg overnight dexamethasone cortisol (1 mg dex) $\geq$83 nmol/l, suppressed ACTH (below 14 ng/l) and midnight cortisol $\geq$150 nmol/l. Seventy-five patients had nonfunctional AI (NAI), mean age 60.23 ± 11.60 years, mean BMI 28.71 ± 5.56 kg/m^2 and mean DHEAS 1.66 ± 1.27 µmol/l. Sixty-five patients had SH, mean age 59.45 ± 7.95 years, BMI 28.53 ± 4.79 kg/m^2, DHEAS 0.70 ± 0.53 µmol/l. We used Mann–Whitney *U* test, ROC curve and linear regression analysis.
There was no significant difference in terms of age and BMI ($P>0.05$). DHEAS and DHEAS ratio levels were significantly lower in patients with SH ($P<0.001$). However, we could not identify the value that would be specific and/or sensitive enough for the detection of SH. Univariate analysis with 1 mg dex being the dependent showed that both DHEAS ($P=0.004$, $\beta=-0.250$) and DHEAS ratio ($P=0.004$, $\beta=-0.252$) had a significant predictive value. However, this significance got lost in the multivariate regression analysis showing that the only significant predictors were midnight cortisol ($P<0.001$, $\beta=0.627$) and ACTH ($P=0.003$, $\beta=-0.203$).
In conclusion, even though our study did not identify the specific cut off DHEAS value for diagnosis of SH, DHEAS proved to be significantly lower in SH than in NAI making it a valuable additional diagnostic tool for SH.

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What can a tissue measured steroid metabolome tell about adrenal tumor? A tissue steroid analysis of cortisol producing adenoma and an androgen producing adenoma in a second patient with CAH, 21-hydroxylase deficiency

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Introduction
A key feature of a benign adrenal tumor is its hormonal production. It is reflected by serum steroid levels. A tumoral tissue steroid content is not commonly measured.
Methods
A steroid metabolome comprising of 65 steroids was measured in four samples from each of two patients using GC-MS in serum before and after 1mg dexamethasone test, in the tumoral tissue and in the adrenal tissue of two female patients with adrenal adenomas. The first was a patient with CAH, 21-hydroxylase deficiency with a unilateral androgen producing adenoma. The second was a female patient with a cortisol producing adrenal adenoma.
Results
In the patient with CAH and androgen producing adenoma there were less C21 steroids including the most 5α/β-reduced-progesterone metabolites in contrast to the elevated levels of androstenedione and 17oxo-5α/β-reduced C19 steroids in the tumoral tissue compared to the surrounding adrenal tissue, which points to the classic 'frontdoor' pathway of androstenedione metabolism as well as to alternative 'backdoor pathway' in the synthesis of reduced androstanes via cleavage of reduced progesterone metabolites by CYP17A1. In spite of higher testosterone levels in the tumoral tissue there is surprisingly a tendency to lower levels of its 5α/β-reduced metabolites (5α/β-androstane-3α/β,17β diols).
The patient with a cortisol producing adrenal adenoma showed consistently higher levels of both pregnane and androstane steroids downstream the 17-hydroxypregnenolone including testosterone and its unconjugated testosterone metabolites (5α/β-androstane-3α/β,17β diols and 16α-hydroxytestosterone).
Conclusions
In the patient with CAH, there is reduced activity of the C17α-hydroxylase step and elevated activity of the C17, 20 lyase step in CYP17A1 of the tumoral tissue as compared to the adrenal one.
In the tissue of cortisol producing adenoma, the CYP17A1 activity is elevated in both CYP17A1 steps.

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Primary bilateral diffuse large B-cell lymphoma of adrenals presenting as incidental adrenal masses

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Primary adrenal non-Hodgkin lymphoma (PANHL) is extremely rare and constitutes <1% of all NHLs and 3% of extranodal lymphoma. PANHL affects predominantly elderly and males and could arises in the presence of a preexisting autoimmune adrenalitis. Diffuse large lymphomas of B-cell origin (DLBCL) histology is reported in 70% of PANHL cases.
The present case is a primary, bilateral DLBCL of adrenal in 75-year-old male patient admitted for abdominal pain, weight loss and fatigue. He had no known past history of lymphoma or other carcinoma. Abdominal CT scan revealed an incidental, bilateral, marked, homogenous adrenal gland enlargement, measuring 15×8 cm on the right and 9×4.8 cm on the left (both masses >10 HU), with no lymphadenopathy or visceral involvement.
Serum metanephrines, renine, aldosterone and 24-h urine cortisol levels were normal. Depot-ACTH stimulation test demonstrated an insufficient response with an increase from baseline plasma cortisol of 15.2 μg/dl (normal range: 7–22 μg/dl) to 17.8 μg/dl after 4 h and an elevated plasma ACTH of 112.7 pg/ml (normal range 7.2–63.3 pg/ml), indicating a primary adrenal insufficiency (AI). Testosteron and 17OH progesterone were normal. Serum lactate dehydrogenase (LDH) was increased. A biopsy of the adrenals confirmed DLBCL (intense positive CD 20 and negative CD10, CD 99, synaptophisin, Hep-Par expression). Ki 67 was 90%. His bone marrow was not involved at diagnosis. Following hydrocortisone substitution therapy, the patient completed six R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) courses of chemotherapy. FDG PET-CT revealed no tracer uptake in both adrenal masses or in lymph nodes and the patient is still in remision after 8 months. The prognosis is poor and is worsened by increased LDH, increased age, AI, and large tumor size. This case should remind clinicians that PANHL may be a cause of bilateral adrenal incidentaloma with or without AI.

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EP44

A microdeletion of PRKARIA associated with Carney complex

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Background
Carney complex (CNC) is a rare multiple neoplasia syndrome, its commonest endocrine manifestation being ACTH-independent Cushing's syndrome, histologically characterized by primary pigmented nodular adrenocortical disease (PPNAD). There is significant genetic and phenotypic heterogeneity, but deletions at 17q24.2 are rare. We describe the particular characteristics of a patient with a microdeletion in this area.
Case report
A 37-year-old male was referred to the Endocrine Consult Service by the Internal Medicine department, following an episode of severe hyponatremia with altered consciousness and rabdomyolysis. He had a history of cyclical Cushing's syndrome from the age of 5 and had bilateral adrenalectomy at the age of 10. He had been on lifelong hydrocortisone and fludrocortisone replacement, but was not adherent to the medications, due to concurrent problems with alcohol abuse. His GH, IGF1 and prolactin measurement were normal. He had suffered a non traumatic subcephalic right femoral neck fracture 2 years previously and had a total hip BMD of 0.604 and a *Z*-score −2.8 on the left. On examination, he was lean, with pectus excavatum, thoracic spine scoliosis, small testes (8 and 10 ml), and multiple lentigines on the trunk and buccal mucosa. The patient had a normal echocardiogram, testicular ultrasound was significant for bilateral micro calcifications and he had no other clinical or laboratory evidence of endocrine dysfunction.
Chromosomal microarray analysis revealed a 0.98 kb deletion at 17q24.2. Testing of his mother and sister detected no genomic imbalance of 17q24.2. Because the patient's father was deceased, it is not feasible to ascertain whether this was a *de novo* or inherited mutation.
Conclusion
Despite significant but also overlapping phenotypic and genetic heterogeneity, PPNAD – whether clinically indolent or apparent- is the most frequent endocrine manifestation of CNC and should prompt genetic confirmation and long term surveillance for other syndromic manifestations.

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EP45

Prevalence of primary hyperaldosteronism as secondary hypertension; our experience

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Background
Primary hyperaldosteronism is one of the major causes of secondary hypertension, with a prevalence rate of about 4–10% in the hypertensive population. Increased secretion of aldosterone usually comes from adrenal adenoma or their hyperplasia (uni or bilateral). Renines plasma levels are reduced as a result of the body's efforts to curb renine-angiotensin system. It can also be associated with hypokalemi, but not always, more than 60% may not have hypokalemi.
Methods
The study included all of hypertensive patients hospitalized in the Internal Medicine for 1 year. These patients have undergone examinations such as glycemia, uremia, creatinin, liver tests, lipidograma, electrolytes, ECG, Echocardiography. In patients with resistant hypertension has been realized abdominal CT and in cases of suspicion of Conn adenoma is received plasma aldosterone and plasma renines activity.
Results
The total number of patients with hypertension was 399, age 59.47 ± 13.64 years, of whom 162 (40.6%) were male and 237 (59.4%) women. Of these 141 (35.3%) were patients with resistant hypertension, and of these 35 (8.93%) resulted in the Conn Adenoma, confirmed by imaging and laboratory. Men were 23 (63.9%) patients and female 13 (36.1%). Of these 7 (19.4%) patients were presented for the first time with hypertension. 15 (41.7%) patients were hospitalized with hypertensive crisis. Average K^+ in these patients was 3.89 mg/dl. (s.d. 0.47) Echocardiography in these patients shows TS 12.56 (s.d. 1:42), DTD-VM 49.61 (s.d. 5:59), TP 11:42 (s.d. 2.12).
Conclusions
Primary hyperaldosteronism is one of the most common causes of secondary hypertension. Hyperaldosteronism prevalence was about 9%, with a predominance in males about 64%. The initial diagnostic test to confirm the diagnosis is the aldosteron/renine ratio. Regarding getting in CT imaging, not always unilateral or bilateral hyperplasia or finding a formation of adrenal glands deals with primary hyperaldosteronism.

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EP46

Ipilimumab immunotheraphy for advanced melanoma induced autoimmune adrenalitis

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Introduction
Ipilimumab is a monoclonal antibody against the inhibitory CTLA-4 receptor expressed on T cells. It provokes an upregulation of the immune system. It is known to cause neuroendocrine disorders, such as hypophysitis, hyppothyroidism/thyroiditis and adrenal insufficiency. Althought it is stipulated that thyroid.stimulating hormone (TSH) levels should be evaluated before administration of each dose of ipilimumab as a screen for thyroid diyfunction, there is no requeriment for screening pituitary-adrenal biochemistries.
Case report
A 68 year-old woman presented to Emergency Department with extreme fatigue (2 months of progressively worsening fatigue which provoked her visit to general doctor) and hyponatremia after receiving 4 doses of ipilimumab for metastatic melanoma (three months ago). Elevated ACTH levels, low morning cortisol levels along with failed to repond to cosyntropin stimulation test demonstrated primary adrenal insufficiency. Computed tomography scan of the abdomen showed bilateral enlargement of adrenal glands with metastatic desease in the right one. She was started on replacement dose of hydorcortisona with resolution of symptoms.
Conclusions
We recommend monitoring ACTH and cortisol levels in patients receiving ipilimumab therapy, similar to the routine screening thyroid function tests done to screen for hypothyroidism/thyroiditis, which is less frequent and sympomatic compared with adrenal insufficiency. CT findings of enlarged adrenal glands afther ipilimumab therapy should raise the suspición of drug-induced adrenalitis and may imply a monitoring of the patient's adrenal function.

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EP47

Cardio metabolic parameters in non-functional adrenal adenoma

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Objective
The aim of the present study was to evaluate cardio metabolic risk factors in patients with non-functional adrenal adenoma.
Materials and methods
We studied thirty newly diagnosed adrenal adenoma patients and 30 healthy participants. Fasting glucose, insulin, lipid, hormone profile were evaluated from each patient.
Results
The frequency of diabetes mellitus and hypertension were statistically higher in adrenal adenoma group. Lipid profile was similar between groups. Mean fasting glucose, insulin, HOMA-IR, triglyceride and uric acid levels were higher in adrenal adenoma group compared with the control group, however; the differences did not reach statistical significance. Mean hsCRP and CIMT were significantly higher in adenoma group.
Conclusion
Cardio metabolic risk factors were found to be higher in non-functional adrenal adenoma. Therefore; patients with adrenal adenoma should be monitored for cardiovascular disease.

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EP48

Cushings syndrome due to carneys complex – case series and a report of a new mutation from South Indian Tertiary care centre

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Introduction
Carneys complex is an uncommon cause of ACTH independent cushings syndrome which occurs as a combination of myxomas, spotty pigmentation and endocrine overactivity. Primary pigmented nodular adrenocortical disease (PPNAD) is seen in 25–45% of patients with Carneys complex.
Methods
Three patients who were suspected with carneys complex were studied to look if their biochemical radiological and clinical characters could predict postoperative diagnosis of carneys complex.
Clinical presentation
Mean age of onset of symptoms was 17 years. All the patients had diabetes hypertension, cushingoid features and spotty pigmentation of the face.
Investigations
Elevated blood sugars, normal serum electrolytes, Baseline cortisol (mean 17.3 μg/dl) Dexamethasone suppressed cortisol was significantly higher (mean 19.9 μg/dl) than baseline cortisol, supressed serum ACTH, CT abdomen showed unilateral nodular lesion in two cases with other adrenal normal sized with nodular borders and one case showed bilateral normal sized adrenals with nodular borders. Gross and HPE was suggestive of bilateral PPNAD. To confirm PPNAD, sequence analysis and deletion testing of PRKAR1A gene was done. Mutation was found in 2 out of 3 patients. A new variant in PRKAR1A gene was identified in one patient (C769G > A; E 257K). Genetic testing is negative in one patient.
Conclusion
Multiple lentiginosis, a higher dexamethasone suppressed cortisol compared to basal cortisol suppressed ACTH and radiological evidence of nodular adrenals can predict carneys complex in a patient with cushings syndrome. Genetic testing could be negative, which is not unusual as positive genetic testing is found only in 60–70% of patients.

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EP49

Cushing' s disease, hasimoto's thyroiditis and severe hyperandrogenemia

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Introduction
Cushing's disease (CD) is caused by high *adrenocorticotropic hormone* (ACTH), usually by a pituitary micro*adenoma*.
Material and method
This is a case report investigated in several Romanian centers by performing: morning plasma cortisol, circadian rhythm of plasma cortisol, plasma ACTH, dexamethasone (DXM) suppression tests.
Case data
A 57-year female, known with hypertension and osteopenia, was admitted for high blood pressure, fatigue, anxiety, sweating and hirsutism. Clinical examination revealed: moon face, plethora, hirsutism (on upper lip, lower jaw, sideburn, lower abdomen and thigh; Ferriman-Gallwey score of 18, centripetal obesity; buffalo hump, enlarged supra-clavicle fat pads and cervical. Endocrine evaluation indicated normal thyroid function with positive anti-thyreoglobulin antibodies (283.3 UI/ml, normal < 50 UI/ml), high levels of morning plasma cortisol (249 ng/ml, normal 70–225 ng/ml) with loss of circadian rhythm, ACTH level within the upper reference range (41.1 pg/ml, normal < 46 pg/ml) and a very high testosterone level (6.1 ng/ml, normal 0.2–0.75 ng/ml). Biochemical parameters indicated hypertriglyceridemia, low potassium and neutrophilia. Non-suppression at DXM 1 mg overnight test and 50% suppression at high dose of DXM leaded to a diagnosis of CD. Imagery did not identify any tumor. No ovarian, neither adrenal tumor was found in correlation to high testosterone levels so CD was considered the only cause.
Therefore the patient was treated with steroid synthesis inhibitor-Ketoconazole (800 mg/day), with clinical improvement: decrease of hirsutism and normal-ization of testosterone level to 0.2 ng/ml within months. Follow-up and a definitive therapy is needed.
Conclusions
Severe hyperandrogenism as seen here in CD is rare, most probably is correlated with adrenal androgen production and thyroid autoimmunity is incidental; therapeutically control of CD represents a clue of the etiological diagnosis of hyperandrogenemia.

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EP50

Adrenal infarction in antiphospholipid syndrome despite therapeutic anticoagulation

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We report a case of acute adrenal crisis in a patient with the antiphospholipid syndrome in a man who was on a therapeutic dose of warfarin. A 64-year-old man presented with vomiting and abdominal discomfort. Temperature was 37.8 °C, pulse 85/min and BP 100/63 mmHg. On examination, there was generalized hyperpigmentation. He had a history of deep venous thrombosis of the lower limbs on two occasions and was on warfarin. He previously diagnosed primary antiphospholipid syndrome with a strongly positive anticardiolipin IgG antibody. Serum sodium was 127 mmol/l, and serum potassium was 5.7 mmol/l, urea 9.8 mmol/l and Creatinine 103 μmol/l. Haemoglobin was 12.6 g/dl, white cell count of $7.3/10^9$/l. INR was 3.1 on warfarin, APTT 133 secs and prothrombin 32.7 secs. Primary adrenal insufficiency was suspected. The Tetracosactrin (Synacthen, 250 ugrams) test had a maximum stimulated cortisol of 43 nmol/l (normal > 550 nmol/l) confirming adrenal insufficiency. CT of Abdomen revealed bilateral adrenal enlargement (right adrenal: 3.1 cm × 2.9 cm, left adrenal: 3.0 cm × 2.5 cm). At the time there was diagnostic uncertainty and biopsy considered risky, Tuberculosis was considered and was treated for a number of months though no bacteriological or other clinical features diagnosed were established. PET scan was negative for evidence of malignancy. Double stranded Anti-Nuclear Antibody was negative. Beta-2 glycoprotein was positive. Adrenal antibodies tested negative. On a repeat CT Abdomen 4 months later, his adrenal glands shrunk to 1 cm bilaterally and on review suggested that there was

haemorrhagic infarction initially. He made a good recovery on hydrocortisone and fludrocortisone. INR target was increased to 3.5. After 5 year follow up there was no further infarction. Learning Point: this case illustrates that adrenal infarction can occur in antiphospholipid syndrome despite conventional anticoagulation perhaps because of the adrenal vascular has only single venous drainage but multiple arterial arcades making it more susceptible to thrombosis and haemorrhage.

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EP51

Pediatric Cushing's disease and paraduodenal tumor

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Introduction
Cushing's disease (CD) in youth represents a challenge especially related to the therapy and long-term management.
Materials and methods
We report the medical history of a child with CD who was followed-up for 7 years. Suggestive endocrine panel and imagery is exposed.
Case presentation
A 19-year female was diagnosed at age of 12 with CD. Clinical assessment revealed: weight gain, headache, hyperpigmentation predominantly on the areas subjected to friction. Hormonal profile found: plasma ACTH of 48.9 pg/ml (N:7.2–63.3 pg/ml), baseline plasma cortisol (8 a.m) of 486.4 nmol/l (N:172–497 nmol/l) and (8 p.m.) of 220.1 nmol/l (N:71.1–286 nmol/l), plasma cortisol after 1 mg overnight dexamethasone (DXM) suppression test of 347.6 nmol/l (N: $<$50 nmol/l) and after 2 days$\times$8 mg DXM of 41.7 nmol/l, suggestive for ACTH-dependent hypercortisolism. The initial pituitary MRI did not detect anomalies but a subsequent examination described a pituitary microadenoma. Adominal CT scan with and without enhancement and abdominal MRI revealed a periduodenal tumor of 12/8 mm, which raised the question of a neuroendocrine tumor which was not confirmed by pathological report based on biopsy (via superior digestive endoscopy). The patient underwent transsphenoidal surgery with selective removal of the pituitary microadenoma and persistent CS intermittently treated with steroidogenesis inhibitors and imagery follow-up of the periduodenal mass. Currently, high plasma ACTH levels of 95.56 pg/ml with elevated basal plasma morning cortisol of 404.7 nmol/l and inadequate suppression after 1 mg DXM overnight of 81.2 nmol/l. Pituitary MRI was status quo and pasireotide was recommended.
Conclusion
Despite the potential differential diagnosis with ectopic Cushing's syndrome related to the paraduodenal tumor, pediatric CS represents a rare yet severe event and the methods to achieve the disease control in this particular population are still suboptimal.

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EP52

Adrenal leiomyoma: a rare cause of adrenal incidentaloma

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Introduction
Leiomyomas are benign tumors originating from the smooth muscle cells. They occur more frequently in the uterus and in the gastrointestinal system. Adrenal leiomyomas are rare tumors arising from the smooth muscle of the adrenal vein and its tributaries.
Case report
Man, 72-years-old, referred to Endocrinology in the context of an adrenal incidentaloma (20 mm maximum diametre) detected in abdominal-pelvic CT performed for the study of splenomegaly. He had arterial hypertension, well controlled with two antihypertensive drugs. Family history was irrelevant and physical examination did not reveal any sing suggestive of adrenal hyperfunctioning. CT scan performed 12 months after diagnosis (January 2013) showed a left adrenal nodule with 25 mm, with density values compatible with atypical adenoma. Biochemical evaluation confirmed that it was nonfunctioning. CT scan was repeated on April 2015 showing a nodule with irregular borders, with 38 mm, with 34HU and slow contrast washout. Considering the lesion characteristics the patient underwent left adrenalectomy. The histological result was in favor of a well-differentiated smooth muscle neoplasm with leiomyoma characteristics. Immunohistochemical study confirmed the diagnosis of leiomyoma with positive cells for alpha-actin and desmin and negative for c-Kit and S100 protein.
Conclusions
The adrenal incidentaloma are often found during the investigation of other diseases not related to adrenal and may be a variety of tumors. The leiomyoma is very rare and should be considered in the differential diagnosis of incidentalomas.

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EP53

Ectopic expression of serotonin receptors in adrenocorticotropin-independent macronodular adrenal hyperplasia

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In ACTH-independent macronodular adrenal hyperplasia (AIMAH) causing Cushing's syndrome, cortisol secretion is controlled by illegitimate membrane receptors. In the normal adrenal gland, agonists of 5-HT4 receptors have a powerful effect on aldosterone secretion but little effect on cortisol secretion *in vitro*.
The aim of our study is to describe the clinical and hormonal features of patients diagnosed with aberrant serotonin receptor expression.
We report the cases of three patients diagnosed with bilateral AIMAH. All patients were females, aged 40, 30 and 74 years respectively. The AIMAH was associated with clinical Cushing's syndrome in a patient and a subclinical Cushing's syndrome in two others. The presence of aberrant serotonin receptors was associated with aberrant GIP and angiotensin receptors in a patient, to catecholamine receptors in the second and isolated in the third.
Serotonin receptors are probably the most functional receptors in AIMAH. Indeed, their frequency is high in many published series. The simultaneous expression of several aberrant receptors linked to G protein makes difficult to identify the action of each receptor and the part of cooperation between the different receptors. The characterization of the pharmacological profiles of ectopic receptors in AIMAH provides opportunities for development of new pharmacological therapies. Because numerous adrenal hyperplastic tissues express more than one type of illegitimate receptor, drugs targeted to common transduction mechanisms of illegitimate receptors, including T-type calcium channel blockers, may prove to be useful for reducing cortisol synthesis and/or cellular proliferation in AIMAH.

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EP54

Cushing's syndrome in King Chulalongkorn Memorial Hospital: experience from a single tertiary referral hospital

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Objective
To assess clinical characteristics, management and outcome of treatment of Cushing's syndrome (CS) in King Chulalongkorn Memorial Hospital (KCMH).
Method
We performed a retrospective evaluation of 82 patients with CS in KCMH during 2001–2015. Median follow-up time was 36 months [interquartile range 11–35].
Results
Of the 82 patients, Cushing's disease (CD) was diagnosed in 45 patients (55%). Twenty-six patients had adrenal tumor and 11 patients had ectopic ACTH syndrome. Median age at diagnosis was 38 years old. Median time between first presentation and diagnosis was 12 months. 24% of the patients had normal body mass index. Skin abnormalities (purplish striae, facial plethora, easy bruising) were found in 21–37%. The preoperative ACTH was higher in ectopic ACTH

syndrome and CD compared to adrenal Cushing's syndrome. In CD, 34 patients (76%) had pituitary microadenoma and 11 patients had pituitary macroadenoma (24%). Twenty-five patients (74%) with pituitary microadenoma were cured after their first transphenoidal surgeries. All patients with persistent hypercortisolism were cured after subsequent treatment. In patients with pituitary macroadenoma, five were cured after the first surgeries. Only one patient had remission of CS after subsequent treatment. In adrenal Cushing's syndrome, cortisol-producing adrenal adenoma was the most common etiology. Median size of tumor was 3 cm. All patients were cured. Ectopic ACTH syndrome were diagnosed in 11 patients. Primary tumors were located in eight patients (bronchial and thymic carcinoids, small cell lung cancer, medullary thyroid carcinoma). Seven patients died and three patients had persistent hypercortisolism. Only one patient was cured.
Conclusions
CD was the most common etiology of CS. However, higher prevalence of adrenal CS was observed. Lower prevalence of patients with overweight or obesity as well as skin abnormalities compared to previous studies. In all subtypes of CS, surgery remained the mainstay of treatment.

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EP55

Outcome with surgical treatment in subclinical hypercortisolism

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Introduction
Subclinical hypercortisolism (SH), a condition of biochemical cortisol excess without the classical signs or symptoms of overt hypercortisolism, is thought to be present in the 5–30% of patients with incidentally discovered adrenal mass (adrenal incidentalomas). Some evidence suggest that this condition may lead to long-term consequences of cortisol excess, but indication and potential benefits of adrenalectomy in this state are still in doubt. We analyse a series of patients with SH operated in our center to assess its clinical course after surgery.
Methods
Retrospective study in 25 patients (19 women, 6 men) with an average age of 61.4 years (45–83) between 2001 and 2015. Indication for surgery was performed if they met at least two of the following criteria: urinary free cortisol levels higher than 100 µg/24 h, serum cortisol levels after a 1-mg overnight dexamethasone suppression test (Nugent) $>$ 1.8 µg/dl, ACTH levels lower than 10 pg/ml and low serum DHEAS (for sex and age). Clinical and laboratory characteristics of the pre and postoperative state are collected.
Results
The cause of diagnosis was mainly adrenal incidentaloma (84%). At diagnosis, 76% of patients had hypertension, and 64% GAA or DM. All patients but one had Nugent $>$ 1.8 mcg/dl. Adenomas were mostly left (76%), with an average size of 34.8 cm. Of the 21 patients with more than 1 year of postoperative follow-up, 62% experienced improvement in blood pressure values or carbohydrate metabolism. Postoperative replacement therapy with glucocorticoids was required in 60% of patients, with an average duration of 4.6 months (3–15). No preoperative biochemical, clinical or radiological parameter was associated with postoperative clinical response.
Conclusion
In 60% of our cases adrenal surgery for SH led to a marked improvement in glycemic control and/or hypertension. We found no biochemical parameter for predicting this favorable response.

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EP56

Addison's disease warrants large package of care costs due to substantial comorbidity

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Introduction
Patients with Addison's disease are burdened by substantial comorbidity and likely require a large package of care. There is a proportion of South African patients who can afford private health-care, comparable to health-care offered in a developed country. We hypothesised that comprehensive package of care costs for Addison's disease is relatively high.
Methods
We identifed 131 patients with Addison's disease within a private sector cohort, using ICD 10 code (E27.1). Demographic, co-morbidity and cost analysis data from claims were collected as of November 2015 (Rand/EURO = 0.06), for the duration that the patients were members of a medical insurance company.
Results
The median (IQR) ages were 51 (37–67) in 2015 and commencement of membership 46 (33–62.5) years, respectively and membership duration 61.9 (36.4–103.5) months. There were 56% female patients, 75 and 100% received hydrocortisone and fludrocortisone, respectively. The most prevalent comorbidities were: hypothyroidism (34%), hypertension (32%), hyperlipidaemia (28%), gastro-oesophageal reflux disease (12%), congestive cardiac failure (8%), depression (8%), ischaemic heart disease (7%), and type 2 diabetes mellitus (6%). 15 and 7% of patients with Addison's disease had at least one adrenal crisis and one admission for ischaemic heart disease, respectively within the study period, with median number of admissions per patient of 2 (1–4). From the perspective of the provider, mean overall and mean monthly overall direct costs for patients with Addison's disease were €15 163.80 and €304.26, respectively. The mean comparable costs for patients with both hypertension and hyperlipidaemia were €10 911.47 and €181.50, and for AIDS patients on antiretroviral treatment (ART) were €10 643.93 and €236.00, respectively.
Conclusions
Substantial comorbidity, predisposition to adrenal crises, ischaemic heart disease contribute to the higher average package of care cost of Addison's disease, compared to patients with both hypertension and hyperlipidaemia, and patients on ART.

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EP57

Testosterone and cortisol co-secretion by an adrenocortical adenoma presenting as secondary polycythemia

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Background
Androgen co-secretion in patients with adrenal Cushing's syndrome is considered a marker of malignancy. Mixed secretion by benign adrenocortical tumors is rare. We describe a case of a middle aged woman presenting with Cushing's syndrome and polycythemia.
Case report
A 57-year-old lady was referred by the Hematology Service to our Endocrine Clinic for evaluation of an adrenal mass found in an abdominal CT in the course of investigating secondary polycythemia. The patient, a 35 pack-year-smoker, had presented with upper arms petechiae and a hematocrit of 52 and hemoglobin of 17, while it was up to 42 up to 5 years previously. *Jak*2V617F mutation analysis was negative. Her past history was notable for natural menopause at age 45, recent onset hypertension and dyslipidemia. She had noted worsening hirsutism on her trunk and arms. On clinical examination the patient had the classic Cushinoid features, Ferriman Gallwey score 17, marked female pattern hair loss but no other signs of virilization. The pertinent lab findings were as follows: Hb 16.3 g/dl, Ht49.1%, K 4.8, glucose 115 mg/dl, ALT 29 mg/dl, cortisol after overnight dexamethasone suppression 483 nmol/l ($<$50 nmol/l), 24 h UFC 405, ACTH 1 pg/ml (7.2–63.6), aldosterone 6.24 ng/dl (4–31), plasma renin activity 0.17 ng/ml per h (0.5–4.7), testosterone 3.49 nmol/l (0.43–1.24), estradiol 18 pg/ml ($<$50), DHEAS 50.8 Δ4-androstenedione 3.4 ng/ml (0.3–3.3) 17OH-progesterone 2.64 ng/ml (0.2–1), erythropoietin (EPO) 18 mU/ml ($<$25), 24 h-urine metanephrines 66 µg (52–341) TSH 2.18 µIU/mL and O_2sat 98%. On laparoscopic adrenalectomy, a 2.5 cm adrenal adenoma, Weiss score 0, was removed without complications and oral hydrocortisone supplementation postoperatively. One month following excision, her labs were as follows: hematocrit 42%, hemoglobin 13.6 g/dl, potassium 4.9, testosterone 1.27 nmol/l (0.43–1.24), EPO 14 IU/l (2.6–34), DHEAS 7.2 µg/dl (18.9–205) and undetectable Δ4-androstenedione.
Conclusions
i) clinically apparent androgen co-secretion in adrenal Cushing does not necessarily equate to malignancy ii) secondary polycythemia may be a noteworthy multifactorial presentation of a secretory adrenal adenoma independent of smoking status, mediated by direct EPO tumor production and marrow stimulation by cortisol testosterone.

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EP58

Endosonography – an important diagnostic tool in identifying a small aldosterone-producing adenoma in a patient with primary hyperaldosteronism – case report

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Introduction
Primary hyperaldosteronism is still an underdiagnosed cause of hypertension. The challenge lies however, not only in diagnosing the primary hyperaldosteronism, but also in the distinction between aldosterone-producing adenoma (APA) and idiopathic adrenal hyperplasia (IHA). Establishing the correct diagnosis is after all essential, because surgery is only effective in patients with adrenal adenoma.
Case report
We report about a 67-year-old patient, who presented with hypertensive crisis with blood pressure up to 250/120 mmHg and intermittent hypokalemia below 2.8 mmol/l. Pheochromocytoma and Cushing's syndrome have been excluded. The routine laboratory tests displayed however an elevated plasma aldosterone/renin quotient as well as an elevated 24-h urinary excretion of aldosterone. At this point the patient was being treated with five antihypertensive drugs and the blood pressure was still indicating levels over 200/100 mmHg. It was therefore not possible to discontinue the interfering antihypertensive therapy in order to conduct further diagnostics. Both CT and MRI detected no abnormalities or adrenal adenoma. The endosonographic examination of the adrenal glands identified however a unilateral 8×6 mm small adrenal adenoma, which exhibited the typical morphological signs of an APA. The patient underwent surgery. After resection of the small adrenal adenoma, the aldosterone/renin quotient become normal and the patient presented a stable blood pressure below 135/70 mmHg.
Discussion
This case indicates that in the differential diagnosis of primary hyperaldosteronism, endosonography is more important than previously assumed in the literature. Especially in difficult cases, the use of endosonographic examination should be considered.

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EP59

Retrospective evaluation of adrenal incidentelomas

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Introduction
Adrenal incidentelomas are new era of the endocrinology. We aimed to see the results of adrenal masses retrospectively.
Methods
Patients admitted to the Internal Medicine outpatient clinic for different complaints were retrospectively evaluated. Patients whom abdominal imaging like ultrasonography, magnetic resonance imaging or computed tomography were done and incedentally established adrenal masses were evaluated. Patients with a history of hypertension, findings of hypokalemia, hypernatremia were excluded from the study. Patients were hospitalised and adrenal function tests were done.
Results
There were totally 59 patients, 24 male (40.67%), 35 female (59.32%), and mean ages were $57.54 + 11.29$ years (32–75 years) in men and $55.71 + 11.72$ years (31–81) in women. Adrenal function tests revealed that 53 (89.83%) incidentelomas were nonfunctioning. Totally 6 (10.16%) patients' adenomas were functioning, 3 (5.08%) of them were pheochromacytomas, 1 was subclinical Cushing syndrome and 2 (3.38%) were primary hyperaldosteronisms. 3 (5.08%) of nonfunctioning adenomas were diagnosed as metastasis in computerized tomography, one was small cell carcinoma, and one was prostate malignancy. The other patient was operated and diagnosed as adrenal adenocarcinoma. In the nonfunctioning group, two patients had cyst hydatid disease and were having treatment for it and also two patients had accessesory spleen in the tomography.
Conclusion
Patients with adrenal incidentelomas should be evaluated for hyperfunctioning and also metastasis from other organs should be kept in mind.

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EP60

Primary hyperaldosteronism: clinical and therapeutic approach of a center

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Introduction
Primary hyperaldosteronism (HAP) is the main cause of secondary hypertension, with a prevalence estimated between 6 and 20% in resistant hypertension. Clinical suspicion is critical, especially if *aldosterone*-to-*renin ratio* (ARR) >25, however the diagnosis is dependent on confirmatory evidence, including aldosterone suppression tests.
Methods
Retrospective evaluation of 44 patients with suspected PAH, identified between 2010 and 2015 at a single center.
Results
Sixteen of 44 patients had hormonal findings consistent with the diagnosis: nine men, seven women; mean age 60.50 ± 9.75 years. Median time of hypertension: 9.00 years.
Fourteen patients had adrenal masses on CT evaluation (dimensions 1.44 ± 0.88 cm): 12 with unilateral nodules and two bilateral.
Aldosterone-to-renin ratio >25 in 14 patients and two patients presented with ARR >20, associated to aldosterone >10 ng/ml with suppressed renin. All of them with positive saline infusion test (SIT).
Eight patients undergone laparoscopic adrenalectomy; anatomopathological result: adrenal cortical adenoma in seven patients and adrenal hyperplasia in one. Of these, four kept medical therapy with reduction of antihypertensive drugs. Eight patients maintained medical therapy due to bilateral lesions, absence of surgical conditions or intervention refusal.
Follow-up at 6 months: significant reduction of systolic BP (143.00 ± 17.15 vs 133.00 ± 13.37 mmHg; $P = 0.008$) and the number of required antihypertensive drugs (2.00 ± 0.85 vs 0.50 ± 1.26; $P = 0.004$); systolic BP was also significantly lower on surgically treated patients (120 ± 13.22 vs 140 ± 7.36 mmHg; $P = 0.021$).
Conclusions
On follow-up at 6 months, it was found a significant overall reduction in the levels of systolic blood pressure and the number of antihypertensive drugs.
Surgical treatment produced a more significant reduction in the levels of systolic BP compared with medical treatment alone. The reduction of serum aldosterone levels was also higher in the group undergoing surgery.

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EP61

Circadian rhythm of salivary cortisol & 6 – sulfatoxy melatonin in night shift nursing professionals and actual day workers

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Objectives
The present aimed to investigate the circadian pattern of salivary cortisol & sulfatoxy melatonin level in night shift professionals and actual day workers & to find out these changes in the circadian pattern produce by night shift are reversible in due course of time.
Methods
56 Nursing professionals of both gender who perform day and night shifts and 56 actual controls were also recruited in this study. Saliva and urine samples were collected at ~ 8 h interval in their night shift and day shift schedule and in the control subjects. Groups were compared by applying paired and unpaired *t* test.
Result
Significant difference was found in night cortisol levels among night (4.08 ± 3.28) vs day shift (2.62 ± 2.37), ($P < 0.005$), while in controls (1.82 ± 1.18) ($P < 0.0005$) when compared to night shift. Alteration in mean morning cortisol level was also found between night (3.88 ± 2.54) vs day shift (54.79 ± 2.46) ($P < 0.05$), while in controls (5.71 ± 3.55) $P < 0.005$ when compared to night shift. Night melatonin level was found declined as compared to morning level and this pattern was significant when compared night melatonin between night (17.65 ± 12.20) vs day shift (22.41 ± 13.70), while in controls (25.45 ± 17.20)

($P<0.05$) when compared to night shift. morning melatonin level between night (21.08 ± 14.50) vs day shifts (27.36 ± 14.46) ($P<0.05$), while in controls (28.91 ± 16.20) ($P<0.05$) when compared to night shift. Difference was insignificant when cortisol and melatonin levels found in night shift were compare to actual controls and it elucidates the circadian pattern was recovered in day shift.

Conclusion

Alterations in circadian pattern of salivary cortisol and melatonin sulfate were found during night shift due to internal desynchronization. Sleep loss might be associated with decreased melatonin level leads to endocrinal and cardiovascular diseases.

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EP62

A case of subclinical primary aldosteronism and subclinical Cushing's syndrome without risk factors of cardiovascular disease

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A 49-year-old woman was referred to our hospital for the evaluation of adrenal incidentaloma. She had no past medical history and no family history of notable illness. The patient was 150 cm tall and weighed 60 kg. Her blood pressure was 103/60 mmHg. She had no Cushingoid features. Osteoporosis was absent. Routine laboratory examinations were within the normal ranges including normokalemia. The hormonal examination revealed normal circadian variation in serum cortisol levels (11.7 μg/dl at 0800 h and 3.3 μg/dl at 2300 h) and plasma ACTH level was undetectable (<2.0 pg/ml). Plasma cortisol level was suppressed after the low-dose overnight dexamethasone suppression test but was not suppressed after the high-dose test. The plasma aldosterone concentration (PAC) level was normal (110 pg/ml) and the plasma renin activity (PRA) was suppressed (0.1 ng/ml per h). The captopril test and furosemide-upright test were positive, whereas the saline-loading test was negative. CT scans of the abdomen showed bilateral adrenal tumors. Adrenal scintigraphy revealed bilateral adrenal activity. To determine the laterality of the excessive cortisol or aldosterone secretion, we performed adrenal venous sampling (AVS). Finally, we made a diagnosis of subclinical primary aldosteronism (PA) caused by both adrenal glands and subclinical Cushing's syndrome (CS) caused by both adrenal tumors. Interestingly, this patient had no risk factors for cardiovascular disease such as hypertension, obesity, diabetes mellitus or dyslipidemia. Thus, we are observing her without medical therapy. Three years after diagnosis, she has not been detected hypertension, hypokalemia, cardiomegaly in echocardiography and atherosclerosis in carotid ultrasonography. One important remaining question is why excessive hormone secretion did not affect the cardiovascular status of this patient. In this regard, several possible mechanisms have been reported including mineralocorticoid resistance. Further study is going to resolve this issue.

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EP63

The relationship between androgen levels and NLR in hirsutism

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Introduction

Hirsutism is a disease in which, women chin, upper lip, chest, abdomen, showing the terminal structure to increase hair growth in the male pattern of distribution as androgen sensitive back and thighs are seen. Neutrophil/lymphocyte ratio (NLR) has been proposed as a simple inflammatory marker of response. Increased value of NLR cardiovascular venture in patients was found to be an indicator of poor prognosis. In our study, we aimed to determine the association between regardless of the etiology in patients with complaints of hirsutism, androgen levels in blood neutrophil/lymphocyte ratio.

Materials and methods

248 patients admitted Hirsutism was examined. Hirsutism and menstrual histories menarche, number of pregnancies and live births and infertility history of individuals, were questioned. In addition, hair loss, acne was recorded as signs of hyperandrogenism. Patients FSH, LH, E2, PRL, DHEAS, 17-OHP, androstenedione, total testosterone, free testosterone and follicle tests were measured phase.

Results

The study included between 16–70 years (mean age 28.67 ± 9.29 years) were enrolled 248 patients. Patients with ($n=73$) and without ($n=175$) hipeandrojenemi were compared. When the groups with and without hyperandrogenemia are compared there occured no statistically significant difference between the NLR ($P>0.05$). In contrast, significant differences were found between hematocrit levels ($P<0.05$).

Conclusion

The presence of hyperandrogenism in hirsutism clinical practice cases are being investigated. The relationship between hyperandrogenism and a parameter NLO which is an early used parameter may be guider to the detection of inflammatory or cardiovascular risk.

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EP64

ACTH-independent massive bilateral macronodular adrenal hyperplasia

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Introduction

The estimated annual incidence of Cushing's disease ranges from 2 to 4 per million. Bilateral macronodular adrenal hyperplasia (BMAH) accounts for <1% of Cushing's syndrome causes.

Case report

We present a case of 58-year-old man who had been suffering typical clinical signs of hypercortisolism for 5 years. He presented hyperglycemia, arterial hypertension, central obesity, thin skin, hemorrhagic diathesis, edemas, weakness and emotional lability. Endocrine evaluation of adrenocortical axis proved hypercortisolism of adrenal origin with increased 24-h urinary free cortisol (UFC) (792 μg/24 h [4.3–176]), a low doses dexamethasone test with not suppression (21.6 μg/dl [<1.8]), a loss of cortisol circadian rhythm (16.1 and 20.6 μg/dl [<7.5]) and low ACTH concentrations (<5 pg/ml [3.7–19.4]). Magnetic resonance imaging of the adrenal gland demonstrated bilateral adrenal masses (the right and the left adrenal measured were $3.1\times5\times3$ and $5\times7\times3$ cm respectively). A NP-59 iodocholesterol scintigraphy showed an increased uptake of both adrenal glands.

With the diagnosis of Cushing's syndrome ACTH-independent caused by bilateral adrenal masses surgery was made. Bilateral adrenalectomy was performed and histopathology revealed massive BMAH with multiple nodules ranging in size from several mm to 3 cm. The weight of right and left adrenal gland was 85 and 105 g respectively.

After that, hypercortisolism was solved and patient's phenotype, diabetes and hypertension disappeared.

Conclusions

BMAH is rare cause of Cushing's syndrome. It more often presents as an incidental radiological finding with underlying subclinical hypercortisolism. It is usually detected in the fifth or sixth decade of life. Bilateral adrenalectomy remains the main treatment for BMAH but unilateral adrenalectomy has been proposed in selected cases.

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EP65

Schmidt's syndrome – case report

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Introduction

Polyglandular autoimmune syndrome type II (PGA-II) or Schmidt's syndrome is a very rare autoimmune disorder and difficult to diagnose because the symptoms of this syndrome depends on the gland which gets involved first. Approximately 14–20 people per million population are affected by polyglandular autoimmune syndrome type II. It is characterised by the obligatory occurrence of autoimmune Addison's disease in combination with thyroid autoimmune diseases and/or type 1 diabetes mellitus.

Case presentation
A 40-year-old lady presented to the Emergency Department with complaints of progressive weight loss 13 kg in eight months, anorexia, headache and vomiting. Physical examination on admission revealed: Hyperpigmentation was mostly expressed in the face, upper part of thorax, dorsal part of the hand. pulse was 114/mins, BP-80/60 mmHg and respiratory rate-22/mins. leucocyte count-6200 cells/mm^3, Platelet count-31 4000 cells/mm^3, fasting blood sugar-86 mg/dl, renal function tests, liver function tests, serum potassium 8.1 (3.7–5.5) sodium 135 (136–148) Free T_3 – 2.8 pmol/l, Free T_4 – 10.6 pmol/l, TSH – 12.16 IU/ml, random cortisol-2.23 ng/ml anti TPO level, Ac anti Tg 477.5 IU/ml. Hyperpigmentation, low cortisol level and high potassium raised the possibility of Type II polyglandular autoimmune syndrome. cosyntropin test was suggestive of primary adrenal insufficiency. Normal Abdominal CT and Pituitary MRI. Antibody against 21 (OH) were high 23 Norma <10. She was diagnosed as polyglandular autoimmune type 2 (or Schmidt's syndrome). She was started on steroid replacement therapy. thyroxin 2 weeks after the steroid therapy. During her follow- up after one year later she developed also Diabetes Mellitus and insulin treatment was started. Our patient was treated and improved with corticosteroid, thyroxine and insulin therapy.
Conclusion
Every patient with endocrine deficiency should be screened for other insufficiency of other endocrine organs.

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EP66

Iatrogenic Cushing's syndrome due to misuse of topical corticosteroids: a case report

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Introduction
Because of their anti-inflammatory effect, topical corticosteroids are widely used in dermatological diseases. Topical use is typically safe, but serious adverse effects induced by systemic absorption are occasionally reported. We report a patient who developed Cushing's syndrome due to long-term misuse of topical bethametasone and clobetasol.
Case Report
A 24-year-old man presented with rapid weight gain and purple strias in multiple areas. He had moon face, supraclavicular fat deposition and purple strias bilaterally on the medial aspects of his arms, thighs and abdomen. We diagnosed Cushing's syndrome clinically, but his serum ACTH and cortisol levels were extremely low. When we questioned him about using corticosteroids, he stated that he did not use any medications. We performed an ACTH stimulating test but he had no cortisol response. We interrogated him again about medication use and learned that he had been using a steroid-containing ointment for two years due to itching in his groin region. We asked him to stop using the ointment and within 3 months, his signs of Cushing's syndrome abated.
Discussion
Because of their anti-inflammatory and anti-proliferative effects, topical corticosteroids have been used succesfully to treat dermatological diseases for a long while. Although absorption of topical corticosteroids is low, long-term application of these agents at high doses can increase the probability of systemic adverse events. As use of superpotent agents has increased, reports of local and systemic side effects have also increased. The risk for developing systemic side effects depends on the agent's potency, the length of treatment, application frequency, epithelial integrity, extensiveness of applied area, and use of concomitant therapies. The most common etiology of Cushing's syndrome is iatrogenic. The use of topical agents should always be queried when taking a medication history in order to discover any sources of exogenous steroids so that appropriate treatment may be started.

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EP67

Non-Hodgkins B cell lymphoma presenting as acute adrenal crisis

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We present a rare case of Non- Hodgkins large B Cell lymphoma presenting as circulatory collapse and acute adrenal insufficiency. A 47 year old woman was referred with a 1 month history of weight loss of 7 kg and vomiting. Shortly after admission her condition deteriorated and she developed acute hypotension, BP was 92/58 mmHg, heart rate 100/mn and required volume resuscitation. Examination revealed a thin woman with generalised hyperpigmentation. Serum sodium was 130 mmol/l, serum potassium 5.1 mmol/l, creatinine 112 μmol/l and urea 7.1 mmol/l. Full blood count was normal. She had a history of depression, peptic ulcer, hysterectomy and was taking Escitalopram 10 mg daily. Acute adrenal insufficiency was suspected and peak post-Tetracosactren (*Synacthen*) cortisol was 150 nmol/l (Normal >550 nmol/l). CT scan abdomen revealed massively enlarged adrenals; 8.6×5.7 cm on the left and similar on the right. There were also solid polar masses in the kidneys with extrinsic compression of the inferior vena cava. She rapidly improved with hydrocortisone and fludrocortisone. Adrenal biopsy demonstrated a diffuse large B cell lymphoma (non-germinal center subtype). Proliferation fraction was 60%. PET scan demonstrated uptake in the right rib, bone marrow aspiration did not show evidence of infiltration. Staging was 4b. She was treated with Rituximab, Cyclophosphamide, Doxorubicin and Vincristine (CHOP). Antiphospholipid screen IgG antibody was negative. She subsequently went into a partial remission with a modest reduction in adrenal dimensions. Lymphoma with partial adrenal hypofunction has been reported to involve the adrenals in 3% of cases.
Learning points: i) This Lymphoma presented as an adrenal which crisis while very rare, would have been life threatening if missed. In addition adrenal hormone replacement therapy was critical for toleration of subsequent chemotherapy, ii) the case illustrates the importance of imaging the adrenals in cases of primary adrenal insufficiency.

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EP68

The frequency of tissue transglutaminase antibodies in the monoglandular and polyglandular autoimmune endocrine disorders

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Introduction
Generally, symptoms of celiac disease is not accompanied when present together with autoimmune endocrine diseases. In this study, we aimed to investigate the prevalence of silent celiac disease in the APS and autoimmune monoglandular disorders by measuring tissue transglutaminase antibodies (ttgAb).
Methods
A total of 103 patients with monaglandular or polyglandular autoimmune endocrine disorders and 32 control subjects were enrolled in the study. At least the existence of two diagnoses with type 1 diabetes, Addison's disease, autoimmune thyroid disease, vitiligo, pernicious anemia, hypoparathyroidism, gonadal failure were considered APS and patients with only one of those type 1 diabetes, Hashimoto's thyroiditis or Addison's disease were enrolled as monoglandular endocrine disease. Serum samples were collected from patients and were studied at one time for tissue transglutaminase antibodies.
Results
Hashimoto's thyroiditis was present in the sixty-eight patients of 103 patients including OPS and monoglandular endocrine disease, type 1 diabetes was in the forty-four patients and Addison's disease in the seventeen. In the 13 of 103 patients (12.6%) ttgAb IgA were positive and in the 8 of 103 (7.8%) ttgAb IgG were positive but in the healthy control group both IgA or IgG antibodies were not present. Highest rates of positive ttgAb IgA frequency was detected in the Addison's disease with 29.4% (5/17). It was 13.6%, in the type 1 diabetes, 8.8% in the Hashimoto's diasease and 16.7% in the APS. There were not observed statistically significant difference between the groups and the ttgAb IgG positivity was observed with lower rates.
Conclusion
The prevalence of silent celiac disease was higher in the patients with autoimmune endocrine disorders when compared with the healthy control group. The frequency of ttgAb is not not higher in the APS then monoglandular endocrine disorders and Addison's disease likely has highest prevalence of silent celiac disease.

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EP69

Hyperparathyroidism healing in patients treated for hyperaldosteronism: three cases

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Introduction
Hyperaldosteronism usually presents with hypertension and hypokalemia; however, there is recent evidence of a relationship with the parathyroid hormone. There are different theories to try to explain this relationship. Hyperaldosteronism treatment is medical or surgical depending upon etiology. We present three cases in which treatment solely for hyperaldosteronism also cured hyperparathyroidism.
Materials and methods
We report three patients in whom hyperaldosteronism was diagnosed during 2015 and detected simultaneously hyperparathyroidism. We recorded epidemiological data, pre- and post-surgical phospho-calcium metabolism, as well as hyperaldosteronism.
Results
Case 1: A 38 year old male was referred for suspected hyperaldosteronism. A nodule was detected in left adrenal in TC image. Levels of PTH 150 pg/ml were objectified with normal serum and urinary calcium and phosphorus. Levels of vitamin D were 19.9 ng/ml. After left adrenalectomy, PTH levels were normalized. Case 2: A 55 years old woman referred for study of hypokalemia. Her PTH levels were 162 pg/ml with normal serum phosphorus and urinary calcium. Lesion 20 mm in left adrenal was detected in TC image. After adrenalectomy, PTH levels down to 34 pg/ml. Case 3: A 63 years old woman was referred to rule out hyperaldosteronism. She presented PTH levels of 136 pg/ml and normal levels of serum calcium and phosphorus. Vitamin D levels were 24 ng/ml. MRI image showed right adrenal injury that was removed. After surgery, PTH levels diminished.
Conclusions
In cases of primary hyperaldosteronism is advisable to assess the phospho-calcium metabolism, especially PTH. The effect of hyperaldosteronism on bone long-term is still unknown. In any case, the calcium/phosphorus levels were not pathological. Sometimes treatment solely of hyperaldosteronism can simultaneously treat hyperparathyroidism.

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EP70

Large aortic aneurism and left coronary artery calcifications: incidental findings at adrenal incidentaloma assessment

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Introduction
In cases with high-risk metabolic profile the investigations may lead to the discovery of an adrenal tumor (AT). Complex endocrine investigations including computed tomography (CT) scans may point anomalies of the vessels as coronary artery or abdominal aorta.
Aim
We report a case associating an AT and severe cardiovascular anomalies which are discovered during endocrine investigations.
Case data
A 72-year prior smoker male is known since the last decade with high blood pressure, type 2 diabetes mellitus, stable angina, hyperlipemia. Although partially compliant to the medication used for lowering arterial hypertension, a complex cardiologic evaluation was performed for episodes of elevated blood pressure. An abdominal ultrasound was used to evaluate the kidney status (consistent with mild potassium elevation of 5.5 mmol/l, N:3.5–5.1 mmol/l) and a right AT of 2.4 cm was found. Consecutive endocrine test were needed. On admission, a high uric acid of 9 mg/dl (N:2.6–7.2 mg/dl) was consistent with increased metabolic risk. The thyroid was normal, so was the plasma cortisol after screening dexametasone suppression test (of 1.22 µUI/ml), the plasma chromogranin A (of 50 ng/ml; N:20–125 ng/ml), plasma metanephrines (of 15.22 pg/ml, N:10–90 pg/ml), plasma normetaneprines (of 36.8 pg/ml, N:15–180 pg/ml). An abdominal IV contrast CT scan was used to confirm the echography findings. Right AT of 2.15/2.92/1.95 cm was found together with a right kidney cyst of 1.8 cm, an aortic aneurism of 2.96 cm diameter having a length of 5.05–7.05 cm, a left coronary artery calcification of 2.52 cm. Doppler ultrasound also confirmed a wall thrombus at the level of aortic aneurism. Despite the non-secretor endocrine profile, the vessel anomalies made necessary consecutive cardiac investigations and an angio-magnetic resonance imagery as well as arterigraphy was recommended.
Conclusion
A multidisciplinary approach is necessary is patients with high blood pressure uncontrolled by usual medication. Otherwise, the imagery scans performed for an adrenal incidentaloma may lead to previously unknown incidental findings as anomalies of large vessels.

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EP71

From mild abdominal pain to large right adrenal cyst

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Introduction
Cystic lesions of the adrenals are rare and they may develop asymptomatically for a long period of time. Females seem to be more affected and lesion is typically unilateral.
Aim
We report a case of young female case incidentally found with a large adrenal pure cystic mass.
Case data
A 24-year non-smoking female patient with regular menses since the age of 14 complained of mild abdominal pain for a few days without correlation to prior menses. Normal intestinal transit was presented and the specific analyzes infirmed a urinary infection. An abdominal ultrasound detected a large cyst which first was suspected to be connected with the liver. Computed tomography scan (with IV contrast) revealed a large right adrenal cyst of 8 by 7 by 8.5 cm containing homogenous fluid, encapsulated (a wall of 0.2 cm) with a parietal micro-calcification and a thin interior septus. The mass has contact with right kidney and with sixth and seventh hepatic segments. Endocrine profile was assessed without any anomalies: chromogranin A of 41 ng/ml (*N*: 20–125 ng/ml); neuron specific enolase of 4.54 ng/ml (*N*: 0–12 ng/ml), plasma metaneprines of 40.2 pg/ml (*N*: 10–90 pg/ml), plasma normetaneprines of 27.6 pg/ml (*N*: 15–180 pg/ml), serum serotonin of 246.3 ng/ml (*N*: 80–450 ng/ml), circulating calcitonin of 0.5 pg/ml (*N*: 5.17–9.82 pg/ml), baseline ACTH of 45.98 pg/ml (*N*: 3–66 pg/ml), baseline plasma morning cortisol of 29.42 µg/dl was suppressed after 1mg of dexametasone to 1.4 µg/dl. Coagulation tests (as well as blood ionogram and parasites assays) were within normal limits. Consecutive surgery was performed and confirmed the benign features.
Conclusion
Large adrenal cysts are exceptional findings and their removal is necessary because of local complication as pain, hemorrhage or infection. Some congenital elements may be involved but they may develop up to the adult age without being detected. Despite poorly suggestive clinical picture the prompt intervention is needed especially in lesions with high dimensions.

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EP72

Adrenal failure secondary to bilateral adrenal metastasis as a presenting feature of lung cancer – a case report

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Metastatic infiltration of the adrenal glands is a common finding of malignancies, but few case reports showed primary adrenal insufficiency being the presenting manifestation of underlying malignant tumors. Here, we report a case of adrenal insufficiency secondary to metastases from lung adenocarcinoma.

A 69-year-old man was admitted to emergency department with weakness, altered mental status, hypotension, fever and weight loss. He had 100 pack-year history of smoking. At the time of presentation, physical examination revealed a blood pressure of 80/40 mmHg, subfebrile fever of 37.2°C and abdominal tenderness. His skin was hyperpigmented and cachectic appearance was recorded. The initial laboratory evaluation revealed hyperkalemia, hyponatremia and elevated creatinine levels. During initial evaluation cardiac arrest occurred and the patient was resuscitated successfully. Echocardiography showed massive pericardial effusion. Pericardiocentesis was performed and biochemical analysis of pericardial fluid showed exudate fluid characteristics. After blood samples were obtained for adrenocorticotrophic hormone and cortisol measurement, intravenous methyl-prednisolone and saline infusion were administered. After administration of steroid therapy, patient status improved within a few hours. Serum cortisol and ACTH were, respectively, 0.4 μg/dl (6.2–19.4 μg/dl) and 716 pg/ml (0–46 pg/ml). Abdominal computed tomography revealed multiple lesions in both adrenals, measuring 4 cm in greatest diameter. Thoracic computed tomography showed right hilar mass and multiple mediastinal lymph nodes. Pulmonary adenocarcinoma was diagnosed with transbronchial biopsy. Patient was switched to oral hydrocortisone and fludrocortisone therapy. He was referred to oncology department and chemotherapy was planned for his primary disease.
Although metastasis to adrenal glands is relatively common, they are usually without clinical significance. Moreover, adrenal deficiency is very rare. It should be kept in mind that adrenal insufficiency may be associated with undiagnosed malignancy.

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EP73

Clinical case of yatrogenic hypercortisolism in pregnant woman with adrenal insufficiency

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Background
Adrenal insufficiency (AI) in pregnant women is difficult to manage because of similarity between clinics of decompensation of AI and gestational toxicosis. Objective difficulty is absence of clinical guidelines of management of pregnant patients with AI. We present a clinical case where the management of pregnant patient was not careful, which led to overdose and iatrogenic hypercortisolism.
Clinical case
Pregnant woman, 29years old, asked second opinion about established diagnosis and treatment. Her complaints were high blood pressure, face edema, hyperglycemia, weight gain. She was on 22 week of gestation. Anamnesis was notable for AI, which was diagnosed few years ago. Before pregnancy she took 50 mg of hydrocortisone per day. When she became pregnant, the dose was increased to100 mg/day because of fatigue and dizziness. From that moment her condition worsened. She was seen by obstetrician, endocrinologist. Preeclampsia and gestational diabetes were suspected, antihypertensive drugs and insulin were prescribed. Patient was not sufficient with recommendations and asked about second opinion. Firstly, she had AI with treatment by supraphysiological doses of hydrocortisone, secondly, complaints developed after increased doses in first trimester, when preeclampsia is not possible to happen. Diagnosis of iatrogenic hypercortisolism was established. The dose of hydrocortisone was gradually decreased to 25 mg/day, her condition became better in a few days. Insulin, hypotensive drugs were stopped. In one month complaints disappeared. Her obstetrician was consulted by experienced endocrinologist about details of delivery and postpartum in women with AI.
Conclusion
In the first trimester treatment of AI may be difficult because symptoms of AI are seen in pregnancy. It is easy to assign insufficient doses. At the same time, clinics of iatrogenic hypercortisolism is similar to preeclampsia, the risk of overdose is high. Because of absence of clinical guidelines, doctors must strictly follow to existing recommendations in order to avoid such mistakes.

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EP74

Adrenal insufficiency due to X-linked adrenoleukodystrophy diagnosed in late adulthood

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Introduction
X-linked adrenoleukodystrophy (X-ALD) is a rare condition presented mainly in males during childhood and early adulthood. It represents almost 10% of primary adrenal insufficiency (PAI) or Addison's disease cases.
Clinical case
A 67-year-old male was diagnosed at the age of 61 with PAI during testing for mesenteric paniculitis while admitted in Internal Medicine service. He was treated with hydrocortisone and referred to outpatient endocrinology clinic. The patient did not attend and restarted follow-up 6 years later. His past medical history included dyslipidemia, anxiety and parkinson-like syndrome since 2012. He was taking hydrocortisone 20-5-5 mg, with no mineralocorticoid. He had normal blood pressure with no significant changes between supine and orthostatic position. Blood tests showed normal levels of serum sodium, potassium, testosterone and renine. Aldosterone was in the lower limit of normality. 21-hidroxilase antibodies were negative and the abdominal CT scan showed normal adrenal glands. Due to the normality of these two tests, plasma levels of very long-chain fatty acids (VLCFA) were assessed. They were elevated. Genetic study demonstrated a mutation in the ABCD1 gene. Skin biopsy revealed high levels of VLCFA in fibroblasts and low levels of ALD protein. MRI of the brain showed no alterations in the white matter. The patient had a 24 year old son and a 30 year old daughter who wanted children. She presented high levels of plasma VLCFA and the genetic study showed a mutation in the ABCD1 gene too. She was referred to genetic counseling.
Conclusion
To consider X-ALD in males diagnosed with PAI at any age because of its implications, one very important being the transmission to offspring.

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EP75

Massive bilateral pheocromocytomas – a rare case

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Introduction
Pheochromocytoma is a rare catecholamine-secreting tumor that arises from the chromaffin tissue of the adrenal medulla. Of the reported cases, only 10% consist in bilateral lesions and the probability of multiple endocrine neoplasia should always be investigated.
Case report
Female patient, 19 years old, presented with a clinical history with 2 years of evolution, characterized by episodes of palpitations, headache and abdominal discomfort.
It was performed ultrasound study that showed 'bilateral cystic perirenal lesions' and after that, abdominal CT confirmed 'cystic adrenal formations, the right with 11.3 cm and the left with 7.8 cm of larger diameter, without infiltrative aspects.' Analitycal evaluation: serum metanephrines 7386.4 pg/ml (<60), calcitonin 55 pg/ml (<10) and PTH 41 pg/ml (9–72). The 123I-MIBG scintigraphy showed 'massive bilateral pheochromocytomas and abnormal fixation on the topography of the left thyroid lobe'. Cervical plus thoracic CT confirmed a thyroid nodule on the left lobe, with larger diameter of 1.1 cm, without other lesions. Histological result of thyroid fine-needle aspiration biopsy: thyroid medullary carcinoma.
Patient underwent bilateral laparoscopic adrenalectomy and after that total thyroidectomy with central lymph node dissection, both without complications. Anatomopathological study revealed bilateral benign pheochromocytomas (Ki67 2%) and medullary carcinoma of the thyroid T1bN0M0;R0.
Genetic analysis confirmed mutation c.2080 T>C in exon 11 of the RET gene, consistent with a diagnosis of MEN2A; genetic study of relatives in the first degree was negative.
Currently, the patient is clinically stable and presented: calcitonin <2.0 pg/ml (<10), PTH 32 pg/ml (9–72), calcium 9.5 mg/dl (8.8–10.6) and serum metanephrines 47.2 pg/ml (<60).
Conclusions
In the presence of bilateral adrenal tumors and young age, multiple endocrine neoplasia probability is higher, and should be carried out biochemical, imaging and genetic investigation. If confirmed, genetic evaluation of first degree relatives should be performed. Furthermore, because of the high possibility of recurrence, these patients should maintain close and long-term monitoring.

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EP76

A rare case of ectopic ACTH syndrome originated from malignant renal paraganglioma

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Introduction
Ectopic adrenocorticotropic hormone (ACTH) syndrome is characterized by hypercortisolism due to the hypersecretion of non-pituitary ACTH-secreting tumor leads to the Cushing's syndrome. Herein, we present a case with Cushing's syndrome, which is diagnosed ACTH-secreting renal malignant paraganglioma.
Case
A 40-year-old woman presented with a 5 month history of newly diagnosed hypertension and diabetes, weakness, hyperpigmentation, oligomenorrhea, hirsutism and acneiform lesions. She showed cushingoid features including moon face, facial hirsutism, facial and truncal acne, hyperpigmentation and severe muscle weakness of the limbs. She had not the findings including striae, supraclavicular fat accumulation and buffalo hump. Laboratory examination showed the presence of hypopotasemia, hyperglycemia, hyperthyroidism and leukocytosis. Serum levels of ACTH, cortisol and the urine free cortisol were markedly elevated. Cortisol value after an overnight 2 mg dexamethasone suppression test was 46.1 mcg/dl and there were no suppression after 2 day 8 mg dexamethasone administration. Magnetic resonance imaging (MRI) of the pituitary gland indicated two microadenomas. An abdominal MRI scan revealed horseshoe kidney, bilateral adrenal hyperplasia and a mass with dimensions of 35×31 mm in the left kidney. Inferior petrosal sinus sampling showed no evidence for a central to peripheral gradient of ACTH. A positron emission tomography/computed tomography scan was showed intense increased activity in the lower pole of left kidney. Left adrenalectomy and left partial nephrectomy were performed. The resected tumor were diagnosed as the ACTH-secreting paraganglioma in the pathological examination that was confirmed by immunohistochemical studies with chromogranin, synaptophysin and ACTH The periadrenal lymph node was evaluated as a metastatic lymph node.
Conclusion
Only few cases of paragangliomas as the cause of the ectopic ACTH syndrome have been reported. To the best of our knowlege, this is the first case of renal malignant paraganglioma resulting in Cushing's syndrome due to the ectopic ACTH hypersecretion.

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EP77

Adrenal venous sampling is useful for a definitive diagnosis in Cushing's syndrome with bilateral adrenal tumors

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We report three cases of Cushing's syndrome (CS) with bilateral adrenal tumors. When bilateral adrenal tumors are encountered, the differential diagnosis is difficult, especially in the functioning bilateral adrenocortical adenoma. Adrenal scintigraphy has become a standard technique to determine the laterality of excessive hormone secretion; however, this examination results in bilateral adrenal activity in the functioning bilateral adrenocortical adenoma. Our three patients were diagnosed with adrenocorticotropic hormone (ACTH)-independent CS based on biochemical testing, and an abdominal computed tomography (CT) scan detected bilateral adrenal tumors. Adrenal scintigraphy, which has become a standard technique to determine the laterality of excessive hormone secretion, showed bilateral adrenal activity in all cases. However, adrenal venous sampling (AVS) demonstrated three different hormone-excess patterns (case 1: bilateral cortisol-excess secretions; case 2: unilateral cortisol-excess secretion and bilateral aldosterone-excess secretions; and case 3: bilateral cortisol-excess secretions and bilateral aldosterone-excess secretions). Based on these findings, we could select optimal treatment for each case. Therefore, AVS is useful to obtain a definitive diagnosis and adequate therapy for CS with bilateral adrenal tumors. Moreover, there is no consensus regarding the optimal determination of the laterality of excessive cortisol secretion. Thus, standardized criteria for AVS in CS with bilateral adrenal tumors needed to obtain the optimal determination of the laterality of excessive hormone secretion. In this regard, our cases demonstrated detailed data including CT scans, adrenal scintigraphy, confirmatory tests for primary aldosteronism and pathological findings in addition to AVS. Therefore, our report may be used to formulate standard criteria for AVS in CS with bilateral adrenal tumors in the near future.

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EP78

Non functional unilateral giant adrenal myelolipoma: a case report

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Introduction
Adrenal myelolipoma is a rare benign tumour composed of mature adipose tissue and hematopoietic tissue. Most lesions are small and asymptomatic, discovered incidentally during autopsy or on imaging studies performed for other reasons. Usually small and asymptomatic, but has been reported to present with symptoms such as abdominal pain resulting from tumour bulk, necrosis or spontaneous retroperitoneal haemorrhage.
Case 54-year old woman who presented with a giant abdominal mass and abdominal pain. The dimensions of the mass on MRI scan were as follows, 8.8 cm (cranio-caudal) ×5.2 cm (antero-posterior)×6.3 cm (medio-lateral). The retroperitoneal tumor was resected, and a giant adrenal myelolipoma was diagnosed by pathological examination.
Conclusion
Adrenal myelolipoma are rare non functioning benign tumors, which can be observed expectantly with surgical resection reserved for larger or symptomatic lesions to prevent the occurrence of a rupture or intratumoral haemorrhage.

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EP79

Large bilateral adrenal metastatic melanoma

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Background
Adrenal metastatic melanoma can be found in up to 50% of patients with melanomas. These tumors are not hormone-secreting, and they usually present with locally advanced disease.
The case
We report on the presence of a bilateral massive metastatic adrenal melanoma in a 56-year old woman with the initial clinical diagnosis of bilateral adrenal cyst or hemorrhage, and chronic adrenal failure. The patient underwent surgery one month before the admission to our hospital, left laparotomic adrenalectomy, for a big tumor in the left adrenal gland 9.6×10 cm. Histological assessment of the left adrenalectomy misdiagnosed an adrenal carcinoma. Since the patient had chronic adrenal failure, the treatment before and after surgery with hydrocortisone 20 mg/day was started.
One month after the surgery she was admitted to our hospital with weight loss, fatigue, and multiple mucocutaneus nodules.
Abdominal CT scan: Multiple liver and spleen metastasis and a large metastasis in the right adrenal gland 9.5×10 cm.
Lab Data: ACTH 165 pg/ml (normal range 10–65); Morning serum cortisol values 1.0 g/dl (normal range 3.4–12.5); FBC: WBC 9260; RBC 4.100.000; Hb 10.4 gr/dl; PTC 371.000; ESR 30 mm/h; Calcium 9.2 mg/dl.

ICH of mucocutaneus nodules and reexamination of biopsy of left adrenalectomy: malignant melanoma.
Total Body Scan with Tc99: Multiple metastasis in the large bone and ribs.
Conclusions
Melanoma metastasis to adrenal gland generally has a poor prognosis. Patients with adrenal metastases from melanoma, either isolated or with a limited number of additional metastases, may achieve a survival benefit from surgery, unfortunately the diagnosis of our case was made in an advanced state and the patient continued only with symptomatic therapy.
Keywords: bilateral adrenal metastasis chronic adrenal failure melanoma.
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EP80

Cushing syndrome with ectopic secretion of ACTH by a lung carcinoma
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Introduction
A form of ACTH-dependent Cushing syndrome is an ectopic production of ACTH. The aetiology can by benign lesion or a malignant non-pituitary tumor, which is more common. The prevalence of endogenous Cushing syndrome is 1 in 26 000. Ectopic ACTH secretion is responsible for 7–15% of the cases. Principal position of the ACTH-producing tumor is in lungs – a bronchial endocrine tumor and small cell lung cancer. Small peripheral bronchial carcinoids can easily be missed by CT examination of the chest. MRI and octreotide scintigraphy are of little value to identify these small forms of bronchial carcinoid (33–44% of tumors are missed).
Case report
We report a case of ectopic ACTH syndrome caused by a lung carcinoma in a 37-year-old male patient with clinical features of Cushing syndrome, serious hypokalemia and hypercortisolismu. Clinical investigation confirmed the diagnosis of ectopic ACTH production. We performed 2 mg dexamethasone suppression test which showed no suppression. In 8 mg dexamethasone suppression test was only parcial suppression present. Sampling from sinus petrosus inferior showed an ectopic cause of hypercortisolism. PET CT scan of the chest showed a solitary deposit (14 mm) in upper right lobe of lungs. The deposition showed only a slight metabolic activity. Consequent thoracotomy and histological examination of the tissue confirmed a primary lung carcinoma. After the extirpation was detraction syndrome present. The treatment consisted of glucocorticoids supplementation with sequential reduction of the dose. Clinical and laboratory features of Cushing syndrome detracted as well. The time period from the first diagnostic tests to the surgical extirpation of the tumor was very short (<4 months).
Conclusions
Localisation of the source of ectopic ACTH can be problematic. Surgery of tumour is normally curative, but it should be performed as soon as possible. Very rapid diagnosis followed by curative surgery prevented the onset of complications connected with hypercortisolemia and also lung cancer.
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EP81

Asynchronous bilateral adrenal masses: from surgery to endocrine follow-up
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Introduction
Cushing's syndrome (CS) is correlated with prolonged exposure to high levels of glucocorticoid hormones. Although the most common cause is exogenous adrenal tumors incidentally discovered (incidentaloma) may underline CS.
Material and method
This is a case presentation of an adult patient. Specific tests for CS have been used: morning plasma cortisol and circadian rhythm, plasma ACTH, testosterone, dexamethasone (DXM) suppression test.
Case presentation
A 50-year male associating diabetes mellitus and hypertension, was admitted for very high blood pressure and centripet obesity. Clinical examination revealed: moon face, plethora, telangiectasia. Normal thyroid tests were found, a morning plasma cortisol of 145.4 ng/ml (N:70–225 ng/ml) with normal circadian rhythm, ACTH of 10.6 pg/ml (N:7–46 pg/ml) and a total plasma testosterone of 2.46 ng/ml (N:0.2–0.75 ng/ml). Lack of suppression at 1 mg DXM overnight test established CS diagnosis of adrenal etiology (a right adrenal tumor of 39 mm was identified at CT scan). The tumor was removed and after surgery clinical improvement was associated with a morning cortisol of 18.99 ng/ml 18 days after surgery and a level of 12.55 ng/ml 3 months later. 9 months after surgery, endocrine evaluation indicated a raise of morning plasma cortisol with normal ACTH and suppression at DXM test. CT detected a left adrenal mass of 24/20/13 mm. Given the results of endocrine evaluation suggesting an incidentaloma, follow-up was recommended.
Conclusions
Adrenal incidentaloma management varies on symptoms, size, lateralization, etc. The pathogenic traits in asynchronous bilateral adrenal masses are still incompletely understood.
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EP82

Adrenocortical carcinoma: report of four cases
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Introduction
Adrenocortical carcinoma (ACC) is a very rare neoplasm with an incidence of about one case per million population. It is an agressive tumor (overall 5-year survival 16–38%) and complete resection is the only curative treatment.
Description of methods
We report four cases of ACC. The clinical and biochemical features at diagnosis along with clinical course of the disease are discussed.
Results
Four patients (three female). Mean age at diagnosis 31 ± 14.5 years. Incidentally discovered mass in 50% of cases. CT-scan was the initial imaging test in all cases. Median size 9.23 cm (above 8 cm in all patients). Three patients had functioning tumors (Case 1 hypercortisolism; case 2 hypercortisolism and hyperandrogenism; case 3 hypercortisolism and hyperaldosteronism). Initial Stage was II in three cases and IV in another case. 75% of patients presented local recurrence after surgery. Two of three cases with Stage II at diagnosis developed distant metastases along the clinical course of the disease. 100% of patients with advanced disease had lung metastases. All patients were treated with Mitotane after surgical resection. Three pacients were also treated with chemotherapy (one patient received Etoposide, Doxorubicin and cisplatine; another pacient received Vinorelbine). One patient with bone metastases was treated with palliative radiotherapy. Two patients are still alive (both diagnosed at Stage II). One of them is free of illness alter 41 months. The other patient diagnosed 56 months ago has presented local recurrence and lung and bone metastases. Mean survival in deceased patients was 24 ± 13 months.
Conclusions
ACC are neoplasms with low rate of survival. Stage at diagnosis is related with prognosis. As we can observe in our sample most ACC are functioning. Clinical and radiological features may help in differential diagnosis between benign adenomas and ACC, being size one of the most important predictors of malignancy.
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EP83

Depression and acute kidney injury – unusual presentation of Addison's disease

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Introduction
Addison's disease is the commonest cause of primary hypoadrenalism in the western world. Here, we discuss a case of Addison's with unusual presentation.
Case report
A 39-year-old woman with no previous mental health problems was admitted with history of worsening depression over the last 15 months following her divorce. She had low mood and anhedonia in spite of sertraline for more than a year. This was associated with 40 kg weight loss. She was on Beclomethasone and salbutamol inhalers for her asthma. She was cachectic and was profoundly hypotensive. Systemic examination was unremarkable. Her biochemistry revealed electrolyte abnormalities typical of Addison's but she also had acute kidney injury with Creatinine 339 μmol/l (NR: 64–104). Hypoadrenalism was suspected which was confirmed by random cortisol of only 3 nmol/l. Commencement of hydrocortisone and IV fluid replacement led to clinical (including depression) and biochemical improvement. Subsequent investigations showed a high ACTH 24.8 ng/l (NR: 7–63) and positive anti-adrenal antibodies confirming the diagnosis of Addison's disease. She was discharged home on hydrocortisone and Fludrocortisone.
Conclusion
Addison's patients presenting predominantly with psychiatric symptoms is rare. The etiology of the neuropsychiatric symptoms remains unknown, but may involve electrophysiological, electrolyte and metabolic abnormalities, glucocorticoid deficiency, and high endorphins. Our case was particularly difficult as it was complicated by other elements (divorce) which appeared like the aetiology of depression for the treating primary care physicians. This highlights the fact that the clinicians should have high index of suspicion to look for other causes, if the depression is not responding to the usual antidepressants. Our patient also had acute kidney injury at presentation. About 55% of patients do have a degree of azotaemia but very few have been reported with such a drastic deterioration in renal function. The electrolyte abnormalities in Addison's disease could easily be attributed to AKI and therefore physicians need to be vigilant.

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Adrenal medulla

EP84

Pheochromocytoma/paraganglioma: Histopathological features as clue to the underlying germline mutation in these genetically heterogeneous tumors

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Introduction
Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are rare neuroendocrine tumors arising from chromaffin cells within adrenal medulla and autonomic paragranglia respectively. Recent evidences show that nearly one-third patients harbour germline mutation, namely in von Hippel-Lindau (VHL), REarranged during Transfection (RET), neurofibromatosis type 1 (NF 1) and succinate dehydrogenase (SDH) complex genes. However, the tumor morphology arising in various syndromes has been scarcely documented. Can histology provide a clue to the genotype or more importantly help to target patients, especially with clinically sporadic tumors, who would require genetic testing?
Methods
We tested 63 (40 PHEOs, 20 PGLs, three both PHEOs and PGLs) consenting patients for germline mutation in VHL, RET or SDH genes. The corresponding tumor histology (available in 41) is evaluated by two pathologists blinded to the mutation status.
Results
Germline mutations have been detected in 37 (58.73%) patients; 11, 8, 16 and 2 with VHL, RET, SDHB and SDHD gene mutations respectively. The tumors in multiple endocrine neoplasia type 2 have large cells with abundant eosinophilic cytoplasm, frequent hyaline globules, anisonucleosis and scant vascularised stroma in septa. The VHL-mutated tumors are stroma-rich, contain vessels in septa as well as admixed with cells which are medium to large, often having clear cytoplasm, fairly uniform nuclei and presence of background adrenomedullary hyperplasia (AMH). The SDH-mutated tumors, much akin to the sporadic ones, show diverseness in morphological appearance.
Conclusions
A vessel and stroma rich tumor with at least focal cytoplasmic clearing may hint to the possibility of an underlying VHL mutation in an apparently sporadic tumor. AMH is important corroborative evidence that must be diligently looked for both in gross specimens and histology sections. Likewise MEN 2 associated tumors display histological features that in conjunction may prompt to test for its presence. Histological heterogeneity, however, precludes successful prediction of SDH mutation.

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EP85

Clinical review of patients with pheochromocytoma diagnosed between 2011 and 2015

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Introduction
WHO classification of endocrine tumors defines pheochromocytoma as a tumor arising from chromaffin cells in the adrenal medulla. Almost all pheochromocytomas produce catecholamines. An annual incidence of this tumor in the general population is estimated at 3–8 cases/million/year. 40–50% of patients with pheochromocytoma are characterized by sustained hypertension, a similar percentage – only by paroxysmal hypertension and up to 10% are normotensive.
Aim
The aim of the study was to identify the most common clinical, hormonal and imaging characteristics of the patients with pheochromocytoma hospitalized in our department between 2011 and 2015, based on retrospective analysis of their medical histories.
Results
The whole group covered 27 patients with confirmed pheochromocytomas. 21 patients (12M; 9F) aged 29–77 years (54.4 ± 16.1) have been diagnosed since the beginning of the disease in our department, while the remaining were originally diagnosed and operated on in other centers. In three cases (14.3%) in the same family, finally recognized as MEN 2A, tumors were bilateral. In three patients pheochromocytoma was diagnosed as adrenal incydentaloma. In 18 patients the tumor was one-sided (the nine cases in the left and right adrenal gland). Hypertension, mainly paroxysmal, occurred in 13 patients (62%). Adrenal tumor was initially detected in CT in 13 cases, in ultrasound in five and in MRI in two patients. The largest tumor diameter ranged from 10 to 106 mm (mean 48,5 ± 25.1). Initial tumor CT density ranged between 7 and 51 HU (mean 29.2 ± 12.2) and in all ten patients who underwent contrast CT ("adrenal protocol") a delayed tumor washout index has been detected. Metoxycatecholamines excretion in daily urine ranged from 100 to 3438 μg.
Conclusion
Paroxysmal hypertension, unilateral location, tumor greatest dimension greater than 4 cm, high basal density and low washout index in CT were the most common clinical features of pheochromocytomas in our group of patients.

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EP86

Diagnostic tools for incidental pheochromocytoma and paraganglioma

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Introduction
Pheochromocytoma and paraganglioma are the cause of secondary hypertension, glucose intolerance, arteriosclerosis and associated with increase of mortality. In addition, 10–17% of them are reported to be malignant. Therefore, diagnosis at the early stage is important.
Methods
We retrospectively analyzed the medical records of Japanese patients who were admitted to our hospital from January 2001 to December 2015. They were

confirmed pheochromocytoma or paraganglioma pathologically. We also evaluated the postoperative clinical course. The median follow-up period was 5.5years (ranged 3 months – 15years).
Forty-eight patients were identified. Forty-five of 48 (94%) cases were referred as incidentaloma. Our diagnostic protocol included 24-h urine fractionated metanephrines (24 h-UMN), 123I-metaiodobenzylguanidine scintigraphy (MIBG), and clonidine suppression test (CST). The cut-off values of 24 h-UMN were 0.4 mg/day for metanephrine, and 0.9 mg/day for normetanephrine, respectively. 24 h-UMN and MIBG were performed in all cases. CST was conducted in 34 cases.
Results
Seventeen of 34 cases (50%) were positive for all three examinations. Fifteen cases (31%) were negative for 24 h-UMN. Among these cases, MIBG was positive in 12 cases (80%). CST was positive in 11 of 12 cases (92%). Surgical intervention was carried out when either 24 h-UMN or MIBG was positive. Surprisingly, no recurrence was found, during a follow-up period, though two cases had tumors with capsule invasion. We found better prognosis in our cohort contrary to recent reviews. We can propose two explanations. First, the rate of incidental pheochromocytoma or paraganglioma was higher than previous report by Kopetschke *et al*. who described that it was 59 of 201 (29%). Secondly, our protocol of examination gave us a chance to diagnose incidentaloma as pheochromocytoma or paraganglioma early on.
Conclusion
The combination of 24 h-UMN, MIBG, and CST may enable us to diagnose pheochromocytoma and paraganglioma at the early stage, which may reduce the recurrence and mortality.

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EP87

Importance of long term follow up in pheochromocytoma

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Pheochromocytomas and paragangliomas are rare but life threatening tumors secreting catecholamines. They could be either sporadic or inherited. Either isolated or integrated in genetic syndromes such as Von Hippel Lindau (VHL) (OMIM193300) which is an autosomal dominant disorder resulting from germline mutations in the VHL gene.
Observation
We report a 42-year-old man operated at 8 years old for bilateral pheochromocytoma revealed by adrenergic symptoms and high blood pressure. Unfortunately, at that period he did not have any genetic testing. However, there were not clinical clues for a genetic syndrome. At the age of 42, he had neurological manifestations and chronic diarrhea.
Clinical examination showed a static cerebellar syndrome and central vestibular syndrome.
Cerebral MRI showed supra and infra-tentorial lesions deemed to be hemangioblastomas. The largest lesion was located in the left cerebello-protuberancial area and measured $37 \times 45 \times 33$ mm for which he underwent neurosurgery. Pathology examination confirmed the diagnosis of cerebellar haemangioblastoma. Abdominal Computed Tomography (CT) revealed 03 pancreatic neuroendocrine tumors (PNETs) and a 12 mm mesenteric nodule presenting as a homogenously and typical (NET). The largest PNET had intensive fixation at octreoscan. Ophthalmologic examination revealed retinal hemangioblastoma. The diagnosis of VHL was therefore clinically made. Familial investigation revealed the same syndromic VHL in one sibling who had bilateral pheochromocytoma in his infancy and who is now followed for retinal hemangioblastomas associated to cerebellar hemangioblastomas. Genetic testing would be extremely useful to determine which individuals from his family are harboring the mutated allele.
Conclusion
Patients operated on for pheochromocytoma especially young ones should have genetic screening in order to diagnose genetic syndromes which require a specific and a multidisciplinary approach for the diagnosis and treatment of all associated tumors and lesions.

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EP88

High prevalence of germinal mutations in pheochromocytomas with normal urinary metanephrines results

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Introduction
Pheochromocytomas are tumors derived from the adrenal-medullary chromaffin cells that normally produce catecholamines. Rarely these tumors are non-secreting. In the assessment of a suspected pheochromocytoma, guidelines recommend dosing urinary or plasma metanephrines.
Objective
To evaluate the prevalence of pheochromocytomas biochemically non-secreting and their differences.
Methods
We searched all patients with measurements of metanephrines made in an endocrinology department since 1999 (when Clinical Pathology was computerized). We included all those who had performed adrenalectomy in this institution with pheochromocytoma histology. Urinary metanephrines were measured with spectrophotometric chromatographic method (Pisano).
Results
We analyzed 2336 results of urinary metanephrines. 190 were excluded because it was results from outside patients and therefore could not be correlated clinically. The 2146 results corresponded to 1211 patients, with 37 pheochromocytomas analyzed. 13 cases of pheochromocytoma were excluded due to measurements of metanephrines only after surgery. Of the 24 patients, eight had normal values. Of these, three had positive values after analytical revaluation, (two with tumor <1 cm and 1 with ≥ 3 cm), one had positive values at diagnosis, with a normal value under methyltyrosine and phenoxybenzamine, four patients always had negative values: two with SDHB mutation (tumors >3 cm), one with SDHC mutation (12 cm) and the other with MEN2a (1.5 cm).
All patients had negative assay results also negative vanil-lmandelic acid.
Conclusion
The authors argue that pheochromocytomas may have normal values when they have diameters <1.5 cm or when they have mutations that might interfere with the production of catecholamines (ex: SDHB). Our study reveals the need for repeated measurements of metanephrines, to exclude pheochromocytoma, in the presence of an adrenal tumor in imaging, when the initial measurement is negative.

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EP89

A novel RET mutation presented with VHL-like clinical manifestation

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Abstract withdrawn.

EP90

A case of ectopic Cushing syndrome due to pheocromositoma

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Background and aim
Pheochromocytoma, is a catecholamine-producing tumor, may rarely secrete other hormones such as adrenocorticotropic hormone (ACTH). We aimed to report a rare case of ectopic cushing syndrome due to malignant pheochromocytoma.
Case report
A 42-year-old man admitted to outpatient clinic with headache, irritability, vomiting, nausea, and palpitation. He had paroxysmal hypertension and urinary fractionated metanephrines were measured approximately 30 times higher than the upper limit of normal, during the hypertension attack. Abdominal computed tomography showed 43×62×78 mm mass lesion in the right adrenal gland and lymphadenopathy in the right para-aortic area. Endocrinological examinations demonstrated ectopic ACTH production and hypercortisolemia without overt symptoms of Cushing's syndrome. He was operated for right adrenal mass following appropriate medical preparation. Postoperative pathology revealed that malignant,metastatic pheochromocytoma. Immunohistochemistry was performed and revealed that positive staining for ACTH.
Conclusions
Patients with pheochromocytoma also should have tests to exclude excess cortisol secretion. It must not be forgotten that most pheochromocytoma causes hypercortisolemia due to secreting ectopic ACTH.

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EP91

Neurofibromatosis type 1 associated with pheochromocytoma

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Introduction
Neurofibromatosis 1 (NF1) or von Recklighausen disease is an autosomal condition caused by heterozygous mutations of the NF1 gene. Patients with NF-1 are at an approximately fourfold higher risk of developing tumors than the general population. Pheochromocytoma may occur in about 1% of these patients.
Case report
A 24-year-old woman was admitted to our hospital for further examinations of a 6-cm right adrenal mass, that was incidentally discovered by abdominal ultrasonography during examinations for asthenia and weight-loss and confirmed by abdominal computed tomographic scans and magnetic resonance imaging. Family medical history revealed that the father had a NF-1. In her past medical history, the patient had many episodes of palpitation, sweating and headache one year before and she was diagnosed to have hypertension one month back. Physical examination revealed signs of NF1. She had multiple café-au-lait spots on the trunk and extremities and skinfold freckling. Bilateral opthalmic examination revealed no Lisch nodules. Urinary catecholamines were markedly increased. The treatment with β-blockers and alpha-blockers kept the patient asymptomatic. Right suprarenalectomy was successfully preformed and the anatomopathological examination of the surgical sample confirmed the diagnosis of pheochromocytoma.
Conclusion
Our case highlights the role of screening for pheochromocytoma in all patients of neurofibromatosis wich deserves attention especially with the presence of hypertension.

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EP92

Clinical case of giant pheochromocytoma with low hormonal activity

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Background
Pheochromocytoma (Ph) is the tumor that is fatal if do not suspect and treat it on time. It is supposed that size of tumor is correlated with its synthetic activity. Here we present a clinical case of giant Ph with low synthetic activity that could have been recognized as adrenal cancer, which, in turn, may have led to wrong treatment.
Clinical case
Young woman, 28 years old, presented with the adrenal incidentaloma. She had not any complaints, her history was not notable for any disease. CT showed right adrenal heterogeneous mass 9×8×7.6 cm with native density – 30-69HU, which eclipsed liver and was inseparable from the inferior vena cava. Because of young age, absence of any clinics, parameters of native density, adrenocortical cancer was strongly suspected. According to protocols hormonal examination was performed: plasma cortisol after 1-mg DST was 45 nmol/l (50 nmol/l), 24-hour urinary fractionated metanephrines were 248 mcg (320 mcg), 24-hour urinary fractionated normetanephrines were 2453.0 mcg (390 mcg). Because of discordance between tumor size and relatively low normetanephrines concentration, additional laboratory testing was performed. Hook-effect was excluded, the level of metabolites was the same. Since there was a possibility of concurrent Ph and cortical carcinoma, in order to set definitive diagnosis MIBG-scintigraphy was performed. Scintigraphy revealed signs of hormonal activity of right adrenal tumor. The diagnosis of Ph was made. Patient was preoperatively given alpha-blocker for 14 days. Right laparoscopic adrenalectomy was performed without any complications. Histologic picture proved that there was Ph. Postoperatively catecholamine metabolites were normal. Genetic testing did not show VHL and SDHD mutations.
Conclusions
The size of Ph does not always correlates with its hormonal activity. At the same time, strict adherence to protocols is necessary in all cases despite the fact that sometimes we can see 'obvious' signs of the other disease such as adrenocortical cancer in our case.

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EP93

Hypertension and hypokalemia in a 56-year-old male

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A 56-year-old Swedish male was diagnosed with hypertension, initially attributed to continued use of NSAIDs. These were withdrawn and treatment with 80 mg valsartan was started, but BP remained uncontrolled. A fixed combination (valsartan/hydrochlorothiazide, 80/12.5 mg) was introduced, but blood pressure remained high and hypokalemia (K^+3.3 mEq/l) developed. The patient was referred to our Endocrinology Clinic for study. Treatment was switched to manidipine 10 mg/12 h.
Physical Examination: Weight 78 kg, height 176 cm, waist 98 cm, BMI 25 kg/m^2, BP 155/88 mmHg, HR 76 lpm, no additional findings.
Lab tests: CBC, glucose, Cr, lipid profile, liver enzymes, Na^+: Normal. K^+3.6 mEq/l, aldosterone 12 ng/ml, plasma renin activity (PRA) $<$0.2 ng/ml/h. ECG, chest radiograph, abdominal CT: normal.
Hyperaldosteronism was ruled out due to low aldosterone, and a diagnosis of pseudohypoaldosteronism was considered. Liddle syndrome, congenital enzyme deficiencies and desoxicorticosterone-secreting tumors were deemed unlikely due to the age of debut, absence of family history and normal CT scan.
When directly asked the patient revealed daily intake of 50–75 g of salmiak (licorice with salt and ammonium chloride). One month after stopping licorice intake and withdrawing manidipine, blood pressure was controlled (136/78 mmHg); K^+(4.8 mEq/l), aldosterone (128 ng/ml) and PRA (0.9 ng/ml/h) were normal. Currently the patient consumes 18-β-glycyrrhetinic acid-free salmiak and his BP and lab tests remain normal.
In conclusion, the patient presented with hypertension, hypokalemia, suppressed PRA and low aldosterone, leading to the diagnosis of pseudohyperaldosteronism. The finding of the habitual high intake of licorice was the key to diagnosis and treatment, since its withdrawal led to the normalization of BP and lab tests. The usual intake of $>$2 mg/kg/day of 18-β-glycyrrhetinic acid is a cause of pseudohyperaldosteronism, which can be a diagnostic challenge.

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EP94

Asymptomatic 'giant' pheochromocytoma discovered as adrenal incidentaloma

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Introduction
Adrenal incidentalomas are defined as adrenal lesions incidentally discovered during radiological imaging of the abdomen without prior suspicion of adrenal disease. Approximately 70% of adrenal incidentalomas are non-functional adenomas. Pheochromocytoma presents only 5–7% of the remaining functional incidentalomas. Asymptomatic pheochromocytoma-incidentaloma is usually smaller than 1 cm. Large pheochromocytoma, incidentally found, without any clinical signs such as sever hypertension, headache, sweating and tachycardia are very rare.
Patient case report
Herein, we present young woman (32 years old) admitted to Endocrinology Clinic, after incidentally discovered right adrenal mass, size 60×70 mm, on abdominal sonogram, performed during regular systematic examination. Computed tomography confirmed 'giant' tumour, size 70×74 mm, with cystic and necrotic areas and inhomogeneous contrast captivity.
Endocrine evaluation of the patient verified normal cortisol, ACTH, vanillylmandelic acid in 24 h diuresis, plasma catecholamine and chromogranin serum level. Electrolytes (sodium, potassium, calcium phosphorus, magnesium) were in normal range.
The patient underwent [131I]-meta-iodobenzylguanidine ([131I]-MIBG) scan which revealed large area of increased uptake above the right kidney indicating giant right adrenal pheochromocytoma. After adequately preoperative preparation, right adrenalectomy was performed. The procedure and postoperative course were uneventful. The histopathological examination confirmed pheochromocytoma.
Conclusion
Due to technological advances the frequency of adrenal incidentaloma diagnosis is constantly increasing. Every incidentally found adrenal mass has to be carefully examined regardless of its clinical presentation in order to prevent fatal oversight of possible secreting nature and/or malignant potential of the lesion and to ensure an adequate curable treatment.

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EP95

Abstract unavailable.

EP96

Usefulness of assessment of urinal metoxycatecholamines secretion in everyday clinical practice – pheochromocytoma as diagnostic challenge

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Introduction
Adrenal incidentaloma is an adrenal mass found on imaging studies done for other reason than suspected adrenal disease. The majority of them are non-functioning adenomas, however pheochromocytomas could be also observed. Currently, in diagnosis of incidentalomas, the assessment of hormones of adrenal cortex and medulla is performed. The aim of the study was to assess the incidence of pheochromocytoma in patients with incidentaloma.
Methods
Medical records of 380 patients with incidentaloma hospitalized during 14 months in our clinic were retrospectively reviewed. Diagnostic imaging pictures, the incidence of hypertension, urine metoxycatecholamines secretion (normetanefrine or metanefrine), as well as hormonal assessment of adrenal cortex were analyzed.
Results
Seventy eight percent of patients were hypertensive. Most of lesions have benign features on imaging study. There were only nine histopatologically confirmed pheochromocytomas, which comprises 2.37% of all cases. In those nine patients, only one person have adenoma-like characteristic on imaging study. Accurate levels of metoxycatecholamines were known in 304 patients of total 380. Forty-three patients (14.1%) have elevated level of metoxycatecholamines. In this group of 43 patients 7 (16.3%) patients have histopatologically confirmed pheochromocytoma. Thirty five patients do not have pheochromocytoma in spite of elevated metoxycatecholamines. Moreover, two patients with pheochromocytoma have unelevated metoxycatecholamines secretion with benign features on imaging study in one of those patients.
Conclusion
1 The assessment of urine metoxycatecholamines secretion seems to have limited usefulness in diagnosis of pheochromocytoma, mainly because of low incidence of elevated level of metoxycatecholamines and possibility of false positive results.
2 Moreover, normal level of urine metoxycatecholamines secretion were also oberved in some patients with pheochromocytoma.
3 In diagnosis of pheochromocytoma, clinical symptoms and radiological imaging picture should play the most important role.
4 Assessment of urine metoxycatecholamines secretion should be performed in justified cases.

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EP97

Abstract withdrawn.

EP98

From EFOS to ExFOS, active treatment phase – similarities and differences of the Greek cohorts' results

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Introduction
Extended Forsteo® Observational Study (ExFOS), a multinational, non-interventional, prospective, observational study, designed to evaluate fractures, back pain (BP), adherence and health-related quality of life (QoL) in teriparatide (TPTD) treated patients, based on the extension of treatment duration (24 months) and the addition of new indications (glucocorticoid-induced and male osteoporosis) was compared with EFOS.
Methods/design
Baseline data showed that Hellenic EFOS patients share similarities and noticeable differences with female ExFOS patients[1]. To further evaluate such similarities/differences between the two studies, we aimed to compare the active treatment results of the Greek cohorts between EFOS[2] ($n=301$, all female) and ExFOS ($n=416$, 92.1% female). No statistical comparisons between studies were performed.
Results
Approximately 80% of patients in both cohorts were on treatment one month before maximum treatment period. Lumbar T-score (mean + SD) increased from -3.46 ± 0.67 ($n=175$) at baseline to -2.54 ± 0.74 ($n=120$) at study end in EFOS and from -3.39 ± 0.73 ($n=263$) to -2.36 ± 0.63 ($n=78$) in ExFOS. QoL and BP parameters had similar improvements, as shown by examples depicted below:
Conclusions
Two similarly designed studies, in comparable Hellenic populations, yielded similar results that should be interpreted in the context of observational studies.

	Baseline	3 m	6 m	12 m	18 m	24 m
BP (in previous month)						
ExFOS	86.2%	79.3%	72.2%	65.6%	59.2%	42.2%
EFOS	93.2%	84.6%	77.8%	66.4%	64.2%	
BP frequency (every/almost every day)						
ExFOS	43.8%	12.4%	6.6%	4.3%	4.7%	0%
EFOS	39.9%	7.5%	3.9%	2.5%	2.2%	
BP severity (moderate/severe)						
ExFOS	76.2%	50.4%	32.8%	20.9%	22.2%	18.6%
EFOS	89.9%	69.4%	50.7%	42.4%	32.4%	
EQ-5D Mobility (some/extreme problems)						
ExFOS	57.9%	38.9%	29.9%	22.5%	17.7%	16.2%
EFOS	62.3%	36.7%	24.0%	18.3%	14.8%	
EQ-5D VAS						
ExFOS	57	66	71	75	77	83
EFOS	54	64	69	74	80	

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EP99

Vertebral and non-vertebral low-traumatic fractures in patients with type 2 diabetes mellitus

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Introduction
Recent evidence suggests that the skeleton might be another affected organ in patients with type 2 diabetes mellitus (T2DM). This study evaluates the prevalence of low-traumatic vertebral and non-vertebral fractures and their risk factors in subjects with T2DM.
Materials and methods
We invited outpatients with T2DM, who were under observation in a single outpatient clinic. The subjects were interviewed regarding the presence of low-traumatic fractures and underwent lateral X-ray imaging from T4 to L5. Age, sex, postmenopause and disease duration, complications, HbA1c, calcium intake, risk factors for fracture (FRAX) were registered. Handgrip strength was measured by dynamometer.
Results
Two hundred (141, 70.5% females) consecutive T2DM patients were enrolled. The median of age (Q25–Q75) 66 (60–74 years), BMI 31 (27–36) kg/m^2, disease duration 8 (4–14) years (neuropathy was diagnosed in 113 patients, retinopathy-94, nephropathy-8), HbA1c 7.4% (6.7–8.5). Fractures were reported in 68 (34%) patients, in 26 (13%) cases there were vertebral fractures and in 52 (26%) low-traumatic non-vertebral fractures. In 10 cases multiple fractures both vertebral and/or non-vertebral were registered. The most frequent fractures were of low-extremities including 2 hip and 26 shin fractures; the upper-extremities were the next most frequent location including 3 humerus, 19 wrist and 4 ulna fractures. Subjects with any fractures were older $P=0.004$, but did not differ in disease duration $P=0.196$, HbA1c $P=0.99$, or calcium intake $P=0.62$. It seems that subjects with retinopathy fractured more −42.9% as compared to patients without retinopathy −27.6% $P=0.001$, no difference in any other complications were found. Subjects with fracture had lower grip strength in both hands 30.0 (24.6–39.5) vs 26.5 (22.7–31.5) dAN $P=0.019$ right hand; 27.7 (22.1–37.5) vs 25.0 (20.0–31.8) dAN left hand $P=0.013$.
Conclusions
Patients with T2DM have high prevalence of low-traumatic fractures (34%), mostly of low-extremities, which might be related to both ageing and general frailty as well as diabetes complications such as retinopathy.

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EP100

Osteoporosis and osteopenia in older Emirati men with type 2 diabetes mellitus

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Introduction
Osteoporosis is an important cause of morbidity and mortality in older men, but the extent of the problem amongst Emiratis has not been previously reported. A screening programme has been in place for older men in a large diabetes centre in the UAE, allowing patients over age 70 to have DEXA scans; we have investigated the prevalence of osteoporosis and osteopenia in this population.
Methods
Data on 179 consecutive patients with type 2 diabetes over age 70 with DEXA scan reports were retrieved and analysed. T-score at lumbar spine, femoral neck and hip were recorded. Relevant demographic and phenotypic data and laboratory investigations at or closest the time of DEXA and comorbidities list were extracted from individual computerized patient records. Stata13.0 was used for data analysis.
Results
Table 1 summarizes results based on the diagnosis of osteoporosis or osteopenia at any of the five sites studied. Osteoporosis at lumbar spine and left femoral neck was noted in 32.2 and 19.5% of the patients respectively. Significant predictors of bone density (univariate regression analysis) included age (odds ratio-OR 1.14, $P=0.02$), weight (OR 0.96, $P=0.02$) and height (OR 0.87, $P<0.001$). In multivariate analysis including age, weight, height and eGFR, only height (OR 0.88, $P=0.005$) remained a predictor with significance. There was 82.4% osteoporosis range T-scores concordance between the right and left femoral neck levels.

Table 1.

	Osteoporosis *n* (%)	Osteopenia *n* (%)	Normal *n* (%)	*P* value
Number and (%)	83 (46.4%)	73 (40.8%)	23 (12.9%)	–
Non-smoker	64 (77%)	53 (73%)	17 (74%)	0.96
Hypothyrodism	2 (2.4%)	5 (6.9%)	1 (4.4%)	0.41
Hypertension	76 (91.6%)	67 (91.8%)	22 (95.7%)	0.80
CVD	25 (30.1%)	16 (21.9%)	7 (30.4%)	0.47
Insulin therapy	19 (22.9%)	25 (34.3%)	10 (43.3%)	0.1
OHAs	74 (89.2%)	65 (89%)	21 (91.3%)	0.95
Weight (kg)	69.8 (±14.3)	76.4 (±13.2)	80.2 (±10.3)	<0.001
Height (cm)	162.4 (±7.2)	164.4 (±5.6)	169.04 (±6.4)	<0.001
eGFR ml/min per 1.73 m^2	66.7 (±33.3)	74.4 (±24.9)	80.3 (±16.3)	0.07
HbA1c (%)	7.1 (±1.3)	7.4 (±1.5)	6.9 (±0.9)	0.22
Serum calcium (mmol/l)	2.3 (±0.1)	2.3 (±0.1)	2.3 (±0.1)	0.31
Strgm vitamin D (nmol/l)	76.9 (±27.4)	76.4 (±24.1)	82.6 (±32.9)	0.6
TSH level (milli IU/l)	2.7 (±1.4)	2.6 (±1.5)	2.7 (±1.2)	0.94
DM duration (years)	12.5 (±8.9)	16.2 (±10.2)	15.3 (±10.9)	0.05[a]

CVD, cerebrovascular disease; OHAs, oral hypoglycemic agents; testing based on one-way ANOVA and χ^2 test.
[a]DM duration not normally distributed, median test *P* value = 0.25.

Conclusion
Compared to European reports, prevalence of osteoporosis in this population of Emirati men with type 2 diabetes is much higher. Specific local factors such as relative inactivity in old age and lack of sun exposure may be responsible for such high prevalence figures and need to be further investigated in a larger group of patients.

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EP101

Abstract withdrawn.

EP102

A rare cause of hypocalcaemia: pseudohypoparathyroidism

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Introduction
Pseudohypoparathyroidism (PHP) is a rare disease characterized by end-organ resistance to parathyroid hormone, causing hypocalcemia with hyperphosphatemia and elevated parathormone (PTH) levels. A prevalence of 3.4/million has been reported. Here, we present a rare case with PHP.
Case report
A 28-year-old male patient with spasms in hands and feet was evaluated in the outpatient department of neurology and was referred to endocrinology clinic due to calcium level of 5.9 mg/dl.
Physical examination results: He had facial dysmorphism. Trousseau and Chvostek signs were positive. Moderate mental retardation was observed.
Laboratory tests results: Serum total Ca: 5.7 mg/dl (8.2–10.6 mg/dl), P: 5.9 mg/dl (3–5 mg/dl), PTH (intact): 873 U/l (12–88 pg/ml), uric acid: 2.3 (3.5–7.2) 24-h urinary Ca: 9 mg and urinary P:441 mg. Serum vitamin D level: 29 nmol/l. Urine cAMP and Gsa subunit assays were not available in the tests.
The roentgenogram of the hands revealed that he had short bilateral fifth metacarps and soft tissue calcifications in his left hand and bilateral forearm (Figure 1). His electrocardiogram was normal. QTc interval was 42 ms. In Cranial CT, symmetrical diffuse calcifications were observed in both hemispheres and in the central part of the caudate nucleus and the level of nuclei lentiform of the basal ganglia (Figure 2).
Conclusion
PHP is classified as types 1a, 1b, 1c and type 2. Patients with type 1a have hypocalcamia, hyperphosphatemia and elevated serum PTH. These patients are characterized by short stature, obesity, moderate mental retardations, round faces, dental hypoplasia and brachydactyly; shortening of the metacarpal bones particularly the third, the fourth and the fifth as well as the features of Albrights hereditary osteodystrophy.
PHP type 1 is inherited in an autosomal dominant pattern. GNAS gene is located on chromosome 20q13 and defects are heterogeneous and complex. Our patient did not have GNAS mutations (but we only looked at exon 8).

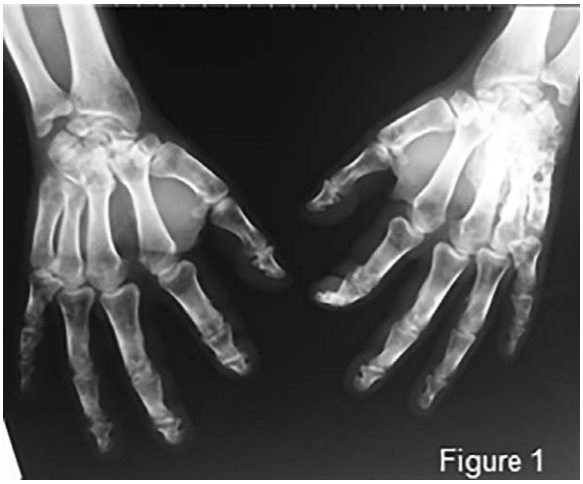

Figure 1.

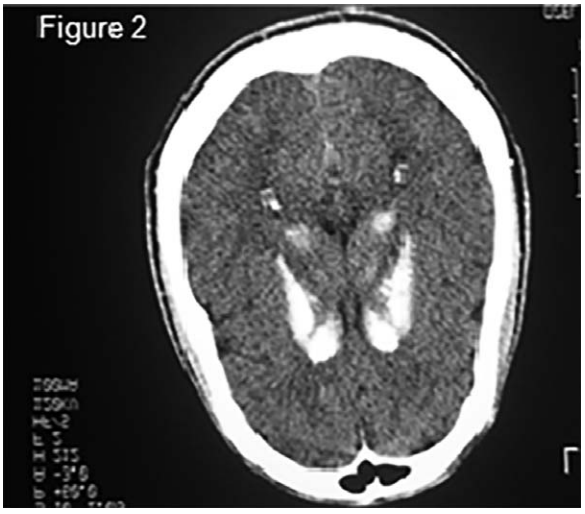

Figure 2.

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EP103

Association between household size, residential area, and osteoporosis: analysis of 2008–2011 KNHANES

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Abstract withdrawn.

EP104

Association of vitamin D receptor gene with development of osteoporosis in patients with hypothyroidism

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Polymorphism of the vitamin D receptor (VDR) gene has been reported to play a major role in variations for genetic regulation of bone mass. The current study is an attempt to examine the association of these variations with osteoporosis in patients with hypothyroidism. The purpose of this study was to determine distribution of genotypes and allelic frequencies of polymorphism of rs731236 (C+61968t; TaqI) VDR gene, and also risk of development and association with risk factors of bone mineral density changes in women with hypothyroidism.
Methods
There were 95 women with hypothyroidism under a supervision in age from 34 to 65 years. Exposure of vitamin D receptor gene polymorphism *in vitro* was produced by the method of PCR.
Results
The prevalence of mineral bone density disorders among patients with hypothyroidism was 46.3%, including with osteopenia 32 (33.7%) and osteoporosis in 12 (12.6%). Presence of homozygote on major allele VDR gene rs731236 (C+61968t; TaqI) possesses protective effect on development of osteoporosis, while the presence of homozygote on minor allele of this polymorphism of T/T assists to development of osteoporosis.
Conclusions
Presence of genotype *major allele* (C) is diminished with the 3.8 times greater risk of osteoporosis development, while presence of minor allele (T) is promoted with the 3.9 times greater risk. Presence in the genotype of homozygote on minor allele T/T combines with more expressed decline of mineral bone density. Minor allele (C) is associated with hypocalcemia, by the decline of bone mineral density, hyperphosphatemia, activation of osteocalcin.

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EP105

A rare differential diagnosis of Paget's disease

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Hypertrophic osteoarthropathy (HOA) is a syndrome characterized with proliferation of bones at the distal parts of extremities. Clubbing, periostitis of tubular bones and non-inflammatory arthritis of lower extremities are commonly seen as a part of this syndrome.
66 years old male patient was admitted to our hospital with painful swelling of his left lower extremity for 2 months. He denies any other systemic symptoms such as fever and weight loss. He had history of aortailiac bypass surgery 5 years ago. On physical examination there were pitting edema on his left leg and clubbing of the toes, no hyperemia or temperature increase was found. His bone scan revealed increased osteoblastic activity on left anterior iliac spine and also diffuse expansive heterogen osteoblastic activity was seen on left humerus, tibia, fibula and digital bones. This involvement was decided as Paget's disease and he was treated with parenteral zoledronic acid in another center. On his admission to our hospital, periostal reaction of bilateral femur and tibia was seen on plain radiographs. HOA was decided as preliminary diagnosis. Positron emission tomography (PET) was performed in order to identify the etiology of HOA and revealed bilateral heterogen periostal reaction of lower extremities confirming HOA. Also there was increased FDG activity on abdominal aorta and iliac bifurcation indicating aortitis. Contrast enhanced abdominal CT showed periaortitis caused by a fistula between aortic graft wall and 3. part of the duodenum. The fistula tract was not connected with vascular lumen. Daptomicine 350 mg/day and Ertapenem 1 g/day were started. Revision of the graft was planned during cardiovascular surgery consultation. The patient will be operated after 6 weeks of antibiotic treatment is completed.
Vascular graft infection, as reported here, is a rare cause of secondary HOA, but it might be strong and important sign of infection of vascular prosthesis.

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EP106

An uncommon reason of osteoporosis: spondyloepiphyseal dysplasia congenita

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Introduction
Spondyloepiphyseal dysplasia congenita (SEDC) is a rare congenital disease of skeletal system,which is characterized by short stature, shortage of trunk and mostly affect vertebral column and epiphysis of long bones. In this case report, we aimed to represent a patient complaining of short stature and referred to our hospital,who was detected to have an early onset osteoporosis accompanied by proximal femoral aplasia; in the light of literature.
Case
A 21 years old female, referred to our hospital since she was complaining of short stature. According to this first assessment, her height was 125.7 cm, weight 35.7 kg and had a pelvic deformity. By performing a skeletal scanning in that period;a platispondilia like appearance in the vertebral column, an increase in lumber lordosis,disappearance of both femoral heads,shortening of femoral neck, lateral subluxation of proximal femur were detected and bilateral femoral osteotomy and a fixation were performed respectively. In the physical examination we noticed coxa vara, scoliosis and has a flattened face. The biomedical parameters are all summarized. In the skeletal examination we noticed deformation and stabilization materials in the femur heads and counter rotation developed in cervical axis which was not exist previously, mild loss of intervertebral disc height in C3, C4, C5, C6. We calculated lumbal total Z score as −3.2. It was thought that the reason of premenopausal osteoporosis was SEDC. We prescript teriparatide because of her age and high grade of osteoporosis.
Discussion
Although osteoporosis was reported in Spondiloepiphyseal dysplasia tarda cases, we did not notice any report mentioning about the relationship between SEDC and osteoporosis; in the literature. As a conclusion, skeletal dysplasia which is mostly presented with short stature, should be in mind as one of the prediagnosis in any case of early onset osteoporosis with short stature.

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EP107

Bone microarchitecture assessed by trabecular bone score in liver transplants with New-Onset Diabetes after transplantation

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Background
The increased risk for fractures in type 2 diabetes mellitus despite higher bone density is unexplained. Trabecular bone score (TBS) is a novel texture index related to bone microarchitecture and it is independent of bone mineral density (BMD). The aim of this study was to investigate the relationship between TBS, BMD and body composition in patients with New-Onset Diabetes after transplantation (NODAT).
Methods
In a cross-sectional study, TBS was examined in 28 patients with NODAT (mean age 58.5 ± 9.6), and 43 non diabetic LT patients (mean age 55.4 ± 11.5), classified according ADA criteria. Lumbar, femoral BMD and body composition were measured with DXA densitometer (QDR 4500, Hologic, USA). Body composition parameters included total body mineral content (BMC), total fat mass (FM), total fat free mass (FFM) and percentage of fat mass (%FM). Bone biomarkers included: Osteocalcin (OC, electrochemiluminiscence assay, NMID Osteocalcin, Roche Diagnostics) and b-CrossLaps.
Results
TBS showed positive correlations with lumbar BMD ($r=0.2637$, $P<0.05$), femoral neck BMD ($r=0.26$, $P=0.03$) and total BMC ($r=0.26$, $P<0.05$). An inverse correlation was found between TBS and FM ($r=-0.34$, $P<0.05$) and %FM ($r=-0.27$, $P<0.05$). No correlations were found between TBS and OC and b-CrossLaps. No differences were found between non-diabetic and NODAT patients in terms of TBS and lumbar or femoral BMD.
Conclusion
In LT patients, TBS is related to fat mass parameters and lumbar and femoral neck BMD. We have not found deterioration of bone microarchitecture in patients with NODAT, assessed by TBS.

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EP108

Serum leptin, adiponectin and ghrelin concentrations in post-menopausal women: is there an association with bone mineral density?

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Introduction
Adipokines and ghrelin exert well-documented effects on energy expenditure and glucose metabolism. Experimental data also support a role in bone metabolism, although data from clinical studies are conflicting. The purpose of this cross-sectional study was to investigate the association of serum concentrations of leptin, adiponectin and ghrelin with bone mineral density (BMD) in post-menopausal women.
Methods/design
BMD in lumbar spine and femoral neck, and circulating leptin, adiponectin and ghrelin concentrations were measured in 110 healthy post-menopausal women. Patients with secondary causes of osteoporosis were excluded.
Results
Osteoporosis was diagnosed in 30 (27%) women and osteopenia in 54 (49%). Serum leptin concentrations were positively correlated with both lumbar spine ($r=0.343$, $P<0.01$) and femoral neck BMD ($r=0.370$, $P<0.01$). Adiponectin concentrations were negatively associated with BMD at both sites ($r=-0.321$, $P<0.01$ and $r=-0.448$, $P<0.01$ respectively). No significant correlation between ghrelin concentrations and BMD was found. Osteoporotic women had lower body weight, BMI and leptin concentrations, but higher adiponectin concentrations compared with non-osteoporotic women. In multivariate stepwise regression analysis, the association of adiponectin concentrations with BMD remained significant only for femoral neck, after adjustment for body weight or BMI.
Conclusions
An inverse association between adiponectin and femoral neck BMD was found in post-menopausal women, independently of body weight. The positive association between leptin and BMD was dependent on body weight, whereas no effect of ghrelin on BMD was evident.

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EP109

Bone turnover markers in women with postmenopausal osteoporosis depending on the level of vitamin D

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Introduction
It is indisputable importance of vitamin D for the preserved integrity of the skeleton and bone metabolism.
The aim of the study was to analyse bone turnover parameters in relation to the vitamin D status in women with postmenopausal osteoporosis.
Materials and methods
This study included a total of 195 postmenopausal women with osteoporosis. Osteoporosis is diagnosed by DXA scan of the spine and hip. Bone turnover markers osteocalcin, beta-crosslaps and 25OHD were determined by ECLIA method on Elecsys apparatus. Vitamin D status is defined as a deficiency if 25OHD <30 nmol/l. Within the range of normal values of 25OHD (30–100 nmol/l), insufficiency is defined if level of 25OHD is 30–75 nmol/l and a sufficient level of 25OHD >75 nmol/l.
Results
The mean age was 60.30 ± 6.33 years and mean duration of postmenopausal period was 11.8 ± 5.51 years. The average BMI was 25.41 ± 4.26 kg/m^2. The average value of 25OHD was 39.98 ± 17.97 nmol/l, the average value of osteocalcin was 32.31 ± 11.97 ng/ml and the average value of beta-crosslaps was 545.31 ± 212.07 pg/ml. 25OHD level of <30 nmol/l in 59 (30.26%) subjects, the level of 25OHD 30–75 nmol/l had a 128 (65,64%), and vitamin D levels >75 nmol/l, had an 8 (4,10%) of subjects. There was a statistically significant difference in levels of osteocalcin and beta-crosslaps compared to the levels of vitamin D defined as a deficiency, insufficiency and sufficiency. Average values of osteocalcin in the above defined groups of vitamin D were 35.15 ± 14.26 vs 31.49 ± 10.77 vs 24.59 ± 5.38 ng/ml; $P<0.1$. Average values of beta-crosslaps in the above defined groups of vitamin D were 584.16 ± 230.77 vs 539.30 ± 201.33 vs 354.88 ± 128.33 pg/ml; $P<0.01$.
Conclusions
In women with postmenopausal osteoporosis dominates deficit and insufficient levels of vitamin D. Insufficient vitamin D leads to accelerated bone remodelling with a predominance of bone resorption over formation which contributes to the reduction of bone mass and quality.

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EP110

Clinical characteristics of Paget disease of bone from Turkey

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Prevalence of Paget's disease (PD) of bone as well as clinical and demographical presentation may differ between the populations.
Aim
In this study we evaluate clinical and demographical parameters of Paget's disease patients followed from endocrinology clinics in Turkey.
Method
An invitation was sent to all tertiary endocrinology clinics to complete a survey on demographic clinical, laboratory parameters, treatment modalities of patients with PD. Clinically or histologically proven 185 PD cases reported from 16 centers.
Results
A cohort of PD has female preponderance (FM/M:105/80) with a mean age of 57 ± 10 years at onset. Its clinical features are bone pain, back pain and headache, Fracture and typical skeletal involvement reported in five and 18 patients respectively. Only two patients have family history for PD. 67.5% (n:125) patients have polyostotic disease. Skull (41.6%), pelvis (53.5%), spine (41%) and femur (25.4%) are being the commonly affected bone sites. Seventeen patients with skull involvement reported to have hearing loss. The biochemical profile at diagnosis had a mean alkaline phosphatase (ALP) 5520 ± 652 IU/l (range 280–5762 IU/l), serum calcium: 9.2 ± 1 mg/dl, iPTH:73.9 ± 65 pg/ml, 25OHvitD:32.6 ± 27 ng/ml. Five patients wasn't need treatment. Intravenous bisphosphonates was the most commonly used drugs (42% and 23% of patines treated with zoledronic acid 5 mg and pamidronate 60–90 mg respectively) remaining given high dose oral bisphosphonate (alendronate 40 mg/day or risedronate). Most cases respond well with decreased Serum ALP level (117 ± 114 IU/l) at the 6th month of the therapy. Duration of follow up was 7.5 ± 6.5 years.
Conclusion
In this group of PD from Turkey female predominance and polyostotic disease, no significant family history. Classical clinical and biochemical features respond well to intravenous or high dose bisphosphonate therapy and need a lifetime follow-up.

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EP111

Association of bone mineral density with DXA-determined adipose tissue volume and concentrations of selected hormones in young adult women

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Introduction
The question if obesity may protect against osteoporosis is still a matter of discussion. A breakthrough in this debate may be the introduction of a state-of-the-art densitometric software (CoreScan) suitable for fast and accurate volumetry of total body fat (BF), including android (A), female-type (F) and visceral fat (VAT) volumes.
Aim
The aim of the study was to analyze an association between bone mineral density (BMD]), concentrations of selected hormones, BF, A, F and VAT volumes in young adult women.
Material and methods
The study was a retrospective analysis of densitometric scans and laboratory parameters of 108 women (age: 20–33 years). Two groups of patients were identified based on their body mass index (BMI), with BMI <25 kg/m^2 and >25 kg/m^2. The list of analyzed variables included body height and weight, BMI, BMD, DXA-determined BF, A, F and VAT volumes, concentrations of TSH, FT3, FT4, FSH, LH, estradiol, PRL, DHEA-SO4, androstendion, testosterone, SHBG, 17-hydroxyprogesterone, levels of glucose and insulin measured after an overnight fast and during glucose tolerance test.
Results
Irrespective of the analyzed area (BF, A, F, VAT), adipose tissue volume correlated significantly with BMD L1-L4, BMD total, blood concentrations of free estrogens and testosterone ($P<0.000$). Moreover, a significant relationship was found between VAT volume and concentrations of insulin after an overnight fast, as well as at 60 and 120 min of glucose tolerance test ($P<0.000$). Finally, VAT volume correlated inversely with blood concentration of SHBG ($P<0.003$). The two groups of patients differed significantly in terms of their mean values of densitometric parameters ($P<0.000$).
Conclusions
Greater volume of subcutaneous and visceral fat is likely associated with higher BMD in young adult women and therefore may protect them against osteoporosis. However, high volume of body fat may also predispose to polycystic ovary syndrome and type 2 diabetes mellitus.

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EP112

Relationships between body composition components in women with anorexia nervosa

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Objective
The aim of this study was to assess the relationships between the body composition elements in women with anorexia nervosa (AN).
Description of methods
In this study women with AN and healthy women aged 19–33 years were investigated. Anthropometry for height, weight and body mass index (BMI) was performed. Body composition including lean mass, fat mass, fractional contribution of fat, bone mineral content (BMC), and bone mineral density (BMD) was analysed by dual-energy X-ray absorptiometry (iDXA, GE Lunar). Pearson's correlation coefficient was determined to assess associations. Statistical significance was accepted when $P<0.05$.
Results
In total, 52 females were assessed: 17 AN patients and 35 healthy women, with no differences in average age and height (25.12 ± 4.69 vs 23.49 ± 2.48 years and 1.66 ± 0.05 m vs 1.67 ± 0.05 m, respectively). Compared to controls, women with AN presented lower body mass and lower BMI: 46.9 ± 4.28 vs 59.9 ± 7.07 kg, and 17.10 ± 1.58 vs 21.37 ± 2.02 kg/m^2. Total lean mass, fat mass, fractional contribution of fat, BMC, and BMD were significantly lower in AN subjects. There was no significant difference in android/gynoid ratio between groups. In women with AN, the correlations between percentages of gynoid fat and legs fat ($r=0.942$, $P<0.001$) as well as between legs lean mass and legs BMC ($r=0.724$, $P=0.001$) were found. Lumbar spine BMD correlated with total legs mass ($r=0.55$, $P=0.04$). In controls, more associations were found: gynoid fat (%) correlated with lumbar spine ($r=0.374$, $P=0.027$), total hip ($r=0.341$, $P=0.045$), femoral neck ($r=0.391$, $P=0.02$) BMD, and with legs lean mass ($r=0.442$, $P=0.008$). Also, the legs lean mass was associated with lumbar spine ($r=0.373$, $P=0.027$), total hip ($r=0.406$, $P=0.015$), and femoral neck ($r=0.507$, $P=0.002$) BMD.
Conclusion
In patients with anorexia nervosa, gynoid fat (%) correlated with legs regional fat (%) but no associations between gynoid or legs regional fat and BMD were found.

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EP113

Is carbonhydrate intake a risk factor for postmenopausal spinal osteoporosis?

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Introduction
Osteoporosis is a disease that is characterized by bone mass loss and deterioration in bone micro-architecture. One of the most important risk factors is dietary habits. The effects of the amount of calcium intake via eating, and low calcium consumption on the development of osteoporosis is still an active research area. The intestinal absorption of calcium and its renal excretion are still not understood very well. Even though the effects of carbohydrates on calcium absorption is not known clearly, there are studies that there is a positive relationship between carbohydrates and fractional calcium absorption.
Aims and methods
In our study, we have evaluated the amounts of dietary calcium intake and carbohydrates among postmenopausal women with lomber osteoporosis. There were 30 patients with postmenopausal spinal osteoporosis. Patients that were older than 75, had inflammatory disease, cancer diagnosis, oral feeding problems, intestinal absorption problems, renal disease, and the ones that used proton pump inhibitor, as well as the ones that had only hip osteoporosis or mixed type osteoporosis were not included. The demographic data and the resume of patients were recorded. Their daily carbohydrate and calcium consumption were evaluated using FFQ and calculated as daily consumption. L1-L4 *t*-scores were recorded based on DEXA measurements.
Results
The mean age of patients was 61.1 (49–69), mean BMI was 29.1 (19.5–39.5), L1-L4 *t* score had an average of -2.9, average daily carbohydrate consumption was calculated as 306.8 mg/day, and average daily calcium consumption was calculated as 1016 mg/day. The recommended values for women over 50 are 130 g/day for carbohydrates, and 1200 mg/day for calcium. In our study group, even though the calcium intake has been found to be below the reference value, there are similar studies in literature originating from Turkey. The carbohydrate consumption has been found to be three times the normal value.
Conclusion
There is no prior study that shows a positive or negative effect of carbohydrates on osteoporosis. In our study, we have shown the increased carbohydrate consumption in postmenopausal lomber osteoporosis. There is definitely a need for larger scale studies on this topic.

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EP114

Bone density in the HIP and the lumbar spine in healthy male population

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Introduction
Low bone density is a frequent finding in both women and men of older age. There is not enough data about bone density in younger adults and especially men. In this study we measured bone density in healthy males per decade of age.
Method
We measured bone density (BMD), *T*-score, *Z*-score and body mass index (BMI) in 1902 healthy men, age 20–59 years old. The study population was divided into four groups according to their age: Group A 20–29 years old, Group B 30–39, Group C 40–49, Group D 50–59, and we compared the bone density between the groups. Mean age of the total study population was 39.4 years, mean weight 83.6 kg and mean BMI 26.5 ± 3 kg/m^2. The mean BMD was 1.21 ± 0.16 g/cm^2 and 1.05 ± 0.22 g/cm^2 for the lumbar spine and the hip respectively.
Results
The BMDs per decade for the lumbar spine were as following: Group A 1.25 ± 0.14 g/cm^2, Group A 1.25 ± 0.14 g/cm^2, Group B 1.21 ± 0.15 g/cm^2, Group C 1.20 ± 0.16 g/cm^2 and Group D 1.17 ± 0.18 g/cm^2. The BMDs for the hip were as following: Group A 1.15 ± 0.28 g/cm^2, Group B 1.08 ± 0.33 g/cm^2, Group C 1.01 ± 0.12 g/cm^2 and Group D 0.98 ± 0.12 g/cm^2. Statistical analysis showed that for each age group, there was statistically significant difference ($P < 0.05$) comparing with the other age groups for the hip. However, in the spine this difference was observed only when comparing Group A with all other Groups. There was not any statistically significant difference between Groups B, C and D comparing with each other.
Conclusion
In healthy male population there is a progressive decrease in bone density according to age. This decrease is more obvious in the hip. In the lumbar spine there is also decrease but not statistically significant. One possible explanation is the appearance of osteophytes after the age of 50 which may falsely increase bone density

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EP115

The effect of anorexia nervosa on bone

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Introduction
One of the most common endocrine complications of anorexia nervosa (AN) is the decrease in bone mineral density. The authors evaluated the predictive factors of osteopenia and osteoporosis in AN patients admitted with low weight.
Patients and methods
Retrospective analysis of 45 patients admitted with AN between 2001 and 2015 in the Endocrinology department, corresponding to 63 admissions. Bone mineral density was classified according to WHO criteria. The relationship between clinical and analytical parameters and bone density was evaluated.
Results
Most patients were female (93.3%; $n = 42$), with mean age 20.6 ± 7.7 years. Restrictive subtype in 86.7% ($n = 39$), with the remainder of the purgative type. On admission, mean BMI 14.3 ± 1.6 kg/m^2 and percentage of fat mass 4.2 ± 2.4%. Amenorrhea was present in 48.9% ($n = 22$), euthyroid sick syndrome in 15.6% ($n = 7$), hypogonadotrophic hypogonadism in 51.1% ($n = 23$), Bone densitometry documented osteopenia and osteoporosis in 57.1 and 31%, respectively. Initial weight was statistically different between the densitometry results (normal, osteopenia and osteoporosis; $P = 0.04$), without association with initial fat mass (IFM), measurements of FSH, LH, estradiol, total testosterone, TSH and fT4. Lumbar spine *T*-score was moderately correlated with initial weight ($\rho = 0.58$), IFM ($\rho = 0.39$), initial fat-free mass (IFFM) ($\rho = 0.55$) and estradiol levels ($\rho = 0.37$). Total femur *T*-score was moderately correlated with initial weight ($\rho = 0.48$) and IFFM ($\rho = 0.47$).
Discussion and conclusions
In this group of patients, low weight on admission was associated with osteopenia and osteoposoris. Initial weight was positively correlated with better results of densitometry in lumbar spine and total femur. The greater number of correlations with lumbar spine bone loss is in agreement with the earlier changes in the trabecular bone described in the literature. The low number of patients with normal densitometry ($n = 5$) may have limited the association with other factors, as well as the statistic strength of the presented results.

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EP116

The influence of osteoporosis and cardiometabolic syndrome risk factors on bone mineral density in females with thyroid dysfunction

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Introduction
The effects of TSH and thyroid hormones on bone turnover are well-known. The aim of this study is to examine the influence of osteoporosis (Op) and cardiometabolic syndrome risk factors on bone mineral density (BMD) in the population of age-matched, normotensive and nondiabetic females.
Material and methods
Cross-sectional study involved 76 females (average age 53 ± 10 years), divided into three groups: hypo-, hyper-, and euthyroid. Presence of smoking habit, previous fracture/s and menopause were Op risk factors while body mass index (BMI), waist circumference (WC), triglycerides, and cholesterol levels were cardiometabolic risk factors. Index of cardiometabolic burden (ICMB) consisted of BMI > 30 kg/m^2 and/or WC > 88 cm and showed increase in cardiovascular disease risk. Lumbar spine (LS) and left hip (LH) *T*-scores represented DEXA measured of BMD. Osteopenia and Op were defined as *T*-scores < -1.
Results
Decreased BMD was detected in 46 (60%) participants. The lowest *T*-scores were observed in hypothyroid group. Average LS and LH *T*-scores were -1.1 and -0.75 respectively, and differed between groups (hypo/hyperthyroid vs euthyroid). Significant influences of BMI and triglycerides on LH *T*-score as well as the presence of previous fractures and menopause on LS/LH *T*-scores were detected. The effect of TSH, FT4 and ICMB on BMD was not significant.
Conclusion
In the population of females with thyroid dysfunction on initial presentation, osteopenic BMD was registered. The presence of previous fractures and menopausis, BMI, and triglycerides significantly affected BMD, while TSH, FT4, and ICMB did not affect BMD.

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EP117

Use of Denosumab for treatment of steoporosis at a Tertiary Referral Centre: an evaluation according to the UK National Institute of Health and Care Excellence (NICE) Guidelines

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Aim
To evaluate the use of Denosumab in accordance to the UK National Institute of Health and Care Excellence (NICE) technology appraisal guidelines TA204 – Denosumab indicated for the prevention of osteoporotic fractures in post-menopausal women.
Methods
A retrospective audit involving 129 patients prescribed Denosumab for osteoporosis between October 2011 and March 2015 at Nottingham University Hospitals, UK. Denosumab prescription data was obtained from trust pharmacy and clinic databases, whilst correlating patient information were obtained from electronic hospital records.
Results
A total of 129 patients received Denosumab during this period. One hundred and ten patients were female with a mean age of 77 (range 23–95). Nineteen patients were male with a mean age of 75 (range 47–91). Forty-six patients were treated for primary prevention of osteoporotic fractures, whilst 83 patients were treated for secondary prevention. In the female patients, 68% ($n=75$) met the NICE TA204 criteria for use of Denosumab, whilst in the remaining 32% ($n=35$), oral bisphosphonate use was inappropriate. All male patients had high fracture risk, and oral bisphosphonate use was inappropriate in all cases. Overall, the most common indication for Denosumab use was renal impairment (43%), intolerance to oral bisphosphonates (35%), and other contra-indications (e.g. treatment failure, non-compliance) (22%).
Conclusion
All patients received oral bisphosphonate initially as first choice treatment for prevention of osteoporotic fractures. Denosumab was only considered when oral bisphosphonate became unsuitable. Male patients with high fracture risk received Denosumab when no other suitable alternative could be used.

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EP118

Incident fragility fractures under antiresorbtive therapy in a 76 year old lady: never too late to discover new causes

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Introduction
We report a case of severe osteoporosis with incident fragility fractures during antiresorbtive therapy in the presence of amiodarone induced hypothyroidism.
Case report
A 76 year old female was admitted in our department for the evaluation of antiresorbtive therapy in the context of a recent rib fracture after coughing. Severe osteoporosis (lumbar *T*-score: −2.8DS, femoral neck *T*-score: −2.9DS with multiple fragility fractures) was treated with i.v. Ibandronic acid and vitamin D during the last 16 months.
Her medical history consists of atrial fibrillation, hypertension, severe osteoporosis, Raynaud's syndrome and Amiodarone induced autoimmune hypothyroidism currently under treatment with L-Thyroxine.
Clinical features: Normal BMI, kyphosis with loss of more than 5 cm of height in the last 5 years, Raynaud's syndrome with inflammatory signs of the hands, left bronchial rales, a BP of 110/70 with a HR of 125.
Laboratory: ESR = 36 mm/h, normal serum calcium and 25OH vitamin D, a TSH of 5.89 under 75 μg of L-Thyroxine.
The chest X-rays and CT showed a 4th rib fracture and a revealed T9 and T10 vertebral fractures, and also an important pulmonary fibrosis, which led to the systemic sclerosis diagnosis.
Recent reviews found that the risk of osteoporotic fracture in systemic sclerosis is similar to rheumatoid arthritis, affecting the axial skeleton and caused by the chronic inflammatory state. Consequently, due to the newly increased fracture risk (due to the systemic sclerosis and incident fracture under antiresorbtive treatment) we recommended teriparatide treatment.
Conclusion
The pathogeny of severe osteoporosis, in our case, revealed new findings after <2 years of treatment: besides advanced age and possible effects of L-thyroxine replacement therapy we discovered that the established negative effects of the systemic sclerosis on the skeleton revealed the need for a complete reevaluation during follow-ups for osteoporotic patients.

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EP119

Thyroid and parathyroid secretion disorders in senile osteoporosis

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Introduction
Osteoporosis is a metabolic disease characterised by reduction of the bone mass density and deterioration of architecture of the bone and its strength. Continuous process of modeling and remodeling of bones is regulated by action of numerous circulating hormones. Fracture risk makes osteoporosis clinically important disease. Goal of this study was to examine thyroid dysbalance, parathormone secretion disorder as risk factors for osteoporosis in elderly.
Description of methods
Study involved 195 participants aged 65 or more. Dual photon absorbtiometry (DXA), to confirm osteoporosis. PTH disorder was found in 58%, and thyroid disorder in 30% participants. Linear correlation was used as a statistical method to correlate variables.
Result
PTH levels (84.56 pg/ml ± 3.76) and decreased *T*-score levels showed high statistical significance ($P<0.01$), linear correlation coefficient (r), −0.94. DXA *Z*-score (−1.42 S.D. ± 0.05) and PTH level (84.56 pg/ml ± 3.76) also showed high significant correlation ($P<0.01$, $r=-0.82$). Decreased TSH levels significant correlated with decreased bone mineral density. Correlation was greater in elderly with hypothyreosis.
Conclusion
Thyroid disbalance and parathormone secretion disorder are common in elderly with osteoporosis

Keywords: Osteoporosis, elderly, parathormone, thyroid hormone
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EP120

Hypophosphatasia: a novel mutation

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Introduction
Hypophosphatasia (HPP) is a rare genetic disease of very variable severity (from letal to mild). HPP results from APL gene mutations, which lead to a deficiency of tissue-nonspecifc alcaline phosphatase (TNAP), and accumulation of inorganic pyrophosphate, a potent inhibitor of mineralization that is also a natural substrate of TNAP in the extracelular space. HPP causes mineralization disorders including soft bones (rickets, osteomalacia, fractures) and defects in teeth. The broad-ranging expressivity that is largely explained by its autosomal recessive and autosomal dominant patterns of inheritance involving at least 300 different mutation (predominantly missense) in the TNSALP gen. Five principal subtypes of HPP are described: perinatal lethal, infantile, childhood, adult, odontohypo-phosphatasia and perinatal benign. We report a case of adult hypophosphatasia.
Case report
A 35 years old male patient with a history of loss of permanent teeth at a young age and pain bone (thigh, hip) was referred to our endocrine clinic to study after a recent family history sugestive of HPP.

Laboratory investigations revealed low serum alcaline phosphatase (ALP) (25 Ui/l; *N* 40–150), normal-low bone alcaline phophotase (6 µg/l N 6–30 µg/l), and normal levels of plasma and urine phosphoethanolamine (PEA), pyridoxal 5′-phosphate (PLP) and vitamine D.
Mutation analysis revelead a novel, heterozygous mutation within TNSALP gen (c.567_568 insT; p. Asn190stop)
Conclusions
As this condition is not well known by healthcare professionals, the time to diagnosis and initiation of adecuate treatment is postponed. HPP must be suspect when clinical o laboratory clues include premature loss of primary dentition, pseudofractures or recurrent poorly healing metatarsal stress fractures, a family history sugestive of HPP or low serum ALP activity. Recently has been aproved a fosfatase alfa, a first-in-class bone targeted human recobinant TNSALP replacement therapy with paediatric onset HPP. Bisphosphonates or too high doses of vitamine D are contraindicated.

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EP121

Anorexia nervosa: beyond psychiatry

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Introduction
Despite being a psychiatric disorder, anorexia nervosa (AN) is associated to severe systemic complications. The endocrine complications of AN are an opportunity for the diagnosis and treatment of this condition. The authors report the experience of the Endocrinology Department in the treatment of AN in inpatient setting.
Patients and methods
Retrospective analysis of 45 patients admitted with AN between 2001 and 2015 in the Endocrinology department, corresponding to 63 admissions. During admission, patients had daily multidisciplanary monitoring, including endocrinology, psychology, nutrition and nursing, with support from psychiatry whenever needed. Clinical and analytical parameters, as well as other exams (electrocardiogram and bone densitometry) were performed immediately after admission.
Results
Most patients were female (93.3%; $n=42$), with mean age 20.6 ± 7.7 years. Restrictive subtype in 86.7% ($n=39$), with the remainder of the purgative type. On admission, mean BMI 14.3 ± 1.6 kg/m^2 and percentage of fat mass 4.2 ± 2.4%. Amenorrhea was present in 48.9% ($n=22$), euthyroid sick syndrome in 15.6% ($n=7$), hypogonadotrophic hypogonadism in 51.1% ($n=23$), anemia in 33.3% ($n=15$) and leukopenia in 37.8% ($n=17$). Sinus bradicardia was the most common electrocardiographic finding (22.2%, $n=10$). Bone densitometry documented osteopenia and osteoporosis in 57.1 and 31%, respectively. Admissions had a mean lenght of stay of 44 ± 20 days, and patients had a mean increase in BMI of 1.7 ± 2.3 kg/m^2. Readmission was needed in 35.6% of cases ($n=16$), due to failure to increase weight.
Conclusion
The main indication for admission was the low weight. The most frequent endocrine complications were low bone mass (88.1%), hypogonadotrophic hypogonadism (51.1%) and euthyroid sick syndrome (15.6%). Although prolonged, hospitalization was useful, with improvement in clinical and analytical parameters. These patients need a careful monitoring due to the substantial risk of relapse.

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EP122

Osteoporosis therapy with denosumab in patients after solid organ transplantation

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Introduction
The transplantation- associated osteoporosis became an increasingly important problem with the better survival of patients after the solid organ transplantation (Tx). Adequate vitamin D intake, calcium supplementation and bisphosphonates therapy are currently recommended for osteoporosis treatment. However bisphosphonates may be limited with patients' impaired renal function. Denosumab use is the possible option but till now only a little data exist in solid organ transplant population.
Patients and methods
We investigated 46 patients (M 19, F 27) mean age 56.2 y after solid organ transplantation with mild renal impairment treated with Denosumab inj. 60 mg every 6 months in years 2012–2015 with the mean duration of therapy 1.25 years. The osteoporosis was diagnosed with densitometry (DEXA) using Lunar Prodigy apparatus. Simultaneous pancreas and kidney Tx had 13 patients, liver transplantation 15 patients, solitary kidney Tx 16 patients and two patient underwent heart Tx. We have also measured on the plain CXR the clavicle bone index (BI) at the midpoint of the shaft. BI <0.5 represents osteoporosis.
Results
Osteoporosis of L spine was present in 34/46 patients (74%), hip osteoporosis in 23/46 patients (50%) and in distal radius in 23/46 patient (50%). The bone density of L spine improved in 33/34 (97%) with mean increase in BMD 9.8%, BMD of hips improved in 23/23 patients with osteoporosis, with mean increase 8.0%. Only in two patients with hips osteopenia of BMD decreased. BMD of distal radius improved in 28/44 (64%) patients and decreased in 16/44 (36%) patients after the therapy. Clavicle bone index (measured in 30 patients) was 0.367 and did not change significantly. The therapy with denosumab was well tolerated and we did not register any complications.
Summary
Denosumab therapy improved bone density in osteoporotic patients after solid organ transplantation and was well tolerated.

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EP123

Osteoporosis as a side effect of antineoplazic therapy

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Objective
The aim of this retrospective study is to evaluate the bone status in patients receiving oncological treatment, like radiation, chemotherapy, adjunctive therapies, and surgery.
Material and methods
Medical records of 102 womens (mean age 59.12 yrs) with breast cancer history reffered for endocrine evaluation were retrospectivelly analysed. Demographic data, bone densitometry parameters, prevalent fractures and antineoplastic treatments history were collected.
Results
All of the patients had history of breast surgery and chemotherapy; 10% had also radiotherapy and 87% had a form of hormone suppresive treatment. According to the lowest *T* score, 33% had densitometric criteria for osteoporosis and 55% had osteopenia; 13.1% of the subjects had prevalent fractures at the evaluation moment. 31% of the patients had the lowest *Z* score less than -1S.D. in the absence of early menopause. According to our data, the prevalence of decrese in BMD in serial mesurements was 40.5% in chemotherapy only patients, 62% in AI only patients and 37.5% in patients with sequential combination between SERM and AI. Only four patients out of 34 osteoporotic patients received treatment for their osteoporosis.
Conclusion
Our data suggest an increased prevalence of decrease in BMD in patients related to their history of antineoplazic treatments; from all the combinations, chemotherapy alone had almost the same effect as sequential combination of SERM and AI and the most agresive for the bone was proved to be chemotherapy and AI treatment.

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EP124

Bone mineralization and hormonal status in Turner syndrome patients: cross sectional one population study

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Introduction
Women with Turner syndrome (TS) are known to be at risk of decreased BMD (dBMD). Sex hormone replacement therapy is crucial to ensure the proper BMD formation, although the dBMD remains a problem in TS.
Aim
To investigate the prevalence of decreased bone mineralization and it's association with hormone levels in TS.
Subjects
Women with geneticaly confirmed TS aged $\geq$ 18 year.
Methods
There were 53 women with TS enrolled into the prospective study. To assess the BMD dual – energy – X-ray absorptiometry (DEXA) parameters were analysed. Z-score ≤ -2.0 S.D. was defined as dBMD (International Society for Clinical Densitometry guidelines). The lowest value of Z-score in the spine or in the neck of femur was included into the analysis. The correlations between BMD and the levels of Testosterone (T), Estradiol (E), Thyroid stimulating hormone (TSH), calcium (Ca+), ionized calcium (Ca2+), body mass index (BMI), final height (FH), the duration of E use (DE), were assessed.
Results
Mean age of participants was 29.06 ± 7.19 year. Mean FH was 152.33 ± 6.21 cm, mean weight 57.19 ± 11.40 kg, (mean BMI 24.59 ± 4.82 kg/m^2), mean BMD was 0.787 ± 0.144 g/cm^2. dBMD was diagnosed in 26.5% ($n=13$) of TS, normal BMD was found in 73.5% ($n=36$). The significant correlation between BMD and BMI was observed ($r=0.309$, $P=0.039$). The significant negative correlation between DE and Ca+ ($r=-0.317$, $P=<0.05$) was found. There was no correlation between BMD and T, E, TSH levels.
Conclusions
BMI has positive effect on BMD in TS patients. No relationship between sex hormone, TSH, calcium concentrations and BMD was identified in this study.

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EP125

Osteoporosis in a cohort of 1062 postmenopausal women

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Osteoporosis is a worldwide public health problem, particularly in ageing subjects The objectives of this study were to screen a sample of postmenopausal women aged >45 years for osteoporosis and to identify its risk factors.
Methods
This cross-sectional survey was conducted at the endocrinology department of the Bologhine hospital in Algiers, Algeria. A total of 1062 postmenopausal women participated in this study. Each subject completed a questionnaire designed to identify the different etiologies and to document putative risk factors of osteoporosis. Calcium intake was evaluated using self-report by Fardellone frequency questionnaire. Bone mineral density was measured on 3 sites (lumbar spine, femoral neck and total hip). Patients were classified as osteopenic, osteoporotic or normal according to WHO diagnosis criteria.
Results
The prevalence of osteoporosis according to the NHANES and OFELY reference curves were 35.9 and 29.4%, respectively.
Among the evaluated risk factors, age, puberty, parity, weight and personal history of fracture were found to be major determinants of low BMD.
Mean age of women was 61.11 ± 8.49 years. Mean BMI and weights were 29.53 ± 5 kg/m^2 and 73.07 ± 13.34 kg, respectively. Mean age of puberty was 13.48 ± 1.64 years and the mean number of pregnancies was 5.20 ± 3.68. A history of fracture was noted in 281 patients.
Conclusion
Osteoporosis was frequent in our sample, and was mainly associated with certain potential risk factors which were validated in epidemiological cohorts.

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EP126

Osteoporosis and type 2 diabetes

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Diabetes mellitus and osteoporosis are important comorbidities commonly seen in postmenopausal women. Diabetes can cause bone alterations that increases the risk of fractures. However, in patients with type 2 diabetes, bone mineral density (BMD) often appears not to be decreased, due to diabetes-induced increased weight and body fat mass, which can hamper densitometric assessment of osteoporosis and of fracture risks. The aim of the present study was to compare bone mineral density (BMD) in two samples of postmenopausal women with and without type 2 diabetes.
Methods
This was a cross-section study conducted at the Bologhine Hospital of Algiers (Algeria). The study group consisted of 195 women with type 2 diabetes, recruited from an original sample of 1062 patients (age > 45 years) who were screened for osteoporosis in postmenopausal women. Lumbar spine and femoral neck BMD and other relevant clinical data were compared to those of a control group ($n=867$) comprising the women who did not have diabetes.
Results
Women with type 2 diabetes had significantly higher mean lumbar spine BMD (0.9 ± 0.1 vs 0.8 ± 0.1, respectively, $P<.0.019$) than non-diabetic women. But no difference in mean femoral neck BMD (0.7 ± 0.1 vs 0.7 ± 0.1, respectively, P: 0.81) was observed. The proportion of osteoporotic women was 27.7% in the group of women with type 2 diabetes, vs 29.8% in the control group.
Conclusion
Our findings support those of other studies that found higher BMD in patients with type 2 diabetes compared to the general population.

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EP127

State of bone mineral density in children with Turner Syndrome in Ukraine.

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Background
Low bone mineral density (BMD) and osteoporosis are the frequent consequences of Turner Syndrome (TS).
Objective and hypotheses
We examined the BMD in TS girls with different age and karyotype.

Methods
Measurements of BMD (g/cm^2), Z-score (S.D.) were conducted in 26 girls using X-ray absorptiometry (DEXA) at the lumbar spine L2–L4 depending on the child's age.
Results
According to the National registry of TS in Ukraine there are 453 girls with TS, aged 11 months-18.2 years. The prevalence is 77.5 per 100 000 live female new-borns or 0.06 per 1000 child population 0–18 year. Normal BMD (Z-score (−) 0.26±0.75 S.D.) had 23.13% patients, osteopenia (Z-score (−) 1.73±0.43 S.D.) − 46.21% and osteoporosis (Z-score (−) 2.86±0.41 S.D.) − 30.66% of girls. The smallest age, at which we recorded osteopenia was 9.3 year.

Table 1 State of bone mineral density in children with TS with different karyotype.

Karyotype	45,X (n=18)	45,X/46,XX (n=4)	X-chromosome structural abnormalities (n=4)	P
BMD (g/cm^2)	0.80±0.09	0.81±0.10	0.99±0.24	(P>0.05)
Z-score (SD)	(−)1.72±1.12	(−)1.30±1.53	(−)1.45±1.90	(P>0.05)

In patients with TS were determined statistically significant inverse correlation between age and Z-score (r=(−) 0.46, P<0.05), as well as between the level of FSH and Z-score (r=(−) 0.81, P<0.05).
Conclusion
Karyotype has not impact on BMD, osteopenia is present in all girls with different variants of karyotype. In girls with TS the degree of bone metabolism disorders progresses with age and degree of estrogen deficiency.

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EP128

Osteocalcin as a marker of bone metabolism disorders in girl with Turner syndrome

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Background
One of the markers of bone metabolism is osteocalcin (OC) and Its elevated level indicates osteoporosis.
Objective and hypotheses
We investigated the OC level in 14 girls with TS (45,X (n=8), 45,X/46,XX (n=3), structural abnormalities of chromosome X (n=3): seven patients at 4–11 year and 7 – at 12–18 year.
Method
DEXA (Z-score, S.D.), serum levels of OC, FSH, LH, estradiol.
Results
We observed violations of bone tissue by DEXA at 76.87% girls with TS: namely the osteoporosis - at 30.66%, osteopenia - at 46.21%. Mean OC levels did not differ significantly in girls with TS, aged 4–11 year (98.59±41.11 ng/ml) and 12–18 year. (91.98±51.83 ng/ml, P>0.05), but were higher than children in control age group: 46.23±12.43 ng/ml (P<0.05), and 51.12±22.64 ng/ml (P<0.05), respectively. No significant differences were found of OC level in patients with different karyotype: 45,X - 102.00±36.62 ng/ml, 45,X/46,XX- 53.92±46.04 ng/ml and structural abnormalities of chromosome X-117.59±55.30 ng/ml (P>0.05). No statistically significant association was found of OC level with the content of FSH, LH, estradiol, the degree of bone metabolism (Z- score). At the same time the OC level was higher than the age normal in 60.03% of TS girls over 12 years, and was normal in all patients 4–11 yrear. OC level was elevated in 100% patients with osteoporosis (Z- score > (−)2.5 S.D.) and in 75.0% - with osteopenia (Z-score of (−) 1.0–2.5 S.D.).
Conclusion
The level of the OC in girls with TS was not dependent on its age, karyotype and content of sex hormones. In 71.43% of all girls with TS and in 100.0% with osteoporosis OC level was higher than the normal age indices. Research OC should be carried out to all girls with TS for early detection of osteoporosis and holding his treatment.

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EP129

Adrenal tumors in menopause: bone assessment

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Introduction
Menopause correlates endocrine dysfunctions; whether an adrenal incidentaloma represents one of these it is difficult to establish since an age-dependent pattern of incidence has been described. Bone assays are necessary according to years since last menstruation but also if persistent hypercortisolemia is confirmed.
Aim
This is a series of cases incidentally found with an adrenal tumor (AT) and osteopenia while evaluation of their menopausal status.
Results
Sixty six year female accuses intermittent hot flushes and recurrent urinary infections. The menopause's age is 49. She associates lupus erythematosus, diabetes mellitus, an episode of stroke, and high blood pressure. A right AT was accidently discovered at ultrasound. CT scan confirmed a mass of 1.6/1.9 cm. The endocrine assay revealed non-secretor pattern: normal aldosteron/rennin ratio, suppression of plasma morning cortisol (of 1.8 μUI/ml) after 2 days×2 mg Dexametasone (DXM) with low-normal morning ACTH of 15 pg/ml (N:3–66 pg/ml), plasma metanephrines and normetaneprines within normal ranges (of 29.2 pg/ml, N:10–90 pg/ml, respective of 51.4 pg/ml, N:15–180 pg/ml). Bone profile pointed low 25-hydroxyvitamin D=8.52 ng/ml (N:30–100 ng/ml), and lowest DXA BMD at femoral neck=0.879 g/cm^2, T-score=−1.1 S.D., Z-score=−0.1 S.D.
Eighty three year female is diagnosed since menopause (at age of 50) with calcified myomas. An ultrasound (and later CT scan) revealed a left AT of 3.7/2.5/3.4 cm. She presented normal medullo-adrenal function, as well as aldosteron/rennin ratio. However, a subclinical hypercotisolemia was confirmed and persisted for more than a decade (a value of plasma cortisol of 3 μg/dl after 2 days×2 mg DXM, ACTH of 3.15 pg/ml). Adrenalectomy was refused. Bone profile was also investigated since the diagnosis of AT: osteopenia was stationary during follow-up (lumbar BMD of 0.789 g/cm^2, T-score=−1.8 S.D., Z-score=−0.1 S.D.) in association with vitamin D deficiency.
Conclusion
Adrenal tumors-related bone anomalies are more pronounced in menopause correlated with physiological lack of estrogens. Mild persistent cortisol levels may play a role in low BMD; however the exact component is difficult to establish in this particular population.

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EP129B

Similarities in postsurgical vs nonsurgical patients with hypoparathyroidism: post hoc analysis from recombinant human parathyroid hormone (rhPTH[1-84], parathyroid hormone rDNA) REPLACE study

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Hypoparathyroidism, a rare disorder characterized by absent or low levels of parathyroid hormone (PTH), often results from thyroid surgery. However, nonsurgical etiologies are present in >10% of patients. Data about this group of patients are limited.
In this *post hoc* REPLACE (NCT00732615, EudraCT2008-005063-34) analysis, baseline characteristics and response to 50–100 µg/day rhPTH(1-84) in patients with postsurgical or nonsurgical hypoparathyroidism were evaluated. Demographic and baseline characteristics were compared between groups with chi-square tests for categorical variables and one-way analysis of variance with effect for continuous variables. Responders were defined as patients whose need for conventional treatment with oral calcium and active vitamin D was reduced by ≥50% while maintaining serum calcium at 2.00–2.25 mmol/l.
Of 124 randomized patients, 89 (72%) had postsurgical and 35 (28%) had nonsurgical hypoparathyroidism. Interestingly per criteria in the 2015 ESE guidelines, ≥80% of patients within each subgroup were not well controlled pre-rhPTH(1-84) even after optimization with conventional treatment. Overall, there were more similarities than differences between the two groups. The only significant differences between groups were male gender (9/89 [10%] vs 17/35 [49%]; $P<0.0001$), age at onset (49.1 vs 42.9 years, $P=0.014$), and time since diagnosis (12.1 vs 17.5 years, $P=0.008$). At baseline, mean (S.D.) serum intact PTH levels were 0.79 (0.94) and 0.37 (0.48) pmol/l in the postsurgical and nonsurgical groups, respectively; healthy adult range is 1.48-7.63 pmol/l. In the postsurgical group, the 58% responder rate with rhPTH(1-84) (35/60) was significantly higher than the 3% rate with placebo (1/29; $P<0.001$). In the nonsurgical group, the 46% responder rate in the rhPTH(1-84) group (11/24) was numerically higher than the 0% placebo group rate (0/11; $P=0.007$).
This post hoc analysis did not suggest any differences in response to PTH(1-84) based on etiology of hypoparathyroidism.

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EP130

Long-term use of steroid and secondary ostoporosis to multiple displaced metatarsal stress fracture: with rheumatoid arthritis a case report

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Introduction
In rheumatological diseases have been observed in a rate of 0.8% of non-traumatic insufficiency fractures. The most common sites of insufficiency fractures are pelvis, sacrum, tibia, the sections near to the insertion of the fibula, calcaneus and buttocks. Generally, bone – joint involvement in rheumatic diseases and osteoporosis connected with prolonged use of corticosteroids prepares the ground for these insuffiency fractures. In this case, We aimed to present the metatarsal fractures which we have identified in an unexpected localization in a patient the diagnosis of rheumatoid arthritis who has been secondary osteoporosis for a long time use of low-dose steroids.
Case Presantation
Approximately for 12 years with a diagnosis of Rheumatoid Arthritis, 53-year-old male patient admitted because of the starting complaints pain and swelling in his left foot since 25 days. The patient was using low-dose corticosteroids without a break since approximately the last two years. In the verified surveys, performed in and was verified avascular necrosis of the talus and common arthritic changes depend on Rheumatoid Arthritis foot- ankle involvement, there were sensitiveness with palpation and swelling in the metatarsal region of the patient's examination. In radiography,it was seen the displaced of 2nd, 3rd, 4th metatarsal basis' and nondisplaced fracture line in his 5th metatarsal basis, it was intact of lisfrank joint.
The patient's L1–L4 *T*-score was found of −3.2. The was learned that ever now the patient didn't receive any treatment about osteoporosis. The patient which treated of orthopedic aspects, was started Alendronate sodium 70 mg and 2800 IU Vitamin D_3 treatment
Discussion
The frequency of osteoporosis in patients with rheumatoid arthritis (RA) ranges from 4 to 24% and the frequency of osteopenia ranges from 28 to 61.9%. Glucocorticoid use was associated with decreased bone mass in 56.2% of subjects with RA.

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EP131

Barrett's esophagus and osteopenia: Report of a case

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Introduction
Barrett's esophagus is metaplasia in the cells of the lower end of the esophagus. It is characterized by the replacement of the normal stratified squamous epithelium lining of the esophagus by simple columnar epithelium with goblet cells. The disease is often related to gastroesophageal reflux and patients have pain necessitating chronic usage of proton pump inhibitors. Proton pump inhibitors have been associated with the development of low bone mineral density.
Aim
The aim was to describe the case of a patient with Barrett's esophagus and chronic proton pump inhibitor usage who developed osteopenia.
Case report
A male patient aged 67 presented with diffuse musculoskeletal pain. He had a 10 year history of Barrett's esophagus. He was being followed for Barrett's esophagus and had been taking proton pump inhibitors for the treatment of pain. Laboratory investigations performed revealed $25(OH)D_3$ 33 ng/ml (normal values >30 ng/ml). Radiology of the spine revealed osteopenic vertebrae. Bone mineral density was measured and revealed a *T* score of −2.3. The patient had normal testosterone levels and a negative family history of osteoporosis. Vitamin D and calcium orally were administered.
Conclusion
The administration of proton pump inhibitors appears to be associated with low bone mineral density and an increased fracture risk (Fournier *et al.* 2009, Fraser *et al.* 2013). In patients with chronic, albeit benign, gastrointestinal disorders, care should be taken that treatment with proton pump inhibitors be limited to the needs of the patients, thus preventing a skeletal side effect, such as osteoporosis.
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EP132

Osteoporosis and recurrent pathological fractures associated with intense cannabinoid use: a case report

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Introduction
Cannabis/marijuana/cannabinoids are the most commonly used illicit drug in the world which can be originated from plants or can be in synthetic forms. Here, an intensive marijuana smoker, 33 years old patient, who has osteoporosis with recurrent pathologic fractures will be presented.
Case
Thirty-three-years-old male patient was referred to the our clinics in order to investigate the causes that may lead a pathologic fracture because the patient had the tibia and fibula fracture without any obvious trauma. The patient's blood calcium, phosphorus, alkaline phosphatase, vitamin D and parathyroid hormone levels were normal. There were no signs and symptoms that can be suggestive of malignancy. Excluding the secondary osteoporpsis reasons. Bone mineral density was measured with dual-energy X-ray absorptiometry (DXA) and *T*-score of L1–L4 = −2.9, *T*-score of the femoral neck = −2.3. We asked him whether he uses any drug for any reason. He answered that he had started to use cannabis when he was fourteen and since then, he has been using the canabinoid as 19–20/day in the form of cigarettes additionally in the form of inhalation and sometimes synthetic forms. He said he had treated for the broken bones (one time for his hand and one time for his foot) twice by an orthopedist before this event. Pathological fractures of the patient were attributed to his intensive cannabis smoking.
Conclusion
Important roles of the cannabinoid receptors during osteoporosis process have been shown by the investigators. We considered our case as cannabinoid-induced osteoporosis.

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EP133

Paget's disease of bone - case report and a review of epidemiology, pathophysiology and management

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Introduction
Paget's disease of bone (PDB) is the second-most-common metabolic bone disease, after osteoporosis, affecting about 3% of the population at age over 40 years. This disease is characterized by excessive and abnormal bone remodeling due to increased bone resorption followed by disorganized bone formation.
This paper will include a case report and a review of PDB epidemiology and pathophysiology, complications and clinical findings, indications for treatment, and the drugs currently available to treat this condition.
Case report
Sixty four years old woman, who addressed to our department in March 2011 for chronic left hip and low back pain, with insidious onset which has increased over time, fatigue, headaches attacks with occipital localization associated with dizziness and intracranial pressure. The evaluation of phospho-calcic metabolism showed normocalcemia, hypophosphatemia, normocalciuria, hyperphosphaturia, normal serum parathyroid hormone level, 25-hydroxy vitamin D level decreased (19 ng/ml) and alkaline phosphatase level increased (572 U/l). Bone scintigraphy revealed intense uptake of radiopharmaceutical in the left femur. The bones X-rays and computed tomography of the left femur showed marked thickening and sclerosis of cortical bone with inhomogeneous ossification of bone structure, osteolysis and small subchondral cystic lesions. Medical treatment was initiated with alendronate, calcium and vitamin D, with favorable evolution during the next months. Long term follow-up is required for monitoring related complications.

Keywords: Paget's disease of bone, bone resorption, alendronate
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EP134A

Depression, Obesity, and Elbow Fracture; a Pathogenic Triangle?

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Introduction
Depression and associated medication, especially Selective Serotonin Reuptake Inhibitors, may associate high fracture risk through serotonin (but not only). Obesity has been recently proved to be correlated with a higher fracture risk for a few sites as ankle, elbow, shoulder, etc. Moreover, depression and some anti-depressants may increase the calories intake and consecutive increased of Body Mass Index (BMI) is registered.
Aim
We present a fragility fracture medical history in a context of depression and obesity as only obvious causes of osteoporosis.
Material and Methods
The bone profile is analyzed in this case report.
Results
Fifty seven year old non-smoking female patient was diagnosed with multi-nodule goiter at age of 49 and total thyroidectomy was performed. Substitution with daily levothyroxine was continued up to present with consecutive normal TSH levels.
Menstruation stopped at 50 years; she suffered of chronic headache. At age of 53 she was diagnosed with depression and she was offered different types of anti-depressive medication for almost 3 years. At age of 56 she suffered a left elbow fracture and the circumstances of fall indicated an osteoporotic type.
Endocrine check-up was done at that moment. The patient had a BMI of 40 kg/m^2; 25-hydroxyvitamin D assay showed an inadequate level of 20.8 ng/ml (N:30–100 ng/ml), with normal bone turnover markers: blood CrossLaps of 0.44 ng/ml (N:0.226–1.008 ng/ml), blood osteocalcin of 25.71 ng/ml (N:15–46 ng/ml), and circulating serotonin of 280 ng/ml (N:80–450 ng/ml). Dual-Energy X-Ray Absorptiometry showed lumbar L1-4 Bone Mineral Density (BMD) of 1.049 g/cm^2, *T*-score = −1.1 S.D., *Z*-score = −1.4 S.D. Weekly oral risendronat with daily vitamin D/calcium supplements were followed for 1 year: BMD increased to 1.14 g/cm^2, *T*-score = −0.3 S.D., *Z*-score = −0.5 S.D.
Conclusion
Obesity and depression might associate vitamin D deficiency. Depression and anti-depressants may act on fall risk by attention and gait anomalies. However, both conditions may be not associated relevant BMD changes.

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EP134B

Negative correlation of osteocalcin with insulin resistance, but not with body fat, in lamin-mutated lipodystrophies

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Bone is involved in both phosphate-calcium and energetic metabolism. Osteocalcin, secreted by the osteoblasts, stimulates insulin secretion and improves insulin sensitivity. FGF-23, secreted by the osteoclasts, increases phosphate urinary excretion and is a marker of insulin resistance. Relationship between insulin-resistance, body fat and bone metabolism remains unclear. Therefore, the aim of this study was to evaluate osteocalcin and FGF-23 levels in diseases differing by body fat and insulin resistance levels, using lipodystrophies, as a model of insulin-resistance without obesity, obese people with and without insulin-resistance, and control subjects.
The population, recruited from the PHRC-Clin.gov2009-AO-1169-48 trial, was divided in five groups: *LMNA*-mutated lipodystrophies (LDM, $n=11$), non-mutated lipodystrophies (LDNM, $n=21$), obese diabetic patients (OD, $n=13$), obese non-diabetic patients (OND, $n=13$), normal-weighed controls (T, $n=19$). Bone and metabolic biomarkers, as well as DEXA-assessed body composition were compared between these five groups.
Osteocalcin, crosslaps, leptin, BMI, body fat mass, lean-body-mass/height^2, fasting blood glucose and C peptide, HbA1c and HOMA-IR levels were

significantly different between the five groups, with a trend for *T*-score, calcemia and 25-OHD. Blood phosphate, PTH, FGF-23 and urinary calcium levels were similar.
The two-by-two groups comparison showed a lower level of osteocalcin in the LDNM (median (IQR): 12 (11–14) ng/ml) and LDM (14 (12–19)) groups compared to controls (24 (23–29)), and in the LDNM compared to OND (17 (13–21)) groups. Osteocalcin was correlated positively to crosslaps ($r=0.74$, $P<0.0001$) and negatively to HOMA-IR (LDNM:4 (0.6–11); LDM:3 (2–5); OD:4 (3–6); OND:1.6 (1–3); T:1.1 (0.8–1.4); $r=-0.50$, $P<0.0001$), lean-body-mass/height^2 ($r=-0.41$, $P=0.0003$) and *T*-score ($r=-0.35$, $P=0.0024$), but not to body fat or leptin (LDNM:15 (8–22); LDM:6 (4–12); OD:27 (24–41); OND:49 (32–67); T:5 (4–12) ng/ml).
Conclusion
The comparison of subjects differing by the level of insulin-resistance and body fat, two characteristics often confounded, shows that osteocalcin is negatively correlated with insulin-resistance and *T*-score, without any influence of body fat or leptin. The role of lean mass in the regulation of osteocalcin has to be further investigated.

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Calcium and Vitamin D metabolism

EP135

From pseudohypoparathyroidism to inactivating PTH/PTHrP signaling disorder (iPPSD), a novel classification proposed by the European EuroPHP-network

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Background
Disorders caused by impairments in the parathyroid hormone (PTH) signaling pathway are historically classified under the term pseudohypoparathyroidism (PHP), that encompasses rare, related but highly heterogeneous diseases with demonstrated (epi)genetic causes. The actual classification is based on the presence or absence of specific clinical and biochemical signs together with an *in vivo* response to exogenous PTH and the results of an *in vitro* assay to measure Gsα protein activity. However, this classification does not take into consideration other related diseases like acrodysostosis (ACRDYS) or Progressive Osseous Heteroplasia (POH), as well as recent findings of clinics and genetic/epigenetic background of the different subtypes.
Objective
The EuroPHP network decided to develop a new classification that encompasses all disorders with impairments in PTH and/or PTHrP cAMP-mediated pathway.
Design and Methods
Extensive review of the literature was performed. Several meetings were organized to discuss about a new, more effective and accurate way to describe disorders caused by abnormalities of the PTH signaling pathway.
Results and Conclusions
After choosing major and minor criteria that need to be considered for the diagnosis of these disorders, we propose to group them under the term of 'inactivating PTH/PTHrP signaling disorders', (iPPSD). This terminology: 1) defines the common mechanism responsible for all diseases, 2) does not require a confirmed genetic defect, 3) avoids ambiguous terms like "pseudo", 4) eliminates the clinical or molecular overlap between diseases. We believe that the use of this nomenclature and classification will facilitate the development of rationale and comprehensive international guidelines for the diagnosis and treatment of iPPSDs.

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EP136

Vitamin D deficiency in pregnancy associates with increased emotional and behavioral problems at preschool age: the Rhea pregnancy cohort, Crete, Greece

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Background and aims
Vitamin D deficiency during the perinatal period has been hypothesized to increase risk for several psychiatric disorders in humans. As newborn vitamin D levels are entirely dependent on maternal vitamin D status, vitamin D deficiency in utero may leave the infant vulnerable to cognitive defects and behavioral problems. Few human studies have examined these associations with inconclusive results. We aimed to investigate the associations of maternal 25-hydroxyvitamin D [25(OH) D] levels with offspring neurodevelopment at 4 years of age, using data from a longitudinal, prospective pregnancy cohort, 'Rhea' study in Crete, Greece.
Design and methods
We included 471 mother-child pairs. Maternal vitamin D status was estimated by measuring plasma concentration of 25(OH) D at the first prenatal visit (13 ± 2.4 weeks). Cognitive function at 4 years was assessed by means of the McCarthy Scales of Children's Abilities (MSCA). Emotional and behavioral development at 4 years was assessed by means of Strengths and Difficulties Questionnaire (SDQ) and Attention Deficit Hyperactivity Disorder (ADHD) Test. Multivariable linear regression analyses were used to estimate the effect of maternal vitamin D status on child neurodevelopment.
Results
Maternal vitamin D deficiency during early pregnancy was associated with a significant score increase in total SDQ (b-coef: 2.07, 95%CI: 0.25, 3.89) scale and specifically in peer relationship problems (b-coef: 0.58, 95%CI: 0.03, 1.12) and hyperactivity/inattention (b-coef: 1.15, 95%CI: 0.36, 1.94) subscales at 4 years of age. Similarly maternal vitamin D deficiency was associated with five points increase in the total ADHD score (b-coef: 5.36, 95%CI: 0.75, 9.98), and two points increase in the hyperactivity subscale score (b-coef: 2.26, 95%CI: 0.25, 4.26) at 4 years of age. Maternal thyroid function in pregnancy or maternal obesity did not modify the observed associations.
Conclusion
Vitamin D deficiency in early pregnancy was associated with increased emotional and behavioral problems at preschool age.

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EP137

Mass Spectrometry coupled with liquid chromatography (HPLC-MS-MS) levels of 25-hydroxy vitamin D (25OHVitD) are associated with prognostic markers of Heart Failure

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Introduction and aims
Heart failure (HF) is a health problem with poor prognosis, despite many treatments available. Vitamin D is the pre-hormone of the active calcitriol (1,25(OH)2D3). It is involved in bone homeostasis, but recent studies suggest extraskeletal functions, including pleiotropic effects on cardiovascular system and

a relationship between low levels of 25OHvitamin D and worse HF prognosis. The aims of the study were: 1) to define 25OH-D levels in the HF population, 2) to correlate25 OHD levels and HF outcome markers (biochemical and instrumental evaluation) in the hypothesis that vitamin D represents a potential modifiable factor risk in HF.
Materials and Methods
We performed a retrospective study on 261 consecutive HF patients (NHYA1-3), collecting clinical, biochemical and instrumental data (echocardiography and cardiopulmonary exercise test – CPET). We retrieved stored blood samples collected at the baseline and developed a fast isotope dilution Mass Spectrometry coupled with Liquid Chromatography (HPLC-MS-MS) method for accurate measurement of 25OHvitaminD levels.
Results
Patients were 47 females and 214 males (ratio M:F = 4:1), with a mean age of 65 ± 12 years and mean BMI of 28 ± 14. They had stable HF disease in prevalent NYHA2 class. Mean EF (ejection fraction) was 33 ± 8%; patients had mild kidney failure (creatinine 1.12 ± 0.3 mg/dl) and they were normocalcemic and normo PTH. Levels of 25OH vitamin ranged 2–45 ng/ml, with mean of 17 ± 9 ng/ml. Twenty-five pecent ($n = 65$) patients had vitamin deficiency (< 10 ng/ml), 62% ($n = 161$) had vitamin insufficiency (between10 and 30 ng/ml) and 13% ($n = 35$) had vitamin > 30 ng/ml, without any supplementation. The linear regression analysis showed that 25OHvitaminD levels were positively correlated with CPET paramethers and negatively with mortality Mecki score and this relation was even stronger in patient with Vitamin D insufficiency.
Conclusion
Our study revealed a strong association between variables from CPET, a well-recognized valuable tool for HF prognosis and 25OHvitaminD levels, detected with a new and accurate method, HPLCMS-MS.

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EP138

Increasing incidence of parathyroid carcinoma – a nationwide study

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Introduction and design
Parathyroid carcinoma (PC) is a rare endocrine malignancy and the diagnosis is difficult. As the incidence seems to be increasing, we examined all cases diagnosed in our country during years 2000–2011 and compared the results to those of atypical parathyroid (AA; $n = 28$) and parathyroid adenomas (A; $n = 72$). All tissue specimens were re-examined.
Results
In 2000–2011, 32 patients were diagnosed with PC in Finland, compared to 19 cases in 1980–1999. Preoperatively, PC patients (median age 61 year, range 17–83) had higher ionized calcium and parathyroid hormone (PTH) concentrations compared to AA and A (1.76, 1.56 and 1.44 mmol/l, $P < 0.001$; and 989, 355 and 160 μmol/l, $P < 0.001$ respectively). They were more often hospitalized for severe hypercalcemia (44% vs 22% and 3%, respectively, $P = 0.01$) and more often suffered from renal (50% vs 48% vs 22%, respectively, $P = 0.01$) and bone involvement (47% vs 15% vs 38%, respectively $P = 0.002$).
Tumor size was larger in PC and AA compared to A (2.95 cm vs 2.0 cm vs 1.6 cm, respectively, $P < 0.001$). Histopathology revealed significant differences in growth patterns, prevalence of fibrous septae, hemosiderin deposits, Ki-67 and parafibromin staining between the subgroups. The hallmarks of PC, i.e vascular, capsular and perineural invasion were present in 72, 72 and 9% of PC tissue specimens, respectively. After primary surgery and a median follow-up of 6.7 years, 9.4% of PC patients had residual and 21% recurrent disease (47% had ≥ 2 operations, 22% radiotherapy, 13% chemotherapy), and 9.4% died of the disease. Overall mortality did not differ between the subgroups ($P = 0.94$).
Conclusions
The prevalence of parathyroid carcinoma has increased significantly in Finland. Parathyroid carcinoma associates with significantly more severe PHPT compared to adenoma, and has distinct histopathological findings.

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EP139

Abstract withdrawn.

EP140

Familial hypocalciuric hypercalcemia secondary to a novel mutation causing severe hypercalcemia

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Introduction
Familial Hypocalciuric Hypercalcemia (FHH) is a benign autosomal dominant condition caused by an inactivating mutation on the gene coding for the Calcium Sensing Receptor (CASR). CASR plays a role in regulating parathyroid secretion and calcium metabolism. The majority of adults with FHH are asymptomatic. This is a case of three young brothers whose genetic tests shows two mutations in each of their CASR gene leading to hypercalcemia and varying symptoms.
Case
A 20-year-old man was being investigated for a non-epileptic seizure and an incidental finding of a serum calcium 3.21 mmol/l was found. On further questioning, he had been complaining of muscle aches, joint pains and fatigue. Subsequent investigations showed paired PTH 2.1–4.6 nmol/l, PTHrP < 0.7, calcium excretion index 0.006 – 0.0006 and 24 h urine calcium of 1.6 mmol/24 h. His sestambi scan revealed no parathyroid adenoma and his DEXA scan showed osteopenia. A detailed family history was obtained indicating his mother had suffered from renal stones secondary to hypercalcemia. His siblings were also tested which revealed two brothers with hypercalcemia. Interestingly, the symptoms vary with his brothers, with one being asymptomatic. Genetic testing in all three have revealed the same two mutations for each brother:
Heterozygous for c.553C > T (p.Arg185X)
Heterozygous for unclassified variant c.1375C > A (p.Gln459Lys)
This second mutation is an unknown variant, which has not been reported in literature. Genetic testing of the parents has shown one altered copy gene in each. First line treatment, Cinacalcet has been used for the symptomatic brothers with one brother showing benefit.
Conclusion
This case illustrates a novel double heterozygous affecting each brother differently. Considering most cases of FHH are asymptomatic, two of the kindred are severely affected as in neonatal hyperparathyroidism. The next step would be to consider a parathyroidectomy to reduce complications.

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EP141

Idiopathic infantile hypercalcemia: presenting in childhood, diagnosed in adulthood – case report

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Introduction
Hypercalcemia can be caused by a variety of pathologies/factors. Vitamin D plays a central role in calcium homeostasis, where a tight control of its metabolism is

necessary. Inadequate 24-hydroxylase-enzime (CYP24A1) activity leads to failure of 25-hydroxyvitamin and 1,25-dihydroxy-vitamin D3 inactivation, resulting in hypercalcemia.
Case report
An asymptomatic, 22-year-old woman was admitted in an Endocrinology appointment for evaluation of persisting hypercalcemia (10.5–11.6 mg/dl). Medical history revealed that the patient suffered a transient period of polyuria during childhood (4–5-years-old), diagnosed as recurrent cystitis. Currently without any known disease or medication. Born to nonconsaguineous parents; no other known familial cases. Further evaluation revealed: hypercalciuria, suppressed parathyroid hormone (PTH) and elevated 1,25-dihydroxy-vitamin D3; with normal levels of 25-hydroxyvitamin D3, serum phosphorus, creatinine and angiotensin converting enzyme. A renal ultrasound demonstrated medullary nephrocalcinosis. Sequence analysis of the CYP24A1 gene was performed, revealing the patient has two mutations in heterozygosity: c.1186C > T(p.Arg396Trp) and c.1226T > C(p.Leu409Ser). Analytic and genetic study of first-degree relatives was performed. The father is homozygous for the c.1186C > T(p.Arg396Trp) mutation, with decreased level of PTH. The mother is a carrier of the c.1226T > C(p.Leu409Ser) mutation, in heterozygosity; with normal analytic evaluation. A 15-year-old sister has the same two mutations as the patient, with hypercalcemia, decreased PTH and medullary nephrocalcinosis. A low-calcium diet, avoidance of vitamin D supplements and sun protection were recommended.
Conclusion
Idiopathic infantile hypercalcemia is an autosomal recessively inherited disease, with an unknown prevalence. This particular case allows emphasizing two main problematics. Firstly, the diagnosis of the underlying cause of hypercalcemia in Endocrinology turns out to be more complex, as the vitamin D has an important role besides PTH. Secondly, the identification of patients with this disease as an at-risk group brings a new aspect to the debate concerning vitamin D supplementation. More studies are necessary to understand the severity of this disease over time.

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EP142

Atypical cases of familial hypocalciuric hypercalcemia: utility of genetic testing in the diagnosis

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Introduction
Familial hypocalciuric hypercalcemia (FHH) has been classically characterized as an asymptomatic disease with mild hypercalcemia, hypocalciuria and inappropriately normal or high serum PTH concentration. The aim of our study is to assess the utility of genetic testing in patients with suspected FHH with atypical clinical manifestations, and the validity of classical biochemical parameters for the diagnosis.
Description of methods
A retrospective study of seven patients with HHF confirmed by genetic testing was conducted. The following variables were measured: calcemia, phosphatemia, renal function, serum PTH, 25-hydroxyvitamin D, 24-h calciuria, urinary calcium/creatinine clearance ratio (UCCR) and type of mutation.
Results
Mean age 51.4 ± 16.2 years. Average serum calcium 11.1 mg/dl ±0.4. Two patients had values above 11.5 mg/dl. Average PTH 51.8 pg/ml ±27.3. Mean urinary calcium was 166 mg 24 h ± 113.6. Five patients presented 24-hour calciuria > 100 mg/24 h. The UCCR was < 0.01 in five patients, between 0.01 and 0.02 in one patient and > 0.02 in one patient although intermittently. In those patients with calciuria > 100 mg/24 h, the UCCR was less than 0.01 in three cases, between 0.01 and 0.02 in one case and one patient alternated UCCR values between 0.01 and 0.02 and above 0.02. Previously to the diagnosis, two patients underwent not curative parathyroidectomy. Three different types of mutation of CaSR gene were observed in genetic testing, one of which has not been previously described in literature (C.2101 C > G).
Conclusion
The isolated use of classical clinical parameters for the diagnosis of HFF can determine errors in the diagnosis of those patients with atypical presentations. We believe that UCCR is preferable to the absolute value of 24-h calciuria, as some patients show no frank hypocalciuria. In these patients, genetic studies can help to avoid unnecessary surgical interventions as well as excessive costs.

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EP143

Sensitivity of localization studies performed by various radiologists whom are not precisely experienced in the evaluation parathyroid lesions

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Objectives
Preoperative imaging studies are being commonly used in primary hyperparathyroid patients to increase cure rate and to decrease complication rate of surgery. In this study we correlated the surgical outcomes with localization studies performed by various radiologists.
Method
A total of 174 patients with primary hyperparathyroidism in which healing of hypercalcemia achieved by parathyroidectomy were evaluated retrospectively. Since our hospital is a teaching hospital numerous radiologists were trained during the period of 2005 to 2015. For that reason preoperative cervical ultrasound (US) and sestamibi scan (MIBI) had been carried out by various examiners. According to laterality, imaging studies were categorized as true or false positive, or true or false negative, and sensitivity and specificity rates were calculated.
Results
A total of 184 lesions were excised from 174 patients (162F/27M, 52.7 ± 12.2 years of age). US and MIBI localization studies matched in 74 and 108 patients, respectively. False positive, and false negative results for US was 3.3 and 68.4% while false positive and false negative results for MIBI was 4.3 and 35.3%. We calculated very similar results for specificity of US and MIBI 95.9 and 95.0%, but sensitivity results were really far from satisfaction with 45.9% for US and 62.4% for MIBI.
Conclusion
Experience of examiner in parathyroid imagining effects primarily sensitivity but not specificity. Parathyroid surgeon should be well practiced to perform ultrasonographic evaluation by himself before operation.

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EP144

Bone mineral density is associated with hypercalciuria in primary hyperparathyroidism

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Aim
The most common clinical presentation of primary hyperparathyroidism (PHPT) is asymptomatıc and it is diagnosed incidentally without developing complications.In our study, we aimed to examine the characteristics of participants with primary hyperparathyroidism and the relationship between bone mineral density (BMD) and hypercalciuria.
Methods
Consecutive 191 normocalciuric (24-h urinary calcium < 400 mg/day) patients with PHPT (51 ± 13 years, F/M:155/36), 61 hypercalciuric (24-hour urinary calcium > 400 mg/day) patients with PHPT (49.2 ± 10 years, F/M:50/11) and 55 healthy controls (38.8 ± 10, F/M:43/12) were included in the current study. Serum calcium, phosphorus, parathyroid hormone (PTH), 25(OH) vitamin D and 24-hour urinary calcium were measured in all three groups. DEXA method was used for BMD measurement.
Results
Serum calcium levels were 11.8 ± 0.9 mg/dl, 10.6 ± 1.3 mg/dl and 9.6 ± 0.3 mg/dl ($P < 0.0001$), serum parathyroid hormone levels were 287 ± 378.2 pg/ml, 212 ± 322 pg/ml and 61.3 ± 28 pg/ml ($P < 0.001$) for hypercalciuric, normocalciuric patients and control group respectively. 24-h urinary calcium levels were 600 ± 173 mg/day in hypercalciuric group, 196 ± 106 mg/day in normocalciuric group and 137 ± 69 in healthy controls group ($P < 0.0001$). Serum calcium levels were observed significantly higher and serum phosphorus levels were observed

significantly lower in hypercalciuric group compared to normocalciuric group and healthy control group ($P<0.0001$, $P=0.005$). Serum PTH levels were observed significantly higher in hypercalciuric group compared to normocalciuric group ($P=0.03$). 24-hour urinary calcium levels showed positive correlation with PTH and serum calcium levels ($r=-0.37$, $r=0.47$, $P<0.0001$) and negative correlation with femur neck and lomber BMD levels in PHPT patients. ($r=-0.23$, $P=0.001$; $r=-0.27$, $P=0.02$). Patients whose serum calcium levels were normal or mildly elevated were tested for CGR mutation and it resulted negative.

Conclusion

Our study also showed that there is positive correlation between urinary calcium levels and serum PTH levels in newly diagnosed PHPT patients. It also supports the opinion that hypercalciuria could be a marker bone loss in PHPT patients.

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EP145

Bone mineral density measurement in newly diagnosed primary hyperparathyroidism patients

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Aim

Clinical presentation of primary hyperparathyroidism (PHPT) differs between populations. In this study, we aimed to examine bone mineral density (BMD) and bone metabolism parameters in newly diagnosed and untreated PHPT patients in a single endocrine center in İstanbul, Turkey.

Methods

Consecutive 256 PHPT patients (50.7 ± 14 years, F/M:205/51) and 89 healthy controls (38.8 ± 10 years, F/M:67/22) were included in the study. Serum calcium, phosphorus, parathyroid hormone (PTH), 25(OH) vitamin D, creatinine, 24-h urinary calcium were measured. DEXA method was used for bone mineral density (BMD) measurement.

Results

Twenty percent of PHPT patients were symptomatic and nephrolithiasis was shown in 20.3% of the patients. Serum calcium levels were 11.2 ± 1.3 mg/dl and 9.6 ± 0.3 mg/dl ($P<0.0001$), serum PTH levels were 273.4 ± 374 pg/ml and 61.3 ± 28 pg/ml ($P<0.001$) and serum 25OH D levels were 21.9 ± 20.1 ng/ml and 10.4 ± 7.1 ng/ml ($P<0.0001$) for PHPT and control groups respectively. 24-h urinary calcium levels were 294.4 ± 213.9 mg/day in PHPT group and 137 ± 69.2 mg/day in healthy control group ($P<0,0001$). Femur neck BMD were 0.82 ± 0.15 g/cm^2 and 0.98 ± 0.14 g/cm^2 ($P<0.0001$) for PHPT and control groups respectively. Femur neck and lumber BMDs, T and Z scores were observed significantly lower in PHPT group compared to healthy controls group ($P<0.0001$). Femur neck and lumber BMD levels showed negative correlation with PTH in PHPT patients ($r=-0.37$, $P<0.0001$). There were osteoporosis in 13.4 percent (n:34) and osteopenıa in 9.9 percent (n:25) of PHPT patients.

Conclusion

In our group of patients osteoporosis was diagnosed lower than expected but BMD measurements were lower in PHPT group. The results of this study show that bone turnover is increased and bone mineral density is decreased in PHPT patients, as stated in previous studies.

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EP146

Serum calcium to phosphorous ratio (Ca/P) as a simple, inexpensive screening tool in the diagnosis of primary hyperparathyroidism (PHPT)

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Background

PHPT is often overlooked/underdiagnosed. Several strategies (biochemical markers alone or combined in complex algorithms) have been investigated to easily diagnose/screen PHPT, but PHPT diagnosis remains challenging at present, especially in asymptomatic patients. As serum calcium (Ca) and phosphorous (P) are inversely related in PHPT, the Ca/P ratio could be a good candidate tool for PHPT diagnosis. Surprisingly, no literature data on Ca/P ratio are available, despite they are very simple biochemical measurements largely available in any clinical lab setting.

Aim

To investigate the Ca/P ratio diagnostic value in the diagnosis of PHPT.

Methods

Data retrospectively obtained from review charts of 97 patients with documented PHPT (69 females; 28 males) [16 (17%) with severe hypercalcemia (>12 mg/dl); 44 (45%) mild hypercalcemia, 36 (38%) normocalcemic PHPT (NCHPT)] were compared with those of 96 controls (C) (44 females; 52 males). Exclusion criteria: age <18 years, severe chronic diseases, cancer, bone metabolic diseases, use of medications affecting serum Ca. Biochemical measurements: PTH, Vitamin D, serum Ca, P, albumin, and creatinine. Normal ranges: PTH (15–88 pg/ml), Ca (8.5–11 mg/dl), P (2.5–5.1 mg/dl). SPSS 19.0 and SigmaPlot 11.0 were used for statistics (group comparisons, ROC curves, cutoffs performance).

Results

Ca and PTH were significantly higher in PHPT [(Ca median:11; min-max:9.4–15.5); (PTH 135.2; 57.6–1748)] than C [(Ca 9.4; 8.3–10.2); (PTH 32.1; 14–106.1) ($P<0.0001$). P was significantly lower in PHPT (2.4; 1.4–3.9) than in C (3.5; 2.1–4.5) ($P<0.0001$). Ca/P ratio was significantly higher in PHPT than in C. ROC curves analyses identified a cutoff of 3.5 for both Ca/P ratio and Ca/P ratio obtained by using albumin corrected-Ca. The sensitivity and specificity were 86 and 87%, respectively for Ca/P ratio and 89 and 93%, respectively for corrected Ca/P ratio ($P<0.0001$). The diagnostic value of Ca/P ratio performed better than PTH and Ca used alone or in combination.

Conclusions

Ca/P ratio is a valuable highly sensitive, highly specific tool for the diagnosis of PHPT. Since Ca/P is simple to obtain, easily accessible in every clinical and lab setting worldwide, and inexpensive even when used in large sample size of patients, this diagnostic tool could be useful for screening PHPT, especially in patients accessing emergency rooms or in the general practitioner setting.

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EP147

Vitamin D status in infants during the first 9 months of age and its effect on growth and other biochemical markers: a prospective cohort study

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Background

We planned this prospective cohort study in term newborn babies, with the objective to determine the incidence of vitamin D deficiency in infancy and to determine the level of vitamin D which triggers the physiological PTH axis of the body so as to differentiate truly deficient from sufficient vitamin D status.

Methods

96 participants at birth were enrolled and followed up till 9 months of age. Serum 25OHD was estimated in cord blood at birth and at 14 ± 1 weeks of life. 77 participants were followed up at 9 months for estimation of serum 25OHD, PTH, Alkaline phosphatase (ALP), calcium and phosphorus. Vitamin D deficiency was defined as serum 25OHD, PTH, Alkaline phosphatase (ALP), calcium and phosphorus. Vitamin D deficiency was defined as serum 25OHD.

Results

Serum 25OHD levels at 9 months of age (15.78 ± 8.97 ng/ml) were significantly increased in comparison to the level of 3 months of age (14.04 ± 7.10 ng/ml) and at birth (8.94 ± 2.24 ng/ml). At birth all the participants (77) were deficient in 25OHD levels. It was found that 16/94 (17%)and 19/77 (24.7%) participants at 3 and 9 months of age respectively became vitamin D sufficient without any vitamin D supplementation. There was a significant inverse correlation between serum 25OHD and PTH concentration ($r=-0.522$, $P<0.001$) serum 25OHD and ALP($r=-.501$, $P<0.001$). It was found that reduction in serum vitamin D level to below 10.25 ng/ml results in surge of serum PTH.

Conclusion

Vitamin D deficiency is common from birth to 9 months of age but incidence decreases spontaneously even without supplementation. Also large number of babies may be falsely labelled as vitamin D deficient with currently followed cutoffs. So a new cutoff for vitamin D deficiency needs to be established for neonates and infants.

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EP148

New onset of epileptic seizures induced by Fahr's syndrome secondary to idiopatic hypoparathyroidism

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Hypocalcemia due to hypoparathyroidism leads to a large spectrum of clinical manifestations but a rare and unusual presentation is onset or aggravation of epilepsy.
We report a 77-year-old man who was found to have profound hypocalcaemia and idiopatic hypoparathyroidism when investigated for epileptic seizures. He had affective disturbances and only mild neurocognitive disorders. Cataract was present. The neurological examination showed an extrapyramidal syndrome with postural tremor and cerebellar ataxia. The deep tendon reflexes were normoactive in all four limbs. Chvostek's sign was present but Trousseau sign was not observed. Laboratory analysis showed: low concentration of serum ionized calcium at 2.9 mg/dl (normal: 4.2–5.4 mg/dl), total calcium at 5.9 mg/dl (normal: 8.8 to 10.0 mg/dl), hyperphosphoremia at 6.4 mg/dl (normal: 2.3 to 4.7 mg/dl) and 2.5 pg/ml intact-parathyroid hormone (normal: 11.0 to 67.0 pg/ml). Alkaline phosphatase, magnesium, calcitonin, serum thyroxin and thyroid-stimulating hormone levels were normal. Brain computed tomography demonstrated a symmetric, extensive, bilateral calcification of the basal ganglia, centrum semiovale, and bilateral dentate nuclei of the cerebellum, typical for Fahr's syndrome. The red nucleus and substantia nigra appeared normal. The diagnosis of Fahr's syndrome, secondary to hypoparathyroidism was posed. A prepontine meningioma was also found. The electrocardiogram showed normal QTc interval and the interictal electroencephalography and electromyography were normal. Bone densitometry was normal. After the patient was treated with oral calcium and active vitamin D (1-alphahydroxy vitamin D3), serum calcium levels returned to normal and seizure attacks ceased progressively resulting in stopping antiepileptic drugs. These cases illustrate the importance of search for disrupted phosphocalcic metabolism but also emphasizes the importance of the role of neuro-imaging in patients with new-onset epileptic seizures in order to detect hypocalcemia secondary to hypoparathyroidism.

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EP149

Investigation of vitamin D deficiency in autoimmune endocrine disease in terms of frequency and causal or consequential relationship

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Introduction
Vitamin D Deficiency has been widely regarded as contributing to autoimmune disease, but low levels of vitamin D in patients with autoimmune disease may be a result rather than a cause like from malabsorbtion due to celiac disease, gastrointestinal disorders related to diabetes or thyroid disease, corticosteroid therapy complications etc...In this study, we aimed to investigate vitamin d levels in autoimmune endocrine disorders and relationship with silent celiac disease.
Methods
A total of 135 subjects (103 patients with autoimmune endocrine disorders and 32 control subjects) were enrolled in the study. Tissue transglutaminase (tTG) antibody levels were determined for the diagnosis of silent celiac disease. 25OHVitamin D (VD) and PTH levels were measured. Patient divide autoimmun disorders and control groups and subsequently compared with tTG antibodies positivity.
Results
Mean age was 37.8±12.0 years, 105 (77.7%) were female and 30 (22.3%) were male in all subjects. Serum VD levels were significantly lower in the patients group than healthy control group (17.2±7.2 and 25.4±7.1 ng/ml, $P<0.001$) and PTH levels were higher (71.2±36.4 and 57.5±22.4 pg/ml, $P=0.083$). Impairment of VD and rise in PTH levels were more pronounced in patients with Addison's disease relative to the other endocrinopathies (13.7±7.2 ng/ml, 106.7±40 pg/ml). Serum VD levels were statistically significantly lower in the patients with positive tTG ab compared to negative ones and control groups and lower in the patients with negative tTG ab compared to control subjects [tTGIgA pozitive (n:13)= 13.3±7.8, tTGIgA negative (n:90)=17.8±6.9, control (n:32)=25.4±7.1 ng/ml].
Conclusion
VD levels were found significantly lower in patients with autoimmune endocrinopathies than control subjects, patients with Addison's disease compared to other endocrinopathies and tTG antibody positive, than negative ones. In Addison's disease, chronic glucocorticoid therapy may be an additive factor for this reason. These results suggesting that vitamin d deficiency is both causal and consequential factors in autoimmune endocrine disorders.

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EP150

Vitamin D status in a HIV-infected cohort from south of Spain: descriptive analysis

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Introduction
Vitamin D deficiency is common among people living with HIV worldwide. There is a lack of studies focusing on prevalence and consequences of low levels of vitamin D in our health care area (south of Spain). The main aim of this study is to know the status of vitamin D and its consequences on parameters related to calcium metabolism in a cohort of patients with HIV infection in our area.
Methods/Design
Cross-sectional study encompassing HIV-infected outpatients treated in our hospital. Epidemiological variables and data related to vitamin D and calcium-phosphorus metabolism (i-PTH, serum calcium and phosphorus) were recorded. Vitamin D insufficiency (VDI) was defined as 25 OH-D levels <30 ng/ml and vitamin D deficiency (VDD) was defined as values of serum 25-hydroxyvitamin D below 20 ng/ml. Secondary hyperparathyroidism related to low levels of vitamin D was defined as i-PTH levels higher than 65 pg/ml.
Results
HIV patients were included (mean age: 46±6.9 years; 87.2% males). Median vitamin D level was 30.9±13.8 ng/ml. Normal levels of vitamin D were observed in 46.8% of the cohort, VDI was present in 34.9% and VDD in 18.3%. We found no differences in prevalence of VDI and VDD related to gender or presence of HCV co-infection. According to status of vitamin D (normal, VDI and VDD), significant differences in laboratory variables related to calcium-phosporus metabolism were not observed except in serum phosphorus levels ($P=0.04$). Secondary hyperparathyroidism linked to low levels of vitamin D was found in the 20.4% of the cohort.
Conclusions
Prevalence of hypovitaminosis D in our HIV-infected patients from south of Spain is very common. However, in our cohort, we found that its repercussions on calcium-phosphorus homeostasis are weak. Nevertheless, further studies are ongoing in our HIV-infected population to expand the knowledge on their clinical implications.

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EP151

Metabolic changes in vitamin D deficiency

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Introduction
The improvement of vitamin D status is necessary to overcome an impaired calcium-phosphorus metabolism and disturbances in other tissues functioning; safety of medical intervention should include analysis of metabolic changes.
Material and methods
Twenty four apparently healthy volunteers 24.9±2 year were included in the study: Group 1 (11/24) with blood serum levels of 25(OH)D <10 ng/ml and Group 2 (13/24) with 25(OH)D levels 10–20 ng/ml. Assessments were made at baseline; 3 h; 3, 7 and 28 days after intake of 200 000 IU of cholecalciferol oil solution.
Results
At baseline we observed significantly higher mean level of PTH (63.0±17.2 vs 35.3±10.2; $P<0.01$) with elevation above the upper level of normal range (ULN)

in 36.4% in Group 1 whereas in Group 2 levels met normal range in all individuals. Urine calcium/creatinine ratio (CCR), mmol/mmol M ± S.D.(Min–Max): Group 1 - 0.25 ± 0.13(0.12–0.58), Group 2 - 0.31 ± 0.21(0.03–0.71); values were less than lower level of normal range (0,1) in 15.4% in Group 2. Blood serum Ca_{tot}, Ca_{ion} levels, Ca_{ion} fraction and P levels were not different between the groups and were within the normal range.
By 28th day 41.6 and 87.5% from all participants achieved 25(OH)D blood serum level > 30 ng/ml and > 20 ng/ml respectively. By 3d day we observed significant decrease of PTH level in Group 1 (by 27%, $P < 0.05$). There was no significant changes in CCR during follow-up period, but in one individual we observed an increase higher than ULN (maxCCR = 0.89) which was transient. We also observed one case of hypercalcemia (maxCa_{tot} = 2.65 mmol/l) which wasn't associated with increase in Ca_{ion}.
Conclusion
High-dose oral cholecalciferol treatment for vitamin D deficiency is efficient and safe in young patients regardless of severity of vitamin D deficiency.

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EP152

Calcium as a marker of metabolic decompensation in glycogen storage disease type-1a

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Introduction
Glycogen storage disease type 1a (GSD1a) is an inborn error of metabolism with several metabolic decompensations including anaerobic glycolysis and lactic acidosis but few known about GSD1a-related hypercalcemia. Here we aimed to present a putative relationship between serum Ca and the affected metabolic parameters during metabolic decompensation of GSD1a.
Case report
Two patients with GSD1a and hypercalcemia were retrospectively analyzed. Fasting plasma glucose, serum calcium (Ca), triglyceride (TG), lactate and HCO3 levels were documented as the markers for metabolic control. Corrected/ionized Ca ratio was used as an indirect marker of serum unbound calcium fraction other than ionized calcium.
Case 1 is a 19-year-old male, diagnosed of GSD1a at the age of eight. Case 2 is 32-year-old female, diagnosed as GSD1a at the age of three. Ionized-Ca levels were normal in both patients despite high levels of the corrected serum Ca and low PTH levels. When the levels of corrected serum Ca matched with fasting plasma glucose, serum TG, lactate and HCO3 levels, a positive correlation between serum Ca and TG levels was observed.
Conclusion
Hypercalcemia in GSD1a might be simply related to an erroneous measurement due to high triglyceride levels. However, it cannot explain PTH-supression. The Corrected/ionized Ca ratio was negatively correlated with PTH levels. During the course of chronic lactic acidosis, bone works as a buffer-tissue by mobilizing CaCO3. Therefore slightly high calcium levels suppressing PTH may be related to release of calcium from the bone tissue. Consequently mild hypercalcemia itself may be a sign of metabolic decompensation like high triglyceride levels in patients with GSD1a.

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EP153

Vitamin D3 deficiency and secondary hyperparathyroidism development in patients with different stages of chronic kidney disease

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The aim was to estimate Vitamin D3 (25OHD) level and it's relation to secondary hyperparathyroidism (SHPT) development in patients with different stages of chronic kidney disease (CKD).
We examined 114 patients, 71 f, 43 m; age 44.6 ± 14.3 years. CKD stage was defined by estimated glomerular filtration rate (eGFR) calculated by MDRD formula. 48 patients have CKD stage 1–2, 26 pts – CKD3, 27 pts – CKD4, 13 pts – CKD5 (not on dialysis). Serum PTH, 25OHD, calcium (Ca) and phosphorus (P) were measured. All patients did not receive vitamin D and/or calcium supplements. Mean PTH level was 120.7 ± 113.4 pg/ml (95%CI 96.0–145.5). Frequency of SHPT was 44.7% in whole group, 12.5% in patients with CKD 1–2 stages, 23.1% - in CKD3, 96.3% - in CKD4, 100% - in CKD5. In patients with eGFR < 45 ml/min elevated PTH level was in 95.6% of cases vs 11.6% of those with eGFR ≥ 45 ml/min ($P < 0.00001$).
Mean 25OHD level was 18.6 ± 8.4 pg/ml (95%CI 17.0–20.1). Only in 7.9% of whole group 25OHD was 30 ng/ml and above (recommended level), in 55.3% - < 20 ng/ml (vitamin D deficiency). 25OHD level significantly correlated with eGFR ($r = 0.47$), PTH ($r = -0.39$), age ($r = -0.23$), Ca ($r = 0.27$) and P (-0.20) levels. Frequency of 25OHD deficiency in patients with eGFR ≥ 45 ml/min was 40.6, and 77.8% in those with eGFR < 45 ml/min ($P = 0.0002$). In subgroup of patients with decreased 25OHD level PTH and P were significantly higher (156.9 ± 147.7 vs 75.8 ± 77.2 pg/ml; 1.33 ± 0.38 vs 1.17 ± 0.22 mmol/l, $P < 0.001$), Ca was lower (2.31 ± 0.30 vs 2.43 ± 0.18 mmol/l, $P = 0.0002$).
We can assume that vitamin D3 deficiency is very common in patients with advanced CKD stages and associated with higher PTH level and more profound mineral disturbances. Screening of both PTH and 25OHD3 levels in patients with eGFR < 45 ml/min seems to be reasonable for choosing of best strategy of medical care.

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EP154

Abstract withdrawn.

EP155

Biochemical and hormonal alterations in women who underwent total thyroidectomy

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Introduction
Postsurgical hypoparathyroidism, (postHypoP), is a common complication of total thyroidectomy. We studied the variation of biochemical and hormonal parameters in patients who underwent total thyroidectomy.
Design
The study included 106 females of a mean age (± S.D.) 51.03 (± 13.42) years who underwent total thyroidectomy for multinodular goiter. We estimated the value of 25(OH)vitD, PTH, CT, adjusted Ca, P, and alkaline phosphatase (Alp), preoperatively and in the 1st and 7th postoperative day.
Results
The patients were devided in groups, A and B, based on the presence of postHypoP. A total of 67 patients experienced postHypoP and were included in group A and 39 without postHypoP in group B. Patients in group A were younger than patients in group B (49.6 ± 14.1 vs 53.3 ± 11 years, $P = 0.031$). The presence of parathyroid tissue in biopsy was significantly related to postHypoP, as observed in 38.1% in group A vs 14.7% in group B ($P = 0.016$). In contrast, malignancy or thyroiditis in histology were not significantly related to postHypoP.
When comparing laboratory values of groups A and B there was no statistically significant difference in preoperative values of Ca, PTH and 25 (OH) vitD between the two groups ($P > 0.05$). The 1st postoperative day Group A had lower mean adjusted Ca levels (Ca: 8.29 ± 0.43 vs 9.34 ± 0.41 mg/dl, $P = 0.023$). From the ROC curve, the best cut-off point of PTH in the 1st postoperative day that differentiated patients who developed postHypoP from those who did not was 13.45 pg/ml with sensitivity of 77% and specificity of 54%.(Area under the curve (AUC) = 0.71, 95% CI = 0.61–0.81, $P < 0.001$).
Conclusion
In patients after total thyroidectomy a PTH value ≤ 13.4 pg/ml the 1st postoperative day and the presence of parathyroid tissue in biopsy are positive related to postHypoP.

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EP156

Association of serum calcium concentrations with fibrinogen and homocysteine in non-diabetic Korean subjects

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Objectives
Considerable evidence shows that increased serum calcium levels are associated with metabolic disorders, cardiovascular disease and increased mortality. This study investigated whether serum calcium, within a normal range, is significantly associated with serum fibrinogen and homocysteine, markers of increased cardiovascular disease risk in non-diabetic Korean subjects.
Methods
A cross-sectional analysis was performed on 1096 subjects (mean age, 55.1 ± 11.1 years; 36.1% women) undergoing a general health checkup. Serum biochemistry was analyzed including serum albumin-corrected calcium (Ca_c), insulin resistance (IR, using homeostasis model assessment [HOMA]), fibrinogen, and homocysteine.
Results
Compared with patients within the lowest Ca_c quartile, those with higher Ca_c levels had increased fibrinogen and homocysteine levels as well as an increased proportion of smoking and dyslipidemia, and HOMA-IR. Correlation analyses revealed linear relationships for Ca_c with fibrinogen and homocysteine in both genders. After adjustment for confounding factors, serum Ca_c was significantly associated with high fibrinogen (odds ratio [OR] for the highest vs the lowest quartile = 1.76, 95% confidence interval [CI] = 1.10–2.83, $P = 0.020$) and homocysteine (OR = 1.82, 95% CI = 1.22–3.71, $P = 0.008$). Multivariate regression models showed that Ca_c was linearly associated with fibrinogen (standardized $\beta = 0.14$, $P < 0.001$) and homocysteine (standardized $\beta = 0.07$, $P = 0.009$).
Conclusions
High normal calcium concentrations were independently associated with increased levels of fibrinogen and homocysteine. Further investigation is needed to validate whether slightly increased calcium levels within the normal range indicate a higher risk of cardiovascular disease.

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EP157

Bone mineral density in postmenopausal women with high levels of parathyroid hormone

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One of the main problems encountered with increased levels of serum PTH is decrease in bone mineral density in the long term. Secondary hyperparathyroidism due to vitamin D deficiency leads to mineralization disorders of the bones, low bone mineral density, osteoporosis and ultimately an increased risk of bone fracture in adults. In this study, we aimed to determine the reasons of secondary hyperparathyroidism for bone mineral density.
One hundred and thirteen postmenopausal women with high serum PTH levels and 43 ones with normal PTH were enrolled to the study. Serum PTH level higher than 68.3 pg/ml was considered as hyperparathyroidism. The measurements of the lumbar spine and the left femur were recorded. The mineral density (g/cm^2) of the second lumbar (L) vertebra and the average mineral density of the L 1–4 vertebrae were compared statistically. Also the mineral density (g/cm^2) of the left femoral neck and the average mineral density of the femoral neck, trochanteric and intertrochanteric regions were compared.
There were no significant differences between the groups in terms of menopausal age and body mass index or in terms of serum calcium levels but serum phosphorus levels were significantly lower in the study group. Serum 25-OH vitamin D levels were low in both groups. There was no significant difference in both regions (Femur and L1-4 vertebrae) in terms of bone mineral density. However, when all cases were evaluated together, the average mineral density of the L1-4 vertebrae showed a negative correlation with serum PTH levels ($r = -0.175$; $P = 0.029$).
In our study, there is no significant difference between the study and control group in terms of bone mineral density and it may be related to the duration of hyperparathyroidism.

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EP158

Investigation of interference with binding proteins in two commonly used 25-hydroxyvitamin D assays

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Background
Adequate vitamin D supply is necessary for bone metabolism and also for the general maintenance of health. 25OHD is transported primarily bound to vitamin-D binding protein (DBP), but also to albumin. Lower concentration of plasma proteins may cause difficulties in immunoanalytics. Our aim was to investigate the protein dependence of the two most often used 25OHD immuno- (CLIA) and protein binding- (ECLPBA) assays.
Methods
levels were measured by CLIA and ECLPBA. Exogenous albumin was added by *in vitro* experiment at five dilution steps to serum pools from patients ($N = 24$) with low albumin while DBP remained permanent. 109 clinical cases were investigated too, 63 patient with subnormal albumin levels (with cirrhosis, nephrosis, malabsorption syndrome, chronic renal failure), and 46 healthy control with normal albumin levels.
Results
In the *in vitro* experiment the bias of 25OHD was markedly positive by increasing concentrations of albumin in case of ECLPBA. By the CLIA the bias of 25OHD was mostly slight and negative. Patient's sera with low albumin showed significantly lower 25OHD levels compared to specimens with higher albumin levels by both methods. Analyzing the obtained concentrations of 25OHD between two methods there was no difference in controls, but it was significant in hospitalised patients. Among clinical subgroups, there were no significant differences between the two methods except cirrhosis.
Conclusion
Our results suggest that CLIA method interact more with DBP and less with albumin, than the ECLPBA. Both 25OHD methods depend somewhat on albumin levels, but it is only marginal in sera with normal albumin levels, but characteristic with lower albumin. Our results call attention to the fact that each method showed a proportionate 25OHD vitamin level change in accordance with the changing albumin levels and DBP/albumin ratio.

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EP160

The relationship between serum vitamin D levels and metabolic syndrome in obese children and adolescents

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Objective
Obesity and vitamin D deficiency are become most important public health problems independently. We aimed to investigate the relationship between vitamin D levels and metabolic sydrome (MetS) in obese children and adolescents.
Patients and methods
51 obese children/adolescents at the age of 12.4 ± 2.73 (7.0–18.0) years and 48 age–sex matched healthy controls were enrolled. Serum 25 OHD, 1,25 (OH)2 D, calcium, phosphorus, *alkaline phosphatase*, parathormone (PTH) were measured

in all participants. Vitamin D sufficiency, insufficiency and deficiency were defined as serum 25 OHD concentrations >20 ng/ml, <20 ng/ml, <15 ng/ml, respectively. IDF, NCEP ATP III and WHO criterias were used to describe MetS.
Results
2% severe deficiency, 35.3% deficiency, 23.5% insufficiency and 39.2% sufficiency of vitamin D was found in the obese group. The serum concentration of 25 OHD was 18.2±6.2 ng/ml, 1,25 (OH)2 D was 28.9±11.7 pg/dl in the obese group, and 25.6±5.9 ng/ml, 25.5±9.3 pg/dl in control group, respectively. Obese children demonstrated significantly decreased 25 OHD levels compared to control group; however their 1,25 (OH)2 D and parathormone levels were similar. Cut-off level for 25 OHD which lead to increased PTH was found 15.8 ng/ml (*specificity* 53.5%, sensitivity 72.5%) by ROC analysis. Also, at the cut-off level of 13.6 ng/ml for 25 OHD, *specificity* increased to 72.5% and sensitivity increased to 81%. There was no association between serum 25 OHD, 1,25 (OH)2 D and MetS.
Conclusions
Obese children demonstrated significantly decreased 25 OHD levels, while their 1,25 (OH)2 D and PTH concentrations were similar with healthy controls. Therefore, we speculated that it was not suitable to detect serum 25 OHD - as it is stored in adipose tissue- in obese children. New methodologies for detecting 25 OHD levels and new detailed studies to determine a new cut- off level for vitamin D deficiency in obese children are needed.

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EP161

Evaluation the relationship between subclinical hypothyroidism and vitamin D level

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Background
Subclinical hypothyroidism is a thyroid disease which encountered in practice, commonly. Thyroid hormones affect metabolic syndrome parameters including HDL cholesterol, triglycerides, plasma glucose levels, blood pressure and abdominal obesity. Furthermore; there have been growing evidences about the relationship between vitamin D deficiency and autoimmune thyroid diseases. Therefore; we aimed to evaluate the association between the metabolic parameters and 25-OH-vitamin D levels in subclinic hypothyroid patients.
Methods
This study consisted of 110 patients (62 subclinical hypothyroid and 48 euthyroid) who attend to Haseki Training and Research Hospital's Internal Medicine outpatient clinics between 2014 January and April. The groups were similar interms of age (51.66±14.64 in subclinical hypothyroid; 47.42±15.57 in euthyroid group; $P=0.14$). Serum fT_4, TSH, total cholesterol, trigliseride, LDL-C, HDL-C, fasting glucose and 25(OH)- vitamin D levels were recorded. Height, weight, waist circumference and blood pressure of all subjects were meaured.
Results
The 25-OH-vitamin D, fasting glucose, total cholesterol, triglycerides, HDL-C, LDL-C and waist circumference levels were similar between euthyroid and subclinical hypothyroid groups ($P>0.05$). The 25-OH-vitamin D level was 20.93±16.5 in subclinical hypothyroid group and 21.88±19.15 in euthyroid group. The increased BMI was found in subclinical hypothyroid group ($P=0.024$). Prevalence of metabolic syndrome was significantly higher in euthyroid group (43.5% in subclinical hypothyroid group, 25% in euthyroid group; *P*: 0.044).
Conclusion
We found the lower vitamin D levels in subclinical hypothyroid group, however the difference did not reach statistical significance. Additionally, the higher metabolic syndrome prevalence is obtained in subclinic hypothyroidism.

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EP162

Correlation of serum vitamin D level with mortality in patients with sepsis

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Background
Sepsis is the leading cause of mortality in the critically ill. Recent studies emphasize early classification and treatment is paramount to improving mortality rates. Recently it has been found in many studies that many trace elements and nutrients do have effect on human body and if supplemented can improve the prognosis in patients with sepsis.
Aim and objectives: primary objective
Whether low vitamin D is associated with mortality.
Secondary objective
To find out association of low vitamin D levels and morbidity in terms of length of hospital and ICU stay.
Material and methods
Following ethical approval, consent will be sought from either the patient, or assent from a near relative. Successive patients admitted to the medical emergency and Intensive Care Unit at tertiary care health centre who fulfil the following criteria for sepsis, within a 24 h time window, were included.
Results
Amongst 88 patients evaluated in our study 15 patients (18.2%) were found to have adequate vitamin D levels and seven patients (8%) were found insufficient and rest 52 patients (73.9%) were found deficient in vitamin D. Age of the patients ranged between 18 and 82 years with mean (±S.D.) 45.02±17.69 years. Mean vitamin D level was found significantly higher among patients with positive outcome than those with unfavourable outcome (Expiry) ($t=2.075$, $P=0.04$). On comparison of length of hospital stay (morbidity) with vitamin D levels we found statistically significant inverse relation between vitamin D levels and length of hospital stay.
Conclusion
Vitamin D deficiency lead to increased risk of mortality in the critically ill along with prolonged hospital stay.

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EP163

The relationship of Beck depression inventory with vitamin D levels and visceral fat mass in cancer patients

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Introduction
The aim of this study is to determine the relationship of Beck Depression Inventory (BDI) with vitamin D levels and total and visceral fat mass in cancer patients.
Methods
A total of 219 patients were included in the study. All patients underwent blood tests including prealbumin, vitamin D. Also patients' BMI values were calculated and total and visceral fat masses of all patients were measured by bio-impedance analyzer. All subjects completed a self-administered BDI questionnaire.
Results
A total of 219 patients consisted of 53.9% ($n=118$) female and 46.1% ($n=101$) male patients with median age 52.41±13.66 (range, 19–84) years. Mean BMI value was 24.70±3.75 kg/m^2; mean BDI score was 13.02±8.72; and mean prealbumin level was 0.21±0.07 g/l. BMI was negatively correlated with BDI both in all study group ($P=0.002$) and in male patients ($P=0.011$) whereas there was no correlation in female patients between BMI and BDI ($P=0.237$). Prealbumin levels, vitamin D levels and hemoglobin levels were negatively correlated with BDI ($P<0.05$ for all). But no significant correlation was determined between total fat mass, visceral fat mass levels and BDI ($P>0.05$). Depression status had a significant relationship with BMI, vitamin D levels, prealbumin levels and malnutrition status in patients ($P=0.008$, 0.001, 0.001, and 0.001, respectively).
Conclusions
We have determined a significant correlation between vitamin D levels and BDI scores which indicate depression status in cancer patients. There was no correlation between BDI and visceral fat mass. There was a negative correlation between BDI score and BMI levels but this was not associated with total or visceral fat mass in cancer patients. Thus vitamin D levels could be used to determine the depression and nutritional statuses which might help to improve the clinical outcomes in cancer patients.

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EP164

4D-CT parathyroid increases the likelihood of localising parathyroid adenoma in patients with primary hyperparathyroidism and indeterminate Tc99m-Sestamibi + I-123 subtraction scan

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Introduction
Tc99m-Sestamibi + I-123 subtraction using planar and SPECT-CT is commonly used to investigate PHPT. Our centre previously published sensitivity and specificity of 92 and 86% respectively for Tc99m-Sestamibi + I-123 subtraction. Five false-negative studies required neck exploratory surgery. One false-positive study incorrectly localised a PA which was not found in surgery ($n = 67$). In recent years 4D-CT parathyroid has emerged as a useful technique to detect and localise PA in the work-up of patients with PHPT. We have been using 4D-CT as a second line investigation following an indeterminate Tc99m-Sestamibi + I-123 subtraction.
Description of methods/design
We retrospectively reviewed case records of patients with surgically proven PA who had also 4D-CT post subtraction scan. A common cause of indeterminate Tc99m-Sestamibi + I-123 subtraction is the confounding factor of multi-nodular goitre or nodules.
Demographic data (age, sex, pre and postoperative calcium/PTH) were presented as descriptive statistics. Histopathology of surgical specimens was also examined. Sensitivity and specificity of 4D-CT was calculated with surgically proven PA as the reference standard.
Results
Eight patients had indeterminate Tc99m-Sestamibi + I-123 subtraction for PHPT; seven had positive 4D-CT parathyroid (six surgical specimens confirmed PA, one normal parathyroid tissue). One had normal 4D-CT and histology confirmed normal parathyroid tissue. In patients with surgically proven PA, 4D-CT parathyroid performed pre-operatively demonstrated a sensitivity of 83% and a positive predictive value of 83%.
Conclusion
In a cohort of patients with indeterminate subtraction scans for investigation of PHPT, 4D-CT parathyroid significantly improved the diagnostic value for pre-operative localisation. It is therefore the preferred second line investigation of choice, with high sensitivity and predictive value allowing accurate pre-operative localisation for minimally invasive parathyroidectomy. The patients can also be better informed of the likelihood of finding of PA prior to surgery.

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EP165

BMI but not visceral adiposity index is related to vitamin D levels in overweight HIV-patients

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Introduction
Several studies have shown that BMI and visceral adiposity index (VAI) are inversely related to serum 25-hydroxy vitamin D (25OHD) in general population. There is a lack of studies performed in HIV population, whose body fat distribution is altered by lipodystrophy or liver disease. We aimed to analyze the cross-sectional associations of VAI and BMI with the 25OHD concentration and parameters related to calcium-phosphorus metabolism in HIV-infected patients.
Methods/design
46 male patients with HIV-infection and BMI > 25 kg/m^2 were included. Sex-specific for males VAI was calculated using a model of adipose distribution (MOAD) defined as: (waist circumference/39.68 + 1.88*(BMI))*(Triglycerides/1.03)*(1.31/HDL). VAI, BMI and 25OHD were divided into two groups at the 75th, 50th, and 50th, percentiles respectively, according to previous studies.
Results
The mean age of the cohort was 43.5 ± 12.6 years. Mean BMI, VAI and 25OHD were 28.9 ± 3.8 kg/m^2, 5.7 ± 3.9 (75th percentile: 8.1) and 30.1 ± 10 ng/ml, respectively. Levels of 25OHD were significantly lower among patients with higher BMI ($P = 0.034$) but non- significant differences were observed between groups of VAI (>75th percentile vs <75th percentile; $P = 0.502$). Though levels of i-PTH and calcium were higher among patients with higher BMI, no significant differences were observed ($P > 0.05$ in all cases). Also, no significant differences in calcium-phosphorus metabolism according to VAI percentile were found.
Conclusions
According to our results, we cannot conclude that the inverse relationship between 25OHD and VAI described in general population, can be observed in our HIV cohort when MOAD formula was used. Nevertheless, the inverse relationship with BMI is present. Anyway, repercussions on calcium-phosphorus metabolism were inappreciable.

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EP166

Hypoparathyroidism and difficult to control hypocalcemia

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Introduction
Autoimmune polyglandular syndrome type 1 (APS-1) is a rare autosomal recessive disorder characterized by autoimmune multiorgan attack. Clinical manifestations are widely variable. Treatment is based on supplementation of the various deficiencies and the prognosis is variable.
Case
An 18-year-old female presented with nail dystrophy and candida infection at age 7. Then, she was diagnosed with primary hyporparathyroidism and Addison's disease at age 9 and 10 subsequently. At age 12, APS was diagnosed. Two years later, primary ovarian insufficiency was diagnosed. The main challenge in her management was maintaining normocalcemia with avoidance of hypercalciuria and nephrocalcinosis. She had several admissions with symptomatic hypocalcemia, (adjusted calcium as low as 1.6 mmol/l) and required intravenous calcium infusions. Despite a high dose of oral calcium (1200 mg three times aday) and vitamin D analogue, normocalcamia was rarely achieved. Therefore, she was started on recombinant human PTH (rPTH). Fluctuations of calcemia unfortunately did not improve, she remained having hypercalacemia (3 mmol/l) as well as severe hypocalcemia (1.64 mmol/l).
In the hope of improving her quality of life, rPTH was delivered by a pump with a rate of 0.3 units/h. Initially she did very well and achieved near normal calcium (1.9–2.2 mmol/l), but recently presented with abdominal pain and vomiting and was found to have adjusted calcium level of 3.03 mmol/l. During admission, calcium fluctuated between 2.4 and 3 mmol/l. It later transpired that the patient was giving herself boluses of PTH to avoid symptoms of hypocalcaemia. After her mother took charge of pump device, calcium normalised at 2.38 mmol/l and she was discharged on rPTH rate 0.25 unit/h with calcium 600 mg twice daily and cholecalciferol 1000 units daily.
Conclusion
Management of hypoparathyroidism remains difficult despite of PTH pump.

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EP167

Adult iatrogenic hypoparathyroidism therapy: between less and more

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Introduction
The hypoparathyroidism (HypoPT) represents a rare condition characterized by low calcium (Ca) and parathyroid hormone (PTH) levels, frequently due to thyroid surgery by direct trauma of the parathyroid glands, devascularization, or their accidental removal. Postoperative hypoparathyroidism-related hypocalcemia may be permanent or transient.
Case report
We report the case of a 64-year-old man presenting with severe symptoms of hypocalcemia (muscle cramps, tingling, burning in the fingertips, toes, and lips, muscle spasms, especially around the mouth, fatigue), 2 weeks after total thyroidectomy for nodular goiter, despite undergoing treatment with daily 1800 mg calcium and 1200 IU vitamin D_3 (cholecalciferol). Laboratory tests showed low ionized serum calcium (1 mmol/l; N: 1.06–1.2 mmol/l), low albumin adjusted total calcium (6.9 mg/day; N: 8.8–10.2 mg/day), low PTH (7.5 pg/ml;

N: 15–65 pg/ml). The histopathological exam confirmed the removal of one parathyroid gland. HipoPT was confirmed and vitamin D/calcium supplements were adjusted: active vitamin D analogues (Alfacalcidol 2 μg/day), calcium supplements (3000 mg/day) and cholecalciferol (2000 IU/day). 5 months later, the patient reported a clinical improvement despite persistent low serum and 24-h urinary calcium levels (as well as PTH). Depression, possibly due to chronic hypocalcemia, was diagnosed and psychiatric treatment was initiated. In addition, abdominal ultrasound found renal sludge, which warranted careful monitoring during treatment with calcium supplement and adequate liquids intake recommendations. Follow-up during therapy is necessary (Alfacalcidol 1 μg/day given its potent inhibitory effect on PTH levels), calcium intake 3500 mg/day, together with cholecalciferol 1200 IU/day).
Conclusion
Treatment of HypoPT might be challenging due to doses of calcium in high doses of vitamin D and calcium to obtain clinical and biochemical control while avoiding the negative effects of calcium excess deposits. In this context, patient's well-being and quality of life may also be difficult goals to achieve.

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EP168

Vitamin D deficiency is highly prevalent in obesity and is related with BMI and inflammation

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Objectives
To study vitamin D deficiency in a cohort of obese males and to evaluate associated clinical and biochemical characteristics.
Methods
Case-control study which included obese (defined by a BMI $\geq$30 kg/m^2) males. Vitamin D deficiency was defined as vitamin D levels $<$20 ng/ml. Estimation of vitamin D status was determined in serum using a commercially available enzyme- immuno-assay designed to measure 25-OH Vitamin D concentrations in serum or plasma (Immundiagnostik, Quantikine, Bensheim, Germany).
Results
225 obese males were included in the study. Prevalence of vitamin D deficiency was 51.3%; mean vitamin D levels was 13.8 ng/ml in the group with vitamin D deficiency and 27.3 ng/ml in normal vitamin D status group ($P<0.001$ for comparison). No differences in age (36.0 vs 37.7, $P=0.1$), insulin resistance (measured by HOMA-IR index) (5.2 vs 4.3, $P=0.11$), calcium levels (9.06 vs 9.0 mg/dl), PTH levels (46.1 vs 44 pg/ml, $P=0.35$) or HbA1c (5.4 vs 5.4, $P=0.6$) was found between patients with or without vitamin D deficiency, respectively. Patients with vitamin D deficiency were more obese (BMI 40 vs 37.4, $P=0.04$) and had higher levels of PCR (7.5 vs 5.3 mg/l, $P=0.01$).
Conclusions
Vitamin D deficiency affects to $\sim$50% of obese males. These patients tend to be more obese and have higher PCR levels than patients with normal concentrations of vitamin D.

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EP169

25-hydroxy vitamin D levels in patients with newly diagnosed of cancer

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Introduction
Recent studies have pointed out a possible role of vitamin D in carcinogenesis. Vitamin D deficiency may be related to a major cancer incidence and mortality. This association would be more relevant for breast and colorectal cancer. Obesity acts as a risk factor for these type of neoplasms on which vitamin D could influence.
Subjects and methods
A cross-sectional study of consecutive out-patients with newly diagnosed cancer: urological, colorectal (CRC), head and neck and 'others'. Patients were referred to the Nutrition Unit for preoperative nutritional evaluation (fast-track protocol) during the year 2014. We assessed body composition by bioelectrical impedance analysis and determined serum 25-hydroxy vitamin D,25(OH)D, levels.
Results
A total of 93 patients were evaluated: 39 had urological cancer, 25 colorectal cancer (CRC), 25 head and neck cancer and four other type.
The mean concentration of 25(OH)D was 53.8$\pm$32.3 nmol/l (95% CI=45.0–63.7). 59.6% showed vitamin D deficiency ($<$50 nmol/l) and 19.1% insufficiency (50–75 nmol/l).
There were differences in vitamin D deficiency depending on the type of cancer: head and neck 70.8%, CCR 64.0% and urological 47.0% ($P<0.008$).
No statistically significant associations were found between 25(OH)D levels and sex, age, smoking, BMI and fat mass. The season of blood collection significantly modified 25(OH)D concentration ($P<$0,030).
Conclusions
We have found a high prevalence of vitamin D deficiency among patients with a new diagnosis of cancer, specially for those with head and neck cancer. The use of laboratory reference values adjusted by season could avoid possible bias. The interesting link between vitamin D and cancer deserves more research.

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EP170

Correlations among calf circumference index, selected anthropometric and biochemical parameters among patients over 60 years

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Introduction
Anthropometric parameters are easy and quickly methods of assess risks of many diseases.
Aim
The purpose of this study was to assess the correlation between calf circumference index, selected anthropometric (such as BMI, BAI, WHR, WHtR index) and biochemical parameters (such as concentration of 25(OH)D3, lipid profile, fasting glucose) among patients over 60 years.
Materials and methods
Cross-sectional study was done in a group of 123 patients hospitalized in the geriatric department in 2013–2015 (66% of the group were women, $n=81$). The study included patients above 60 years, without oral supplementation of vitamin D_3 3 months before hospitalizations, without chronic kidney and liver diseases. Anthropometric parameters were measured in the morning, in light clothes in accordance with generally accepted methodology. Results of biochemical parameters were red from the patients' medical records. The obtained data were statistically analyzed using STATISTICA 10PL. $\alpha=0.05$.
Results
Mean age was 75.66$\pm$7.47 years. The average value of calf circumference index was 34.58$\pm$4.25 cm. The average BMI was 27.44$\pm$5.04 kg/m^2; WHR 0.95$\pm$0.08; WHtR 0.61$\pm$0.08; BAI 33.38$\pm$6.06%. The mean concentration of 25(OH)D_3 was 15.35$\pm$6.65 ng/ml; fasting glucose 110.93$\pm$50.12 mg/dl; total cholesterol 204.32$\pm$51.21 mg/dl; HDL cholesterol 57.09$\pm$19.94 mg/dl; LDL cholesterol 125.82$\pm$42.85 mg/dl; triglycerides 115.87$\pm$57.05 mg/dl. There were observed positive correlation between calf circumference index and 25(OH)D3 ($R=0.23$; $P=0.0266$); triglycerides ($R=0.30$; $P=0.0007$); BMI ($R=0.75$; $P<10^{-6}$); WHR ($R=0.47$; $P<10^{-6}$); as well as BAI ($R=0.30$; $P=0.0008$). There were not observed statistically significant correlation of calf circumference index in relation to fasting glucose ($R=0.13$; $P=0.1393$); total cholesterol ($R=0.13$; $P=0.1558$); HDL cholesterol ($R=-0.09$; $P=0.3264$); LDL cholesterol ($R=0.11$; $P=0.2233$).
Conclusions
The study indicates that the measurement of calf circumference is an easy and fast methods which allow the assessment of concentration 25(OH)D3 in group patients above 60 years.

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EP171

The association between vitamin D deficiency and urinary tract infection in postmenopausal women

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Aim
We aimed to examine whether there is any association between serum levels of 25-hydroxyvitamin D [25(OH)D3] and silent urinary tract infection (UTI) among postmenopausal women.
Methods
Age, postmenopausal period, BMI, white blood cell count, serum C-reactive protein, calcium, phosphorus, alkaline phosphatase, parathormone, serum 25(OH) D3 levels and native urin speicemens were measured in 124 postmenopausal women without signs of UTI, on regular gynecological checking.
Results
A total of 124 women average age of 53.4, with period of 3.5 year after last menstruation were included, 66 had UTI and they were symptom free, other 58 had normal urine. The mean serum **levels** of 25(OH)D3 among woman with UTI were significantly lower than those of controls (26.7 ± 3.1 vs 36.59 ± 4.2 nmol/l; $P < 0.001$). The serum **levels** of 25(OH)D3 were significantly lower in patients with UTI compared to patients without (21.4 ± 2.6 vs 31.9 ± 2.9 nmol/l; $P < 0.001$). Within the study group, mean serum levels of 25(OH)D3 among women with greater BMI > 30.0 kg/m^2 were lower than those of under it (21.8 ± 3.7 nmol/l vs 32.7 ± 4.8 nmol/l; $P < 0.001$). Multivariate analysis showed that the BMI did not correlate with UTI.
Conclusions
Our results suggest that vitamin D deficiency may be a risk factor for UTI in postmenopausal women.

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EP172

Roux-en-Y Gastric Bypass reversal due to recalcitrant hypocalcaemia after total thyroidectomy

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Introduction
Hypocalcaemia is a potential post-thyroidectomy complication. Patients with previous Roux-en-Y Gastric Bypass (RYGBP) are at increased risk of symptomatic hypocalcaemia refractory to treatment. This complication is rare and there is not consensus on how to act.
Clinic case
Female with 34 years old, with a history of Obesity (BMI 45.7 kg/m^2), submitted to RYGBP in 2013, with a total loss of 47 kg (current BMI 27.3 kg/m^2). In October 2014, she had total thyroidectomy for nodular hyperplasia. Postoperative was complicated with symptomatic hypocalcaemia requiring calcium gluconate i.v. and early replacement therapy with calcium and vitamin D as an outpatient. Over the next 6 months she had five admissions in the Emergency Department due to hypocalcaemia, requiring calcium gluconate i.v. administration. For this reason was referred to our clinic in March 2015. After discussing the case with surgeons, due to difficulties in normalizing calcium levels (calcium of 7.1 mg/dl with calcium carbonate 31 500 mg/day and calcitriol 1.5 µg/day and calcium gluconate i.v. 3/3 weeks) decides to reverse the RYGBP in May 2015, which occurred without complications. There was only a partial improvement of the hypocalcaemia. In January 2016, she has calcium of 7.4 mg/dl with calcium carbonate 9000 mg/day, cholecalciferol 2400 UI/day. Phosphorus was 4.6 mg/dl (2.7–4.5) and PTH 4 pg/ml (16–87).
Conclusions
This case shows that patients with hypoparathyroidism and RYGBP have a high risk of recalcitrant hypocalcaemia. For this reason, several authors have argued that performing thyroidectomy after RYBGP should be done after analysing benefits and risks. There are cases described in the literature that after medical treatment failure, the reversal of RYBG can be a solution, as it restores the absorption of calcium and vitamin D places, however we need randomized controlled studies.

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EP173

Evaluation of renin-angiotensin-aldosterone system in patients with asymptomatic primary hyperparathyroidism

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Background
There is some evidence suggesting an interaction between renin-angiotensin-aldosterone system and parathyroid hormone (PTH). Decreased aldosterone levels after parathyroidectomy have been reported in patients with primary hyperparathyroidism (PHPT). Recently, most of the diagnosed patients with PHPT are mild or asymptomatic. Our aim was to investigate plasma aldosterone and renin concentrations in patients with asymptomatic PHPT.
Methods
Thirty-two patients with asymptomatic PHPT and 22 healthy control subjects were recruited for this study. The levels of renin, aldosterone, PTH, calcium, phosphorus and 25-OH vitamin D were investigated.
Results
Median PTH and calcium levels were significantly higher in the patients with asymptomatic PHPT than the control group (155.0 (77.60) pg/ml vs 54.0 (13.20) pg/ml and 10.80 (0.45) vs 9.48 (0.56) mg/dl, $P < 0.05$, respectively)). Median creatinine clearance levels were similar (100 ml/min (22.80) vs 102 ml/min (19.73), $P > 0.05$, respectively). There was no statistically significant difference between plasma renin levels and plasma aldosterone concentrations (5.98 (7.35) vs 5.02 (12.87) and 95.14 (88.77) vs 105.92 (55.17), $P > 0.05$, respectively). There were no correlations between calcium and PTH levels and renin or aldosterone levels ($P > 0.05$).
Conclusion
Our results suggest no major alterations occur in the renin-angiotensin-aldosterone system in patients with asymptomatic PHPT.

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EP174

Vitamin D status among women living in a sunny region: Marrakesh study

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Background
Hypovitaminosis D is associated with poor dietary intake and inadequate sunshine exposure. It is common worldwide. However, recent studies has shown a high prevalence of hypovitaminosis D in Moroccan population.
Objective
We undertook this study to determine the specific prevalence of hypovitaminosis and its relationship to metabolic parameters in pre-menopausal women living in a sunny region.
Methods
The group studied included 105 patients aged from 18 to 45 years. Between March and July, we assessed socio-demographic parameters, metabolic parameters and associated pathologies as well as risk factors for hypovitaminosis. 25 OH Vitamin D, serum calcium, phosphorus and lipid panels were measured. Hypovitaminosis was defined for the values below 75 nmol/l.
Results
All the patients has hypovitaminosis with a mean value of 10.20 ± 8.3 nmol/l. 78.1% had a vitamin D value under 25 nmol/l while 21.9% had insufficiency. Calcium ad phosphorus were normal. The hypovitaminosis severity was not correlated to the metabolic parameters (BMI, lipids, FG, HbA1c).
Conclusion
Our results show that hypovitaminosis is common among young Moroccan women even if they are living in a sunny region. In the absence of precise information regarding the vitamin D intake and the time spent outdoors, this should emphasize the need for evaluation of vitamin D status in every women. Prevention strategies should be initiated by governments regarding the enhancement of vitamin D intake.

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EP175

Severe hungry bone syndrome after incidental parathyroidectomy in hypophosphatemic rickets

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Introduction
Hypophostemic rickets is characterized by phosphate renal loss associated with a primary defect of osteoblasts and metabolism of vitamin D. Marked bone turnover caused by high levels of parathyroid hormone attribute to these patients an elevated risk for hungry bone syndrome after parathyroidectomy.
Case report
A 34-years old woman with a past history of Lynch syndrome and hypophostemic rickets associated with hyperparathyroidism and brown tumours. She had multinodular goitre and 10 years ago she underwent left hemithyroidectomy, isthmectomy, and subtotal right hemithyroidectomy, without immediate complications, but hypothyroidism subsequently developed. Her current daily medications are: 88 mcg of levothyroxine, 120 mg of cinacalcet, 4500 mg of phosphorus and 1 mcg of calcitriol. Goitre relapsed and nodule cytological assessment revealed a follicular tumour. Again, she underwent thyroid surgery and two parathyroids were incidentally removed (one of them was histological suggestive of parathyroid adenoma). She developed hypoparathyroidism and severe hypocalcaemia after surgery. The lowest total calcemia identified was 5.5 mg/dl (8.8–10.6), magnesemia 1.1 mg/dl (1.9–2.5), and phosphatemia 3.5 mg/dl (2.5–4.5). Urinary calcium and phosphate levels, under intravenous calcium infusion, were 108 mg/24 h (<250) and 1032 mg/24 h (400–1300), respectively. Even though she was being treated with intravenous and oral calcium, magnesium and calcitriol, hypocalcaemia remained refractory. Additionally, she developed frequent phlebitis and 20–60 mg of teriparatide was added. Normocalcaemia was achieved after 4 months of intravenous calcium gluconate (total elemental calcium of 150 g), oral calcium carbonate (total elemental calcium of 1.5 kg).
Conclusion
Hungry bone syndrome, associated with hypophosphatemic rickets, is a rare complication of parathyroidectomy, particularly in the setting of tertiary hyperparathyroidism. The treatment of hungry bone syndrome should be directed to the reestablishment of calcium deficit and restauration of bone turnover, which may take several months. The absence of guidelines and the different pharmacokinetics of calcium formulations pose a particular challenge in the management of these patients.

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EP176

Primary hyperparathyroidism detected in a patient undergoing two prior thyroidectomies for follicular thyroid carcinoma: a case report

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Introduction
Primary hyperparathyroidism (PHPT) is usually characterized by overproduction of parathormone (PTH) due to a solitary parathyroid adenoma. Its treatment involves surgical removal of the solitary adenoma or hyperplastic parathyroid glands that secrete PTH. Medical treatment options are used for patients with conditions that preclude surgical operation.
Case presentation
A 57-year-old female patient underwent left total and right subtotal thyroidectomy operations on 18/05/2009 for multinodular goiter. Pathological examination revealed a 5.5 cm follicular carcinoma in the left lobe. On 30.06.2009, she underwent completion thyroidectomy and subsequently received ablative therapy with radioactive iodine (RAI) at a dose of 150 mCi. Elevated calcium and reduced phosphorus levels were found during her follow-up visits. While the findings of several tests were consistent with PHPT, only a slightly echoic, well-circumscribed lesion ($5\times5\times11$ mm) located close to the former place of the inferior pole of the right thyroid gland was detected by neck ultrasound images and its vascularization was shown by Doppler ultrasound. However, no increase in activity or uptake was observed during parathyroid scintigraphy and neck CT did not show a mass formation.
Her serum calcitonin level was normal. The possibility of a thyroid medullary carcinoma was excluded by reexamining of her paraffin-embedded thyroid blocks. The patient who already had undergone two major surgeries and one course of RAI treatment refused another neck operation. Thus, treatment with Cinacalcet was initiated. Calcium values returned to normal after the treatment.
Conclusion
Follicular carcinoma in the presence of PHPT is a rare occurrence. Non-visualization of parathyroid tissue by imaging studies in a patient with two prior thyroidectomy operations and RAI therapy makes our case quite an interesting one. Cinacalcet therapy is a good therapeutic option to control calcium levels in cases where excessive secretion of PTH cannot be achieved by surgical intervention.

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EP177

Calcium and vitamin D metabolism among patients with excess of weight of a docent clinic in Salvador-Ba

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Introduction
Hypovitaminosis D is a biochemical change with high prevalence among the population, especially in obese patients. Its function more known relates to bones metabolism, although recently, many functions have been described.
Methods
A descriptive cross-sectional study, which included women over 18 years old with BMI equal or superior of 25 kg/m^2. Anthropometric measurements were obtained: weight, height, BMI, waist circumference, hip circumference; presence of hypertension and/or metabolic syndrome were obtained by analysing the charts of patients in the study. The criteria for diagnosing hypovitaminosis D was established according to The Brazilian Society of Endocrinology and Metabology: levels $\leq$20 ng/dl means deficiency, 21–29 ng/dl are considered insufficiency and levels between 30 ng/dl and 100 ng/dl are normal.
Results
The sample consisted of 121 women with a mean age of 43 ± 12 years, BMI of 37 ± 6.5 kg/m^2, the waist/hip ratio of 0.86 ± 0.09 and the abdominal circumference of 109 ± 13 cm. The prevalence of obesity was 89.3%; 59% of the population were hypertensive and 20% diabetics. The mean of the level of vitamin D was 23.5 ± 6 ng/dl. Hypovitaminosis D was observed in 84.6% of the population, 25.6% are vitamin D deficient and 59% are insufficient. The values of the biochemical in the groups obesity and overweight were respectively: 26.8 ± 7 ng/dl and 23.1 ± 6 ($P=0.1$) for vitamin D, 41.7 (26.4–37.4) pg/ml and 63.3 ($P=0.03$) for parathormone, 10.1 ± 1 and 9.4 ± 0.7 mg/dl ($P=0.052$) calcium and 3.8 mg/dl ($P=0.84$) in both groups for phosphorus. It was observed an inverse correlation between BMI and the levels of vitamin D ($P=0.04$).
Conclusion
The prevalence of hypovitaminosis among patients with excess of height is higher than in the general population. There is an inverse correlation between the levels of vitamin D and BMI.

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EP178

A Rare Case of Intracranial Calcification: Fahr Disease

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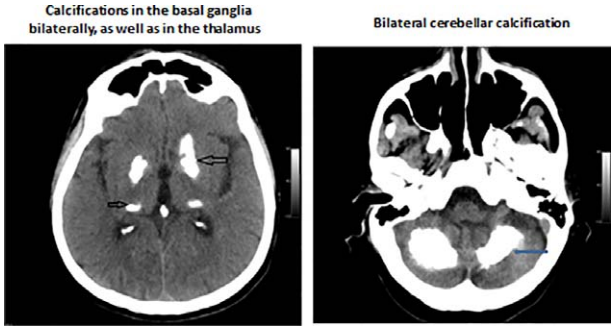
Introduction
Fahr disease, is a rare pathology characterized by neuropsychiatric symptoms and bilateral symmetrical intracranial, especially basal ganglial calcifications. Although the exact etiology is not known, it is often associated with calcium and phosphorus metabolism disorders. We aim to present two brothers who presented with Fahr's disease which is a rare condition.
Case
Sixty-year-old male patient without a medical history of ilness was admitted to the neurology clinic with speech disorder and seizure. After neurological evaluation of the patient, the brain computerized tomography was performed and revealed bilateral symmetrical calcifications in basal ganglia, thalamus, periventricular white matter, centrum semiovale and dentate nucleus of the cerebellum (Figure 1).



Patient was referred to our clinic with the preliminary diagnosis of Fahr disease. In his medical history he had speech disorder for 3 years and received irregular treatment. He didn't have any pathological findings on physical examination. The results of laboratory tests were normal except vitamin D deficiency. The diagnosis of Fahr disease was thought and vitamin D treatment was started. 1 year after brother were evaluated by a neurologist for 5 years with syncope and forgetfulness complaints. Cranial MRI supported Fahr disease. Vitamin D deficiency was found and vitamin D therapy was started. The patients is still being followed by neurology and endocrinology.
Discussion and Results
Patients with Fahr disease frequently admit with neuropsychiatric, extrapyramidal and cerebellar signs, speech impairment and dementia. The association between severity of clinical symptoms and the location and severity of calcification was reported previously. Substitution of calcium and vitamin D corrects the metabolic abnormality and slows down the clinical progression. In conclusion, in patients presenting with neurological symptoms, particularly when bilateral symmetric calcifications of the basal ganglia is detected, the Fahr's disease should be considered in the differential diagnosis and calcium metabolism should be evaluated.

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EP179

Giant-cell tumor: hyperparathyroidisme is not always involved – a case report

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Giant-cell tumor is a skeletal disorder that occurs secondarily to hyperparathyroidism and is caused by long-term stimulation of parathyroid hormone (PTH) excess. The overactivity and proliferation of osteoclasts stimulated by PTH breaks down bone and leads to replacement of bone matrix and thinning of the cortex. True giant-cell tumor is a rare jaw osteolytic benign tumor belonging to the larger family of giant-cell tumors.
We report the case of a 47 years old female patient without significant personal history. The patient was referred to us for hyperparathyroidism after being operated in maxillofacial surgery department for a right mandibular tumor progressing from 1 year associated with muscle cramps and fatigue. The pathology exam found a giant-cell tumor. Blood exams showed: PTH = 81.5 pg/ml, Serum Calcium = 2.5 mmol/l, serum phosphorus = 1.3 mmol/l and creatinine = 63 mmol/l. Cervical ultrasound showed a left lower pole parathyroid adenoma. The para- thyroid scintigraphy showed no parathyroid or ectopic tumor. No other bone lesions were found on bone scintigraphy. Since the calcium rate was normal (2.5 mmol/l), we investigated the 25 (OH) Vitamin D3 level. Our patient had a vitamin D deficiency.
Thus the diagnosis was a secondary hyperparathyroidism caused by a vitamin D deficiency associated to a giant cell tumor. The jaw tumor syndrome was eliminated due to the lack of hyperparathyroidism in the family history and to the absence of uterine fibroids and renal cysts in our patient.
This case illustrates the simultaneous combination of a mandibular giant cell tumor and a normocalcemic hyperparathyroidism. The vitamin D dosage rectified the diagnosis.

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EP180

Which social factors that may be associated with high parathyroid hormon levels in postmenapausal women?

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In this study, we aimed to investigate the causes of elevated PTH levels in postmenopausal women without the use of drugs that may affect of PTH levels and without concomitant diseases.
A total of 156 postmenopausal women, aged $\geq$ 50 years, had no menstruation for at least 2 years and had no disease known to affect calcium metabolism were considered. Education, occupation, average duration of exposure to sunlight per day in summer and winter, consumption of calcium-rich foods of people were questioned. Participants were divided into four groups according to their educational levels, and they were divided into two groups according to their religious beliefs: covered and non-covered people. They were also classified according to their occupational status as housewives, workers and retired people. Sunlight exposure behavior was measured by one question; less than 30 min was considered inadequate exposure, from 30 to 60 min was considered moderate exposure and more than 60 min exposure was considered sufficient. People, who had more than daily 500 mg calcium consumption and less than daily 500 mg calcium consumption, were divided into two groups.
When all cases were evaluated together, serum PTH levels were significantly higher in housewives than workers and retired people ($P < 0.001$); in participants with less than a high school graduates than more than with a high school graduates ($P = 0.008$); in covered people than non-covered people ($P = 0.025$). Living alone and smoking were found to have no effect on serum PTH levels. PTH levels were not significantly different between with adequate calcium consumption and inadequate calcium consumption and between insufficient sunlight exposure and sufficient sunlight exposure.
Considering all cases, women whom are defined as housewife, dressed up covering their head and arms and with education level less than high school have statistically significant elevated parathyroid hormone levels.

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EP181

Mean platelet volume in a patient with hypoparathyroidism: the relationship between metabolic syndrome, impaired fasting glucose and cardiovascular risk

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Background
Parathyroid hormone (PTH) is a key regulator of mineral metabolism, the homeostasis of calcium, phospate, vitamin D and bone turnover. Hypoparathyroidism is a rare disease characterized by hypocalceamia with inappropriately low plasma levels of PTH. Mean platelet volume (MPV) is the measure of platelet size. Increased MPV has been associated with cardiovascular risk.
Objective
In our preliminary study, we aim to show that untreated hypoparathyroid patients compared with hyperparathyroid patients and control group have also increased risk of cardiovascular diseases and metabolic syndrome due to increased MPV.
Materials and Method
Sixty seven hypoparathyroid (45 postsurgical hypoparathyroid and 22 idiopathic hypoparathyroid), 37 hyperparathyroid patients and 32 control were included this study. All the patients have been followed by hypoparathyroidism at least one year. All of them were receiving calcium and vitamin D analog supplements. Patients were not given any drugs affectinf platelet funciyon at least 2 weeks (eg. Aceltyl saliclate, antiepileptics, heparin, antithyroid drugs etc.) chronic illness, smoking and having alcohol was also exclusion criteria. In order to eliminate the conditions that can affect MPV levels, can cause tendencey to cardiovascular diseases and metabolic syndrome fasting glucose and serum lipids were evaluated.
Results
When groups were seperately compared with control group, 7 idiopathic hypoparathyroidism (% 31.8, *P*: 0.02), 16 post surgery hypoparathyroidism (% 29, *P*:0.015), 15 hyperparathyroidism patients (%35.7, *P*:0.003) and 5 control (%10, $P<0.05$) patients had metabolic syndrome. MPV levels were statistically significant higher in postsurgical and idiopathic hypoparathyroidism and hyperparathyroidism gropu than control group. BMI, age and gender were independent predictive factors of MPV. Adjusment for other factors did not alter these relative risks.
Conclusion
These study assesed MPV and relationship between metabolic syndrome and cardiovascular disease risk. In this study, we have shown that MPV levels were higher in hypoparathyroidism groups than control group. The main problem seems to be low calcium levels in patients with hypoparathyroidism. Thus, in hypoparathyroid patients appropriate calcium and vitamin D replacement therapy can protect from cardiovascular risk.

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EP182

Clinical case of chronic calcific pancreatitis in a patient with parathyroid carcinoma caused primary hyperparathyroidism

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Parathyroid carcinoma is a rare cause of primary hyperparathyroidism (PHPT) and is usually presented with severe hypercalcaemia and parathyroid hormone (PTH) elevation. Hypercalcaemia can lead to calcification of parenchymatous organs, including pancreas, and acute or chronic pancreatitis.
Case report
A 46-year-old woman was admitted to the endocrine surgery department of our institution with severe weakness, appetite and weight loss (25 kg in a year), abdominal and joint pain, apathy, skin dryness. Laboratory tests: PTH 2517.4 pg/ml (11–62), total serum calcium 3.36 mmol/l (2.2–2.6), ionized serum calcium 2.14 mmol/l (1.12–1.32), amylase 1280 U/l (<100). Neck US: left lobe of thyroid gland is presented with a heterogenous nodule with cystic degeneration, 5.0×3.0×3.5 cm. Neck CT-scan: a 37×26×51 mm mass near the back margin of left thyroid lobe, 53 HU density in the native examination, 64 HU in the arterial phase of contrast examination and 50 HU in the venous phase. The upper pole of the tumor is located at the thyroid cartilage, the lower pole of the tumor is in the mediastinum. Abdomen CT-scan: pancreas is located normally, with uneven margins and multiple calcifications. A 12 mm cyst in the body of pancreas and a cyst of irregular shape in the tail with thick calcificated border (78×46×48 mm) are detected. Pancreatic duct is not dilated.
At first, parathyroid tumor resection and hemithyroidectomy were performed. After the surgery PTH lowered to 193 pg/ml and hypocalcaemia (total Ca 1.91 mmol/l, ionized Ca 0.94 mmol/l) occurred, treated with calcium and vitamin D supplement. Parathyroid carcinoma was confirmed by histology. Two months later subtotal distal pancreatectomy and splenectomy were performed. Three months after the treatment the patient's health improved, abdominal pain disappeared and she gained 5 kg. PHPT is not persisting.
This case report shows that chronic calcific cystic pancreatitis can develop on the background of hypercalcaemia and improve after parathyroid tumor resection. We suggest that serum calcium and PTH should be measured in all patients with non-alcoholic and non-biliary pancreatitis for PHPT diagnostic and pancreatitis should be diagnosed in all patients with PHPT.

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EP183

The relationship between obesity and serum Vitamin B12, folic acid, vitamin D concentrations in obes adults: a retrospective study

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Background
Obesity is associated with many diseases. e.g. cardiovascular diseases. The most common deficiency associated with obesity seems to be low concentrations of vitamin D that is associated with an increased risk of diabetes and other cardiovascular diseases. Low concentrations of vitamins are linked to accelerated atherosclerosis through increased oxidative stress. The purpose of this research was to investigate the association between obesity and vitamin B12(VB12), folic asid(FA) and vitamin D(VD) levels in patients.
Matherial-Method
The study was conducted at the outpatient clinic at Umraniye Research Hospital, between January and june 2015. We ennrolled 100 patients. Exclusion criteria included being a strict vegetarian, being over 50 or less than 18, current use of corticosteroids or vitamin supplements, long term use of proton pump inhibitors and intestinal absorbtion diseases. Blood was taken after a 8–12 hours overnight fasting and serum VB12, FA and VD levels are measured. BMI was calculated using the following formula: kg/height (m^2). We found $P<0.05$ (statistical significance).
Results
Demographic details are in Table 1. There was no statistically significant correlation between BMI and VB12 or FA levels ($P>0.05$). Significant correlation exists between BMI and VD levels ($P<0.05$). There is no a significant relationship between age and VB12, FA and VD levels.

Table 1 demographics and labratuary findings.

	Total	Male (*n*:18)	Female (*n*:82)
Age (years)	34.39 (0.89 S.D.)	36.1 (2.11 S.D.)	34.0 (0.98 S.D.)
BMI	27.85 (0.74 S.D.)	27.9 (1.30 S.D.)	27.8 (0.87 S.D.)
Vitamin B12	300.6 (13.64 S.D.)	245.8 (16.24 S.D.)	312.7 (15.99 S.D.)
Folic Acid	8.31 (0.32 S.D.)	8.16 (0.53 S.D.)	8.34 (0.37 S.D.)
Vitamin D	12.21 (0.85 S.D.)	12.47 (1.16 S.D.)	12.16 (1.00 S.D.)

Conclusion
We compared VB12 status in patiens with obesity and can't find any significant corelation. There is not enough research about FA levels in obesity but we found no correlation between obesity and serum FA levels. VD deficiency and secondary hyperparathyroidism are known to be prevalent in obesity and we find a significant correlation in our study.

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EP184

Our cases of familial hypocalciuric hypercalcemia

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Familial hypocalciuric hypercalcemia is an inherited disease caused by inactivating heterozygous mutations in the gene encoding calcium-sensitive

receptors, that affects calcium metabolism and generally follows a benign course. It must be also considered in the differential diagnosis of hyperparathyroidism. Six patients presenting to our internal diseases clinic between January, 2010, and June, 2015, were evaluated in terms of clinical and biochemical parameters. The youngest of our patients was 21 and the oldest was 86. Four were women and two were men. The children of five of our cases and the mother of one were assessed in a polyclinic environment. At evaluation, the presence of familial hypocalciuric hypercalcemia was considered on the basis of moderate hypercalcemia, threshold elevated parathormone levels and a significant decrease in daily calcium expulsion in urine. Diagnosis was confirmed in five patients through determination of similar laboratory findings for calcium metabolism in the children,and also in the mother of our young patient, and on the basis of exclusion of other causes of hypercalcemia. Assessment of calcium metabolism following correction of other factors that may be affected will help clinicians avoid misdiagnosis.
Consideration of familial hypocalciuric hypercalcemia in the diagnostic approach to hypercalcemia and at differential diagnosis of primary hyperparathyroidism will prevent unnecessary surgery.

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EP185

'Hyngry bone syndrome': after tertiary hypeparathyroïdism treatment

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Post parthyroïdectomy hypocalcemia is a frequent situation, generally due to a definitive or transient hypoparathyroïdism.
The 'Hungry bone syndrome', is a rare severe hypocalcemia etiology, assigned to an excessive osseous avidity, occurring in intense bone remodeling situations like fibrous osteitis or renal osteodystrophy.
We report a case of a 41 years old woman, presenting a chronic renal failure, at hemodialysis stage, complicated by a tertiary hyperparathyroidism, which was treated by a total parathyroïdectomy.
At immediate post operative follow-up the patient presented a severe hypocalcemia getting to 1.27 nmol/l, associated to a hypophosphoremia and elevation of the alkaline phosphatasis by 4000 UI/L, by what we diagnosed a 'Hungry bone syndrome'.
To control calcemia, we had to administrate a consequent dose of calcium and vitamin D, reaching 8000 mg/day of calcium gluconate, and 4 µg/day of calcitriol.
In conclusion, the 'Hungry bone syndrome', is a rare severe hypocalcemia situation, which is difficult to control; requiring an adequate managing. The prevention of this disease could relie on a good post operative vitamin D deficit supplementation.

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EP186

Calcium intake in Tunisian postmenopausal women: evaluation and impact on diabetes

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Introduction
Calcium intake is important to prevent osteoporosis in postmenopausal women. The objectives of our study were to evaluate the daily dietary calcium intake in postmenopausal Tunisian women, to compare diabetic and non-diabetic postmenopausal women in their calcium intake and finally to propose corrective interventions to promote calcium intake and minimize the complications of menopause.
Subjects and methods
The study involved 73 postmenopausal Tunisian women aged on average 61 years. Demographics and lifestyle were assessed with a questionnaire. Clinical and laboratory data were collected from medical records. Calcium intake was assessed by a food survey type 'food story' and estimated by the BILNUT software.
Results
Average daily calcium intake of our women was 723.8 mg/day. Sixty eight percent of these women had a daily calcium intake less than 800 mg/day. The average daily calcium intake in diabetic women was slightly lower than in non-diabetic (700.41 mg/day vs 778.04 mg/day). Diabetic women with HbA1c $<7\%$ had calcium intake slightly higher than those HbA1c $>7\%$ (741.25 mg/day vs 696.93 mg/day) but the difference was no significant.
Discussion and conclusion
The average calcium intake of our postmenopausal women is considered very low according to WHO. Only 1.3% of the patients had an intake deemed sufficient according to WHO. These alarming results are related to a multiparty and low educational context. These results encourage us to develop educational messages about the importance of calcium intake in postmenopausal especially diabetic women.

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EP187

The role of cinacalcet in a patient with persistent hypercalcaemia despite parathyroidectomy

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Introduction
Parathyroid adenoma is the commonest cause of primary hyperparathyroidism, but 10% of these adenomas can be ectopic, leading to persistent and recurrent hypercalcaemia.
Case
We present a case of 82 years old man was admitted in June 2011 with increasesd confusion, slurred speech, poor balance (ataxia). He had no features of sepsis and no other focal neurology. His past medical history included constipation, dry eyes. He was on Aspirin, hypromellose, and laxido.
Blood test: Hb 15.2, WCC 8.3, Na + 138, K 4.4, Urea 4.9, creatinine 84, ALP 70, Cor ca2 + 3.12, PTH-9.6, phosphate 0.79, ALT 100, Myeloma screen negative, Vitamin D 100, Urine: 24 h urinary calcium 8.2. Imaging;CXR normal, CT normal, sestamibi scan normal. He underwent exploratory surgery left sided parathyroidectomy July 2011 with normalisation of calcium levels initially. Normal looking parathyroid tissue (140 g). One month later he had relapse of hypercalcaemia.Readmitted for i.v. fluids & pamidronate Staging CT chest, abdomen and pelvis-normal apart right subcarina lymphnode measuring 11 mm. He remained hypercalcaemic despite multiple doses of i.v. pamidronate. He was started on cinacalcet 30 mg od daily for presumed ectopic parathyroid adenoma.
Discussion
The commonest cause of hypercalcaemia is primary hyperparathyroidism, but hypercalcaemia due to ectopic parathyroid adenoma although rare is not uncommon.
Conclusion
Cinacalcet can successful be used to control hypercalcaemia in patients with persistent and recurrent hypercalcaemia due ectopic parathyroid adenoma as demonstrated in this case report.

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EP188

Use of recombinant parathyroid hormone with significant improvement of debilitating hypocalcaemia and hypomagnesaemia

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Primary hypoparathyroidism is a rare condition. Contrary to other endocrine deficiencies treated with hormone replacement, recombinant parathyroid hormone (PTH) is not currently licensed for its treatment in Europe. Emerging evidence of efficacy and safety of recombinant PTH in treating resistant hypoparathyroidism will hopefully provide a new tool in managing this challenging condition.
This is the case of a 45 year-old woman presenting with gradually worsening paraesthesia and limb weakness. Initial investigations revealed low serum calcium of 1.58 (2.2–2.6 mmol/l), magnesium of 0.4 (0.7–1.05 mmol/l), potassium of 3 (3.5–5 mmol/l) and normal phosphate 1.21 (0.8–1.5 mmol/l), bicarbonate 27 (22–28 mmol/l), liver and renal function. Clinical examination only revealed a positive Chovstek's sign. Further investigations showed low PTH

at 0.6 (1.3–6.8 pmol/l), vitamin D at 14 (25–200 nmol/l) with elevated 24-h urine calcium excretion at 13.1 (2.5–7.5 mmol/24 h), urine magnesium excretion of 3.9 (2.4–6.5 mmol/24 h), normal thyroid function, haematinics and a basal cortisol of 375 nmol/l. She had osteopenia on dual energy X-ray absorptiometry and normal whole body computed-tomography, gastroscopy and coeliac screen. She was initially treated with intravenous calcium and magnesium, subsequently switched to oral supplements. She had recurrent admissions over 10 months with low calcium and magnesium. Recombinant PTH(1–34) (teriparatide) led to normalisation of calcium and no further admissions.
In this case hypoparathyroidism was attributed to severe renal magnesium wasting, related to an acquired mutation or a hereditary disorder clinically emerging in adulthood. In the United Kingdom, the N-terminal active fragment (1–34) of recombinant human PTH (teriparatide) is currently only licensed for the treatment of osteoporosis. In 2015, the full-length PTH (1–84) was approved for the treatment of hypoparathyroidism in the United States. The 'Efficacy and safety of recombinant human PTH (1–84) in hypoparathyroidism' (REPLACE) study showed good tolerance and therapeutic effect of PTH (1–84) in hypoparathyroidism. Further studies are required to evaluate the role and efficacy of PTH in the management of patients with resistant and/or persistent hypocalcaemia and hypomagnesaemia.

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EP189

Severe hypercalcemia due to the vitamin D intoxication presenting with acute renal failure

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Introduction
Hypervitaminosis D is a rarely reported condition. It may be observed more frequently because of the recent increase in supplement use of vitamin D. Herein, we report a case of vitamin D intoxication which was the first case with this high level of calcium as we searched the literature.
Case report
A 57-year old hypertensive woman admitted to our emergency room with symptoms of constipation, loss of appetite and confusion. Blood pressure, heart rate, and body temperature were 150/90 mmHg, 62 beats/min, and 36.6°C, respectively. Dried mucous membranes and decreased skin turgor tonus were observed. Routine chemistry revealed; glucose 98 mg/dl (70–100), urea 88 mg/dl (10–50), creatinine 3.4 mg/dl (0.6–1.3),albumin 3.8 g/dl (3.5–5.0), serum calcium 22.7 mg/dl (8.4–10.2) , serum phosphorus 2.5 mg/dl (2.3–4.7). Chest X-ray and the renal ultrasound was normal. Corrected QT was found 260 m/s in electrocardiography.
The patient reported that she had been operated due to diagnosis of multinodular goiter and hypothyroidism and hypoparathyroidism had developed postsurgically. She admitted to the another hospital one month ago with a calcium value of 7.6 mg/dl. At the time of admission, she was taking calcium 4000 mg/day, cholecalciferol 3520 IU/day, calcitriol 0.5 μg/day. Treatment was changed as calcium 6000 mg/day, cholecalciferol 5280 IU/day, calcitriol 1 μg/day. She was on 125 μg L-thyroxine therapy with a thyroid stimulating hormone level of 2.4 μIU/ml (0.35–4.94 μIU/ml).
The patient was hospitalized to our endocrinology clinic and taken to the low calcium hemodialysis. After hemodialysis, her calcium level decreased to 13.7 mg/dl. Then she was managed by continuous saline infusion and diuretics. The level of serum calcium and creatinine was 8.5 mg/dl, 1.1 mg/dl, respectively on the 8th day of treatment.
Conclusion
Vitamin D supplementation should be appropriately monitored due to potential risk of intoxication.

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EP190

Case report of osteitis fibrosa cystica

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Female patient named M.F., aged 37 years was complaining of Dull aching pain in her left shoulder, difficulty on lifting the left arm into right angle.
The patient had past history of generalised body aches.
The patient sought orthopaedic consultation because the pain in her left shoulder became severe.
X Ray on her left shoulder revealed an intamedullary infiltrative lesion in the humerus of ground glass (Mouth eaten) appearance.
MRI of the left shoulder which revealed abnormal infiltrative bone marrow signals.
CT chest and body revealed Bony skeleton marrow infiltration, Left lower lung nodule, Multiple hepatic focal lesions, Splenomegaly (Query Leukemia or Deposits) and Bone marrow biopsy was adviced.

- Laboratory investigations showed normocytic normochromic anaemia Serum Calcium: 7.7 mg/dl and Ionised Calcium 1 mmol/l.
- Bone marrow aspiration biopsy which revealed Hyper-cellular bone marrow with erythroid hyperplasia.
- PET scan revealed Multiple medullary based osteo-sclerotic lesions scattered all over the skeleton.
- Other laboratory investigations Vitamin D level: 7.46 ng/ml.
- Parathormone hormone: 198.9 pg/ml (normal range is 12–72).
- Alkaline phosphatase: 315 U/l.
- Patient underwent Bone marrow trephine biopsy from right superior posterior iliac spine which revealed Fibrovascular Bone marrow, consistent with osteitis fibrosa cystica related to parathyroid hyperfunction and that was the final diagnosis.
- The patient received treatment in the form of: Vitamin D supplements, Calcium supplements, Calcitonin inhalation, Alpha calcidiol.
- The patient received this treatment for 4 months, the pain in left shoulder has improved and the body aches also improved.
- February 2015*:* Total calcium: 9.5 mg/dl. Actual calcium: 1.30 mmol/l, Vitamin D: 26 ng/ml. Parathormone hormone: 71 pg/ml.
- The most recent X-ray showed improvement and follow up investigations in January 2016 were all normal.
- Conclusion: osteitis fibrosa cystica can present in a similar way as Malignancy clinically and radiologically and Vitamin D level and parathormone can be the only Key to diagnose it.

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EP191

Influence of hypercalcemia in the type 2 diabetes

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Status of carbohydrate metabolism in patients with hypercalcaemia and the influence of hypercalcemia on the risk of type 2 diabetes continue to be studied.
Objective
To study the prevalence of type 2 diabetes in patients with hypercalcemia and in patients without hypercalcemia.
Materials and methods
Continuous survey of 1000 people, average age 54.68 ± 16.96 (727 women, 273 men) from 18 to 96 years. Examination: total calcium, total protein, creatinine, cholesterol and triglycerides with an analysis of morbidity (osteoporosis, kidney stones, cholelithiasis, ulcer disease, type 2 diabetes, hypertension, coronary heart disease, cardiovascular events, cancer, fractures in history).
Results
Hypercalcemia has been found in 26 people, mean age was 57.42 ± 11.6 years. Type 2 diabetes is detected in 5 (19.2%) patients with hypercalcemia and 118 (12.1%) cases with type 2 diabetes were found among patients without hypercalcaemia.
Significant differences was detected in the prevalence of type 2 diabetes in patients with hypercalcemia and in patients without hypercalcemia ($\chi^2 = 0.57$, $P < 0.0001$).
Conclusion
The results of the study show an increasing prevalence of type 2 diabetes in patients with hypercalcaemia. The results may indicate the influence of hypercalcemia in the frequency of manifestation of type 2 diabetes.

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EP192

Dysarthria: a subject of neurology? What about endocrinology?

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Objective
Dysarthria is a motor speech disorder resulting from impairment in strength, speed and coordination of neural and/or muscular structures that are related to

respiration, voice and speech. They may be classified as motor neuron dysarthria, cerebellar dysarthria and extrapyramidal dysarthria (subdivided as hypokinetic and hyperkinetic). Patients with dysarthria are evaluated primarily by neurology specialists. Though, we present our case to emphasize that dysarthria may not only result from neurological disorders but also metabolical disorders.
Case report
A 51-year-old male patient was brought to emergency clinic with complaint of sudden onset speech disorder. With prediagnosis of cerebrovascular disorder, cerebral magnetic resonance imaging (MRI) and computed tomography (CT) scan were performed. For presence hyperdense lesions in CT scan, he was consulted to a neurosurgery specialist with prediagnosis of intracerebral hemorrhage. Lesions were not considered as hemorrhage by the neurosurgeon did not consider the lesions as intracerebral hemorrhage or subarachnoidal hemorrhage and referred the patient to neurology department for basal ganglia pathology. Patient's clinical and radiological findings was not considered as cerebrovascular disease by neurology. There was no low ADC values to suggest acute stroke in diffusion weighted MRI. Cerebral MRI revealed T2A hyperintensity in supratentorial periventricular regions suggesting leukoaraiosis. Cranial CT scan revealed calcifications in deep gray matter, thalamus, supra- and infratentorial regions and was reported as Fahr's diseased. Total serum calcium level was low (4.5 mg/dl). Ionized calcium study was not available. From his background evaluation, he complaint of tingling in his hands and muscle cramps for a few years. He had a history of pathological fracture in his leg 20 years before and there was gait disturbance.
His physical and neurological examinations were performed. He was awake but dysoriented. Dysarthria was present. Chvostek and Trousseau signs were positive. Respiratory system, cardiovascular system and abdominal examinations were normal. There was genu varum deformity in lower extremities. He had candida onychomycosis in his hands and feet and hyperpigmented regions on the anterior part of tibia secondary to convlescent exematous lesions. Bone mineral density T scores in the distal radius, lumbar spine and femur neck were -5.7, -0.1 and $+1.5$ respectively. Total serum calcium, parathyroid hormone (PTH) and magnesium levels were low, and phosphorus and alkaline phosphatase (ALP) levels were high. Urea, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, potassium, chlorine and thyroid hormone levels were normal. The patient who had primary hypoparathyroidism and mucocutaneous candidiasis is diagnosed with autoimmune polyendocrinopathy type 1. The patient was given peroral calcitriol, peroral and intravenous calcium and peroral magnesium daily. He was in need of high dose calcium. For candida onychomycosis, terbinafine was given.
During follow-up, dysarthia was improved and cramps did nor reccur. Celiac disease was ruled out. He was discharged with peroral calcium carbonate 3000 mg/day and peroral calcitriol 3 μg/day.
Result
Though dysarthria originates mostly from neurological disorders, metabolic disorders should also be looked for.

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EP193

Pregnancy with Fahr's disease: a rare case report

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Introduction
Fahr's disease is a rare, neurological disorder characterized by abnormal calcified deposits in basal ganglia. The clinical characteristics are various and usually appears such as disfunction of the affected areas. According to our knowledge, no case of Fahr's disease together with pregnancy has been described in the literature until now. The objective of this case report was to describe the clinical course of this rare condition in pregnancy.
Case report
We reported 28-year-old pregnant woman with Fahr's disease. She was diagnosed Fahr's disease by using physical, laboratory and radiological examination 3 years ago. She had no complaint about neurological and endocrinological during pregnancy. Her pregnancy was uneventful until the day of delivery.
Conclusion
Fahr's disease may not negative effect the pregnancy. However, in this regard, series of cases are needed.

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EP194

Pseudohypoparathyroidism with seizure: a rare case report

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Introduction
Pseudohypoparathyroidism is characterised by hypocalcaemia, hyperphosphataemia, increased serum parathyroid hormone values and insensitivity to the biological activity of parathyroid hormone. Pseudohypoparathyroidism is often associated with a characteristic phenotype known as Albright's hereditary osteodystrophy. This case was reported in order to remind pseudohypoparathyroidism in patients with hypocalcemic seizures.
Case report
We describe a 50-year-old man who presented with seizure due to hypocalcemia. He has typical features of Albright's hereditary osteodystrophy, which include a round face, short neck and stature and brachydactyly. Diffuse calsifications were seen on the bilateral cerebellum, putamen and dentate nucleus in computarized tomography. The patient is treated successfully by calcium carbonate and calcitriol supplementation.
Conclusion
Pseudohypoparathyroidism can present with unusual manifestations in the adulthood such as hypocalcaemia related seizures.

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EP194B

Surgical treatment the patients with tertiary hyperparathyroidism

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Introduction
Tertiary hyperparathyroidism (THPT) develops for the patients with *chronic kidney diseases* undergoes program hemodialysis. *THPT* is seen in patients with long-term secondary hyperparathyroidism which eventually leads to hyperplasia of the parathyroid glands (PTG) then it leads to adenomatous transformation and autonomization of the PTG.
The purpose of the study is the choice of rational diagnostic and treatment algorithm for the patients with THPT.
Methods/design
From 2013 to 2015 years 38 patients (12 woman, 26 man) with THPT were operated. The age was from 34 to 81 years. 29 people (76.3%) were older than 50 years. We detected levels parathyroid hormone (PTH), ionized calcium and phosphorus. We did make sonography thyroid and parathyroid glands, scintigraphy and MRI neck.
Results
Primordial level ionized calcium was 1.10 ± 0.3 mmol/l, level PTH – 946.3 ± 352.8 pg/ml, phosphorus – 1.72 ± 0.2 mmol/l.
During operations one adenoma was removed at eight patients, on two adenomas removed from six patients. 19 patients have removed three adenomas and five patients – five adenomas. A total of 102 adenomas were removed from 38 people. Repeated operations were conducted in eight cases. The diagnosis were confirmed by histological studies.
Of the 16 patients with multiple lesions of the PTG (3 or more) only in 11 cases with scintigraphy were found signs of one or two gland. Ultrasound detect parathyroid adenomas only in 70–75% cases. MRI identifies adenomas in 31 (96.9%) cases.
In time operation thyroid nodules were found at 15 (39.5%) patients. At five cases were make subtotal thyroidectomies, at 4 cases – hemithyroidectomies and at six cases – resections of thyroid.
PTH after operations decreased to 302.6 ± 195.4 pg/ml, and a week later was within or below the normal reference values at 78.9% of patients.
Conclusion
Sonography and scintigraphy PTG were detect adenomas in 70–75% cases, because the MRI necessary became for the algorithm investigation. Concomitant lesions of the thyroid and parathyroid glands were observed in more than 1/3 of the cases. Patients with THPT have needs for the lifelong follow-up.

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Cardiovascular Endocrinology and Lipid Metabolism

EP195

Liposomal prednisolone promotes macrophage necroptosis in experimental atherosclerosis: does this explain atherogenesis in Cushing's disease?

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Introduction
Patients with a Cushing syndrome – a glucocorticoid driven disease–have a high risk for cardiovascular events, mainly due to atherosclerosis. Atherosclerosis is a lipid-driven inflammatory disease, for which novel anti-inflammatory strategies like glucocorticoids are under evaluation. Thus, the impact of glucocorticoids on atherosclerosis seems to be ambiguous: pro- or anti-inflammatory. To avoid systemic glucocorticoid side effects contributing to atherosclerosis liposomal nanoparticles loaded with prednisolone phosphate (LN-PLP) can directly target the side of atherosclerosis. We aimed to unravel the direct effects of LN-PLP on macrophages residing in the lipid-rich environment of atherosclerosis.
Description of methods/design
Low-density lipoprotein receptor knockout ($LDLr^{-/-}$) mice were fed a high fat diet. Biweekly injections of LN-PLP at 10 mg/kg have been performed over 2 and 6 weeks. Post mortem, local delivery and intrinsic effects of LN-PLP have been studied on the aortic tissue. *In vitro*, murine and human macrophages were exposed to LN-PLP to study the effect of lipid trafficking endoplasmatic reticulum (ER) stress and apoptosis.
Results
We show that LN-PLP accumulated in plaque macrophages and enhanced monocyte recruitment to atherosclerotic plaques after 2 weeks, followed by increased macrophage content, more advanced plaque stages, and larger necrotic core sizes after 6 weeks of LN-PLP administration. *In vitro*, murine and human macrophages polarize into a lipid-avid phenotype after LN-PLP exposure, leading to increased lipid accumulation, ER stress and necroptosis.
Conclusions
These findings indicate that macrophage targeting in plaques with prednisolone may accelerate atherosclerosis by promoting macrophage lipotoxicity and necroptosis, thereby highlighting the challenges of anti-inflammatory therapy in atherosclerosis. This model might explain atherogenesis in Cushing's disease and unravel new mechanisms than can be used for medical treatment reducing the cardio-vascular risk of these patients.

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24-Hour blood pressure homeostasis and renal function in subjects with and without metabolic syndrome

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Introduction
Metabolic syndrome (MS) is related with progressive decrease of renal function. Although hypertension has a major role on this relationship, it is not clear how its behavior is related to decreased renal function.
Objective
To study how blood pressure (BP) measured by 24-hour ambulatory BP is related to renal function in patients with and without MS.
Methods
We designed a cross-sectional study of consecutive individuals ($n=108$; females 74%; 52.8 ± 12.7 years; mean$\pm$S.D.) from the diabetes clinic of a university hospital. Patients were classified according to their BP behavior: normotension (NT; $n=29$), white-coat hypertension (WCH; $n=19$) and ambulatory hypertension (AHT; $n=57$). Fasting and 2 h-plasma glucose levels, lipid profile, creatinine and 24-h urinary albumin excretion (UAER) were measured. Glomerular filtration rate (GFR) was estimated by the CKD-EPI equation. A two-sided P value <0.05 was considered significant.
Results
Estimated GFR (EGFR) was lower in subjects with MS than in those without MS (Mean$\pm$S.D.; 90 ± 20 vs 98.8 ± 16.5; $P=0.047$). EGFR was related to age ($r=-0.666$; $P<0.001$), fasting glucose ($r=0.223$; $P=0.021$), and 24-h systolic BP ($r=-0.196$; $P=0.044$), but not to diastolic BP. EGFR was inversely related to sleep-time BP ($r=-0.224$; $P=0.021$), morning systolic BP ($r=-0.224$; $P=0.030$) and pulse pressure ($r=-0.233$; $P=0.170$). Subjects with WCH and AHT compared to those with NT had lower EGFR (Mean$\pm$S.D.; 89.3 ± 18 vs 89.6 ± 26.3 vs 100.2 ± 14.8; $P=0.036$) and higher UAER (Median [P25–75]; 1 [0–5.3] vs 6.1 [1–19] vs 6.3 [1–16.8]; $P=0.031$).
Conclusion
A higher sleep-time BP, morning systolic BP, and pulse pressure were the components of BP homeostasis mostly related to decreased renal function and may be taken into account in the assessment of subjects with MS. The findings should prompt further research in order to evaluate whether or not interventions impacting on BP during sleep-time and early morning period may prevent renal damage.

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EP197

Effects of gender and menopausal status on serum apolipoprotein concentrations

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Introduction
Inconsistent data exist as to whether menopause is associated with increased cardiovascular disease (CVD) risk. However, few studies have evaluated differences in apolipoprotein metabolism according to menopausal status and gender. The aim of this study was to investigate the effects of gender and menopause on serum apolipoprotein B (apoB), A-I (apoA-I) and A-II (apoA-II) concentrations.
Methods/design
A cross-sectional analysis was undertaken of age and gender-related differences in apparently healthy Caucasian premenopausal and postmenopausal women not taking oral contraceptives or hormone replacement, and Caucasian men. Measurements included serum apoA-I, apoA-II, apoB, total cholesterol, low-density and high-density lipoprotein cholesterol (LDL-C and HDL-C respectively), triglycerides, cholesterol in HDL subfractions 2 and 3 and the apoB/apoA-I, LDL-C/apoB, HDL-C/apoA-I and HDL-C/apoA-II ratios. Analyses were undertaken with and without standardization for confounding characteristics and in 5-year age ranges.
Results
One hundred and nine pre-menopausal women (aged 32.9 ± 5.4 years), 253 post-menopausal women (aged 57 ± 6.5 years) and 307 men (aged 52.4 ± 10.5 years) were included in the analysis.
Overall, apoB concentrations were highest in men but rose with age and menopause in women to converge with concentrations in men in the age range 50-55 years. The LDL-C/apoB ratio was generally higher in women than men, especially postmenopausally.
Both apoA-I and apoA-II concentrations were highest in postmenopausal women and lowest in men. Men generally had the lowest ratios of HDL-C to apoA-I and to apoA-II, but the highest ratios were apparent in premenopausal women. In multivariable analyses, incorporating age, BMI, smoking, alcohol, exercise and number of pregnancies, the above differences were sustained.
Conclusions
Adverse effects of ageing in women, male gender and menopause on apoB concentrations and of menopause and, in particular, male gender on the cholesterol content of HDL particles were consistent with adverse effects on CVD risk, with male gender having the greatest effect.

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EP198

Urinary Albumin Excretion and Cardiovascular Risk in Nondiabetic Middle-Aged Adults: the 2011–2012 Korean National Health and Nutrition Examination Survey

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Introduction
Microalbuminuria is known as a predictor of cardiovascular disease (CVD) in patients with and without diabetes, as well as the general population. The objective was to determine whether there was an association between the urinary albumin excretion and CVD risk by estimating the Framingham Risk Score (FRS) in nondiabetic middle-aged adults.
Methods
This study was based on data from the Korea National Health and Nutrition Examination Survey, which was conducted by the Korean Ministry of Health and Welfare in 2011-2012. From the 16 576 participants, data for 5165 adults who were 40–79 years of age were included in the analysis. Based on the urinary albumin to creatinine ratio (UACR), the subjects were categorized into normal ($\leq$9.9 mg/g), high normal (10.0–29.9 mg/g), and microalbuminuria (30.0–299.9 mg/g) groups.
Results
The mean FRS increased with increases in the UACR: 11.53 $\pm$ 0.09 in the normal, 12.50 $\pm$ 0.28 in the high normal, and 13.18 $\pm$ 0.32 in the microalbuminuria in men; 10.32 $\pm$ 0.14 in the normal, 13.10 $\pm$ 0.32 in the high normal, and 14.00 $\pm$ 0.48 in the microalbuminuria in women. After fully adjusting for potential confounding factors, including lifestyle, sociodemographic factors, known CVD risk factors, and eGFR, high normal levels and microalbuminuria were significantly associated with $\geq$10% 10-year risk of CVD (odds ratio (OR) 1.777 (95% confidence interval (CI), 1.216–2.597) and OR 2.232 (1.197–4.160), respectively) compared with the normal in men. High normal levels and microalbuminuria were also significantly associated with a $\geq$10% 10-year risk of CVD (OR 2.041 (1.173–3.550) and OR 3.115 (1.538-6.308), respectively) after adjusting for the above covariates in women.
Conclusions
Urinary albumin excretion reflects CVD risk in nondiabetic middle-aged adults and high normal levels and microalbuminuria were independently associated with a higher risk of CVD.

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EP199

Hormonal treatment in a young and middle-aged population of transgender persons: impact on metabolic parameters

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The sex-specific sex steroid profile seems to be associated to the gender differences between males and females on metabolic and cardiovascular risk (CVR). Objetive: to examine the effects of cross-gender sex steroid exposure on metabolic and CVR parameters. We incorporated 152 women transgender (WT), age (Median) 31 yr old (16–62) and 76 male transgender (MT) age: 25 yr old (17–53), treated at least by 1 year. WT received transdermal 17ßEstradiol (E2) 50 µg/day + cyproterone acetate (up to 50 mg/day) and MT received transdermal Testosterone (T) 5 g/day or T-undecanoate (1000 mg i.m./12 weeks). Waist and hip circumference, BMI, T, E2, lipids, glucose, insulin and HOMA index, were measured at baseline and after 1-year of treatment. *Group WT*: No changes in the anthropometric variables were detected. T decreased from 5.1 $\pm$ 2.3 to 0.96 $\pm$ 1.4 ng/ml, $P<0.0001$. E2 and prolactin increased: 38 $\pm$ 18.8–196.7 $\pm$ 21 pg/ml, $P<0.0001$ and 19.8 $\pm$ 19.7–27.9 $\pm$ 17.3 ng/ml, $P<0.01$ respectively. HDL-c increased (49.5 $\pm$ 11.9–54.7 $\pm$ 15.1 mg%, $P<0.02$) while insulin and HOMA index decreased: 8.9 $\pm$ 6.3 vs 8.1 $\pm$ 3.8 uU/ml, $P<0.02$ and 2.14 $\pm$ 1.7 vs 1.9 $\pm$ 1.0, $P<0.01$, respectively. *Group MT*: T induced an increment in BMI (24.8 $\pm$ 6.1–25.7 $\pm$ 5.3, $P<0.013$), in ratio waist/hip (0.86 $\pm$ 0.08–0.89 $\pm$ 0.08, $P<0.05$), in T (0.44 $\pm$ 0.19–5.8 $\pm$ 3.1 ng/ml $P<0.0001$), and in HOMA index (1.69 $\pm$ 1.0–2.37 $\pm$ 1.27 $P<0.03$), while E2 and HDL-c decreased (6.8 $\pm$ 79–65.2 $\pm$ 37.7 pg/ml $P<0.0001$ and 59.7 $\pm$ 13.6–52.7 $\pm$ 12.7 $P<0.02$, respectively). Prolactin remains unchanged (19.3 $\pm$ 8.3–17.3 $\pm$ 6.8 ng/ml). There were significant correlations (Pearson) between the percentage increment of HOMA index and increment of both waist circunference (r: 0.438, $P<0.037$) and serum testosterone (r: 0.559, $P<0.03$). In this large number of transgender population treated with similar dosis and drugs, E2 seems to be protective (improvement of insulin-resistance and lipid profile) while T administration to biological women induced deletereous changes on lipid and insulin-resistance parameters.
These results seems to support the hypothesis that estrogens have beneficial effects in men and women but the dual action of T (in genetically men and women) seems to be associated to a gender-specific effect.

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EP200

Free triiodothyronine is a predictor factor of left ventricular remodeling in patients after myocardial infarction and primary reperfusion assessed by means of two-dimensional speckle tracking echocardiography

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Introduction
Left ventricular remodeling (LVR) is the most important consequence of acute myocardial infarction (AMI). The aim of the study was to assess the value of free triiodothyronine (fT3) in the prediction of LVR after AMI and primary coronary angioplasty (PCI).
Methods
Seventy patients (F/M = 17/53, 61 $\pm$ 11 years old) without recognized previous thyroid dysfunction and AMI were enrolled into the prospective observational study. Conventional and global longitudinal two dimensional speckle tracking echocardiography (LSTE) were performed 2 days (baseline) and 50 days after AMI. Thyroid function serum parameters (TSH, fT3, fT4) were measured three times: before, 2 and 50 days after catheterization. Patients were divided into two groups according to the change of LSTE at 50 days follow up (increase - I, decrease - II).
Results
At the baseline, both groups didn't differ in terms of fT3 concentration (mean difference 0.13 pg/ml; $P=0.4$), left ventricular ejection fraction (54% $\pm$ 9 vs 51% $\pm$ 10; $P=0.2$) and global LSTE ($-$17% $\pm$ 4 vs $-$15% $\pm$ 4; $P=0.1$). The difference between fT3 level between 2 and 50 days after PCI was a significant predictor of the change of LSTE (group x time interaction $P=0.015$). According to the ROC analysis the increase of fT3 upper 0.28 pg/ml (sensitivity 69%, specificity 54%) was the most powerful predictor of the increase of LSTE after AMI.
Conclusion
The change of fT3 levels are closely associated with early LVR in patients with AMI and successful interventional treatment, hence might help to distinguish the patients endangered LVR.

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EP201

The dual FXR/TGR5 agonist INT-767 counteracts nonalcoholic steatohepatitis in a rabbit model of high fat diet-induced metabolic syndrome

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Farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5) are interesting pharmacological targets for the treatment of liver and metabolic diseases. FXR-deficient mice on a high-fat diet (HFD) exhibit massive hepatic steatosis, necro-inflammation and fibrogenesis. Moreover, pharmacological

activation of TGR5 in mice promotes protective mechanisms in biliary epithelial cells and inhibits hepatic and systemic inflammation. Thus, we hypothesized that a FXR/TGR5 dual agonist (INT-767) would ameliorate features of nonalcoholic steatohepatitis (NASH) in a rabbit model of metabolic syndrome (MetS). Treatment with increasing doses of INT-767 (3,10,30 mg/Kg/day for 12 weeks) in a rabbit model of HFD-induced MetS, characterized also by NASH, dose-dependently reduced several MetS-associated alterations, including hepatomegaly, insulin resistance, increase of ALT, glucose, cholesterol levels, while significantly increasing HDL levels. ALT was positively associated with all MetS parameters; however introducing all MetS factors in a multivariate analysis, only total cholesterol levels resulted positively associated with ALT level. High macrophage M1 pro-inflammatory/M2 anti-inflammatory ratio was observed in MetS-induced NASH, which was independently associated with serum ALT levels. HFD-induced increase in M1/M2 ratio was reduced by INT-767 treatment and M2 macrophage markers were increased. Genes related to neutrophil apoptosis/apoptotic-neutrophil clearance and to extracellular matrix degradation were also increased by INT-767 treatment. INT-767 also reduced liver expression of IL-6, which preferentially skews the Th cell response towards a Th17-phenotype, while increasing Foxp3 expression, a Treg cell marker. These data indicate that INT-767 can promote the neutrophil- and macrophage-driven resolution phase of inflammation and fibrosis regression. In addition, INT-767 increased genes related to hepatic fatty acid metabolism and lipid droplet formation, suggesting that INT-767 counteracts excess fatty acid mediated lipotoxicity in the liver. Genes related to insulin signaling were also increased by INT-767. Finally, immunohistochemical studies demonstrated that INT-767 treatment significantly reduced both HFD-induced liver inflammation and fibrosis.

In conclusion, INT-767 treatment counteracts NASH in a rabbit model of HFD-induced MetS by promoting insulin sensitivity, resolution of inflammation and fibrosis regression.

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EP202

Adropin as a potential biomarker of nutrition status and cardiac function in hemodialyzed patients

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Introduction
Adropin, a newly discovered peptide hormone, seems to have broad implications in energy homeostasis and metabolism in humans. Its main role is in maintaining appropriate carbohydrate and lipid economy. However, the aim of this study was to look at the novel role of adropin as a potential marker for cardiac function and nutrition status in hemodialyzed (HD) patients. To the best of our knowledge, this was the first study to consider the relationship between serum adropin concentration and clinical status of HD patients.
Description of methods/design
The study consisted of 41 HD patients (29 males; median age ±53 years). Adropin levels along with circulating N-terminal pro b-type natriuretic peptide (NT-proBNP), troponin T (cTnT), albumin (Alb), fasting serum insulin and glucose levels, insulin resistance index (HOMA-IR), insulin-like growth factor 1 (IGF-1) and parameters of lipid economy were assessed. Additionally anthropometric measurements were taken and echocardiography was performed.
Results
Adropin levels were negatively correlated with: body mass ($r=-0.469$), BMI ($r=-0.445$) and triglycerides (TAG) ($r=-0.369$). Also there was a significant relationship between adropin concentration and IGF-1 ($r=-0.374$). However adropin levels were not correlated with glucose and insulin levels and HOMA-IR. Strong positive correlations were observed between adropin level and cTnT ($r=0.325$) as well as NT-proBNP ($r=0.355$). Adropin was related to: left ventricular ejection fraction (LVEF) ($r=-0.499$) and left ventricular systole (LVS) diameter ($r=0.451$). No correlation was found between adropin and blood pressure.
Conclusion
Adropin seems to be a negative predictor of nutrition in HD patients. The relationship between adropin and markers of cardiac insufficiency might indicate a new link between myokines and cardiovascular disease in dialyzed patients. Adropin could potentially be a new candidate for a marker of cardiac insufficiency in HD patients.

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EP203

Follicle stimulating hormone levels and subclinical atherosclerosis in older postmenopausal women

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Objective
Recent studies of perimenopausal women suggest that follicle stimulating hormone (FSH) levels may be associated with atherosclerosis, independent of actions of estradiol (E_2). Whether FSH is related to atherosclerosis in older postmenopausal women, who have completed the menopausal transition, remains unknown.
Approach
We assessed the relation of FSH and E_2 levels with carotid artery intima-media thickness (IMT) among 588 postmenopausal women participating in the prospective Kuopio Ischaemic Heart Disease (KIHD) Risk Factor study (1998–2001). Women were aged 53–73 and not using hormone therapy.
Results
We observed a significant inverse association between FSH levels and IMT. Mean IMT in quartiles 1–4 of FSH were 0.94, 0.91, 0.87, and 0.85 mm, respectively ($P<0.001$). After adjustment for age, E_2, testosterone, BMI, lipids, insulin, glucose, comorbid conditions and other factors, FSH levels remained inversely and significantly associated with IMT (Regression coefficients for quartiles 2–4 vs quartile 1: −0.039, −0.050, and −0.063, respectively; P for trend = 0.01). Findings were strongest in women aged 64–73 (P for trend = 0.005) and did not vary by category of BMI. In contrast, E_2 levels were not related to IMT.
Conclusions
We observed significantly lower IMT in women with the highest FSH levels in older postmenopausal women. Associations were not explained by E_2, adiposity or other factors. Our findings warrant replication and the further exploration of potential underlying mechanisms.

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EP204

Testosterone supplementation and body composition: results from a meta-analysis of randomized controlled trials

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Background
The role of testosterone (T) in regulating body composition is conflicting.
Aim
To meta-analyze the effects of T supplementation (TS) on body composition and metabolic outcomes.
Methods
All randomized controlled trials (RCTs) comparing the effect of TS on different endpoints were considered.
Results
Overall, 59 trials were included in the study enrolling 3029 and 2049 patients in TS and control groups, respectively. TS was associated with any significant modification of body weight, waist circumference and BMI. Conversely, TS was associated with a significant reduction of fat and with an increase of lean mass (standardized means −0.32 (−0.44; −0.19) and 0.51 (0.37; 0.66) for fat and lean mass, respectively; both $P<0.0001$) as well as with a reduction of fasting glycaemia and insulin resistance (−0.34 (−0.51; −0.17) mM and −0.80 (−1.16; −0.45) for fasting glycemia and HOMA index, respectively; both $P<0.0001$). The effect on fasting glycaemia was even higher in younger

individuals and in those with metabolic diseases. When only RCTs enrolling hypogonadal (total T < 12 moles/l) subjects were considered, a reduction of total cholesterol as well as of triglyceride levels were also detected. Conversely, an improvement in HDL cholesterol levels as well as in both systolic and diastolic blood pressure was not observed.
Conclusions
Our data suggest that TS is able to improve body composition and glycometabolic profile particularly in younger subjects and in those with metabolic disturbances. Specifically designed studies are urgently needed to confirm this point.
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EP205

Effects of sex steroids on cardiovascular risk profile in female to male transsexuals with cross-sex hormone treatment
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Introduction
In transsexualism, cross-sex hormone treatment (CHT) both improves and impairs several surrogate cardiovascular risk markers in female to male (FtoM). Few randomized trials on CHT with long follow-up and control group are available, and present evidence is inconsistent. We here assess changes in metabolic and cardiovascular risk after 12 months CHT compared with biological sex in FtoM GID.
Methods
Prospective observational study, including 20 FtoM GID, attended in the Gender Identity Disorder Unit (UTIG) of Hospital Clinic from July 2012 to November 2013, who accepted to participate. CHT in FtoM consisted of intramuscular testosterone undecanoate (1000 mg every 2–3 months) except for one who received transdermal testosterone (50 mg/day). Contraindications for CHT were ruled out; subjects had not previously received hormonal treatment, and had no history of cardiovascular disease or HIV. Anthropometric and body composition by DEXA, hormonal, metabolic and coagulation parameters were assessed at baseline, and at 6 and 12 months of CHT. Also endothelial dysfunction was evaluated by flow-mediated dilation (FMD) and Intima-media thickness (IMT) by carotid ultrasound at baseline, 6 and 12 months.
Results
Changes after 6 and 12 moths of CHT: anthropometry and body composition: increased BMI (P: 0.001), decreased total fat mass (P: 0.050), increased total lean mass (P: 0.007) and decreased ginecoid fat distribution (P: 0.008) Hormonal: decreased LH (P: 0.008), SHBG ($P < 0.001$) and increased testosterone ($P < 0.001$).
Metabolism
Increased total cholesterol (P: 0.043), LDL (P: 0.019) and triglycerides (P: 0.001), and decreased HDL (P: 0.035); increased homocysteine (P: 0.003) and leucocytes (P: < 0.001).
Coagulation
Increased hemoglobin ($P < 0.001$) and hematocrit ($P < 0.001$) and decreased platelets (P: 0.011). No changes in FMD or IMT were observed.
Conclusion
CHT in FtoM has negative effects in the metabolic profile in the first 12 months of treatment which could be associated to an increase the cardiovascular risk.
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Circadian clock expression in hypothyroid male Wistar rats
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Both metabolism and cardiac function fluctuate over the course of the day according to energy supply and demand. The triiodothyronine (T_3) regulates several genes related to metabolism and function in cardiomyocytes. Our previous data have suggested that there is a potential interrelationship between the regulation of cardiac function by T_3 and the intrinsic circadian clock in the heart. Considering that: i) the hypothyroidism is associated to a reduction on cardiac function, presenting lower frequency and duration of ventricular contraction and, ii) the oscillation in the circulating levels of T_3 during the 24 h are changed in this pathological condition, the purpose of the present study was to investigate the expression of clock genes and clock-controlled genes related to the cardiac metabolism and contraction in hypothyroid adult animals. For this, euthyroid and thyroidectomized male Wistar rats were euthanized every 3 h during 24 h. The hearts were excised and the mRNA expression was evaluated by RT-qPCR using cyclophilin as a housekeeping gene. One and two-way ANOVA, as well as, Cosinor analysis were used to evaluate the time-of-day-dependent differential expression for each gene/group and their interactions. In general, the hypothyroidism reduced the expression of *Pdk4,* at dark phase – ZT15, and *Ucp3,* at light phase – ZT2 and 9. No significant changes were noticed in *Bmal1, Per2, Dbp* and *Rora* expression throughout the whole investigated period. Our study shows that in the hypothyroidism there are punctual changes in the content of transcripts related to the cardiac metabolism and function but the expression of core-clock genes are preserved. These results corroborate with our previous investigation showing that T_3 actions in the heart seem to be independent of the clock, acting in specific target pathways like pyruvate dehydrogenase kinase and mitochondrial electron transport chain, which in turn can alter heart metabolism and function.
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EP207

Moderate cross-sex hormone-induced prothrombotic changes of hemostatic variables in transgender subjects
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Context
Little research has been performed on hemostatic changes in transgender subjects receiving cross-sex hormone treatment (CSHT), despite the fact that several studies implicate an increased risk of venous thrombosis (VT) associated with hormones.
Objective
Assessing whether coagulation is relevantly influenced by prolonged CSHT, stratified for the different treatment modalities, in transgenders.
Design and main outcome
Prospective study on CSHT-induced changes of hemostatic variables in transgenders. The main outcome measures were mean paired differences in factor II, IX and XI, protein C and S, fibrinogen, and activated protein C resistance (APCR) over a period of 12 months of CSHT.
Participants
Eighty two subjects were included, of which 41 male-to-female (MtF) and 41 female-to-male (FtM), who used CSHT for 12 months.
Intervention
Oral or transdermal 17β-estradiol, combined with cyproterone acetate, in MtFs and testosterone gel or injections in FtMs.
Results
In MtFs, protein C decreased on average by 0.078 U/ml (95% CI 0.042,0.111), while factor IX and XI increased by 0.152 (95% CI −0.235, −0.069) and 0.148 U/ml (95%CI −0.214, −0.082), respectively. No change was observed in the other factors. No difference in changes between the treatment modalities was observed. Conversely, FtMs only experienced an average increase of 0.104 U/ml (95% CI −0.215, 0.007) in factor IX. None of the other investigated factors showed any change in this group. Several factors changed differently for the treatment modalities. The results will be extended with more patients and hemostatic variables (APCR, TFPI). The complete set of results will be analyzed for the role of treatment modality, age and other relevant factors in these changes.
Conclusions
CSHT induces relevant prothrombotic changes in multiple hemostatic factors in MtFs. In FtMs, no clear effect of CSHT was observed. The change in some variables is modified by the different treatment modalities in FtMs, but not in MtFs.
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EP208

Optimising human hepatocyte models for metabolic phenotype: effects of treatment with DMSO

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Primary human hepatocytes are considered the 'gold standard' to explore metabolic phenotype within the liver, however they come with limitations, such as donor variability, lack of proliferation and rapid phenotype loss. The human hepatoma cell line, HepG2, has been used extensively in cell-based metabolic studies but there are significant limitations including their malignant origin and inherent low rates of triglyceride secretion. The aim of this study was to investigate whether dimethyl sulfoxide (DMSO) supplementation in the cell media could enhance HepG2 cell metabolic functionality leading to development of an improved model that may more closely resemble primary human hepatocytes. HepG2 cells were cultured in cell media containing 1% DMSO for 7, 14, and 21 days and gene expression, protein levels, intracellular triglyceride content and triglyceride, urea and 3-OH-butyrate concentrations in the cell medium measured. mRNA expression of four markers of hepatocyte differentiation (albumin, HNF4A, transthyretin and α1-antithrypsin) increased with DMSO treatment to levels that were similar to those seen in primary cultures of human hepatocytes. In addition, mRNA expression of the tumor marker alpha-fetoprotein decreased. Furthermore, DMSO treatment decreased intracellular triglyceride content (control = 205.1 ± 16.1 nmol/mg, day 7 = 83.8 ± 9.0 nmol/mg, day 14 = 82.3 ± 10.5 nmol/mg, day 21 = 83.9 ± 5.1 nmol/mg), while media triglyceride and 3-OH-butyrate levels increased in a time-dependent manner (TG: control = 2.5 ± 0.3 nmol/mg, day 7 = 1.4 ± 0.1 nmol/mg, day 14 = 5.0 ± 1.2 nmol/mg, day 21 = 6.2 ± 2.0 nmol/mg; 3-OH-butyrate: control = 4.5 ± 2.3 μmol/mg, day 7 = 12.3 ± 0.8 μmol/mg, day 14 = 12.1 ± 0.8 μmol/mg, day 21 = 9.0 ± 1.1 μmol/mg). Urea levels remained unchanged. Moreover, DMSO treatment decreased the mRNA expression of genes involved in lipid metabolism (ACC1, ACC2, DGAT1, DGAT2, FAS, SCD), but increased the levels of those implicated in glucose metabolism (PEPCK, G6PC). Changes in mRNA expression were mirrored by changes at the protein level as measured by western blotting. We have demonstrated that DMSO treatment changes the metabolic phenotype of HepG2 cells such that they more closely resemble primary human hepatocytes and has the potential to signficantly enhance currently available cell systems to study liver biology.

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EP209

Turner's syndrome and liver involvement: prevalence and characterization of a large population with Turner's syndrome

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Introduction
Elevated liver function tests (↑LFTs) are frequent in Turner's syndrome (TS), with a prevalence between 20 and 80%, and increases with age. Their pathogenesis and clinical significance is unclear.
Objectives
To study the prevalence of ↑LFTs and their relationship with karyotype, anthropometric, metabolic and TS-related conditions: 68 TS women, average age 39 years (range 18–61 years), were reviewed.
Results
Twenty six women (38%) had one or more liver enzymes persistently raised (duration 5.6 years ± 3.8 S.D.), with the most frequently elevated enzyme being GGT in 92% of cases, and ALT, ALP and AST in 77, 69 and 38%, respectively. Hepatitis serology and autoimmune-markers were negative, bilirubin was normal and no reported alcohol consumption in all. In the normal-LFTs-group no past history of ↑LFTs was noted.
There was no association between ↑LFTs and anthropometric values (height/weight/BMI), diabetes, HbA1c, renal or cardiac malformations, and either GH or oestrogen therapy. The prevalence of spontaneous menstruation was higher in the normal-LFTs-group. Age was significantly higher in the ↑LFTs-group (42.5 year ± 13.1 S.D. vs 34.9 year ± 12.4 S.D., $P = 0.01$). 48% of patients with ↑LFTs had a karyotype 45,X0 vs 32.5% in the normal-LFs-group. The frequency of hypertension, dyslipidaemia and thyroid autoimmunity was higher in the ↑LFTs-group (35% vs 14%, 23% vs 7% and 27% vs 17%, respectively). Abdominal-ultrasonography was normal in ten cases, suggestive of NAFLD (non-alcoholic-fatty-liver-disease) in four and in one showed nodularity and hepatosplenomegaly. Two patients had a normal Fibroscan and one a normal MRCP. Liver biopsy was performed in three patients: one normal, one NAFLD and one showed chronic hepatitis.
Conclusions
This study confirms that the prevalence of ↑LFTs increases with age, that an adequate oestrogen milieu may be protective, and HRT does not need to be discontinued in the presence of ↑LFTs. It suggests that ↑LFTs may be commoner in TS patients with 45,X0, and/or hypertension, hyperlipidaemia and autoimmunity.

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EP210

Natural history and metabolic implications of the new hormone fibroblast growth factor 21 in uremic patients on peritoneal dialysis

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Background
Human fibroblast growth factor 21 (FGF21) is a new liver hormone that stimulate adipocyte glucose uptake and is involved in regulation of body fat.
Objective
To define the natural history of FGF21 in peritoneal dialysis (PD) patients and analyze its relationship with glucose metabolism, peritoneal function, and residual renal function (RRF).
Methods
We studied 48 uremic patients undergoing PD. Patients were evaluated at baseline, and 1, 2 and 3 years after starting PD. At each evaluation, clinical status, biochemical parameters (including FGF21, glucose, insulin, homeostatic model assessment of insulin resistance index (HOMA-IR) and non-esterified fatty acids concentration (NEFA)), and peritoneal function parameters were assessed.
Results
Plasma FGF21 concentrations significantly increased over the first year and maintained at high levels during the rest of the study period, especially among non-diabetic patients ($n = 37$, baseline 253 (59–685) vs 647 (121–1117) pg/ml at third year, $P < 0.01$). In non-diabetic patients glucose levels did not modify, whereas HOMA-IR showed a significant reduction at second year (1.96 (1.23–4.15) vs 1.65 (0.79–2.86), $P < 0.01$). Baseline FGF21 concentrations significantly correlated with RRF ($\rho = -0.484$, $P < 0.05$) and peritoneal protein losses (PPL, $\rho = 0.410$, $P < 0.05$). Using a mixed model analysis, we found a positive correlation between time on dialysis and FGF21 levels ($P < 0.001$). There was no association between FGF21 levels and age, body mass index, HOMA-IR, NEFA, glucose, glucose load from PD solutions, and peritoneal mass transfer coefficients of urea and creatinine. Patients with RRF had significantly ($P < 0.05$) lower levels of FGF21 than those without it, and there was a significant positive association between FGF21 levels and PPL ($P < 0.05$), independently of the time on dialysis.
Conclusion
FGF21 plasma levels importantly increase during PD therapy. This increment is associated with RRF and PPL. The absence of increment in insulin resistance in spite of maintained peritoneal glucose load suggests that FGF-21 might behave as a protective factor against insulin resistance.

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EP211

Impact of a specific risk factors unit intervention on clinical outcomes in patients with type 2 diabetes after myocardial infarction

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Introduction
In our setting, it is quite common that control of major risk factors of patients with type 2 diabetes (T2D) after myocardial infarction (MI) is not made by specific risk

factors units (SRFU). Here, we conducted a preliminary study to investigate the effects of a SRFU intervention on metabolic and cardiovascular outcomes in T2D patients who suffered from MI.
Methods/design
This retrospective and observational study was performed in one single centre. Data related to metabolic and cardiologic variables were collected at discharge and at 6 and 12 months of follow-up. Variables were compared according to whether risk factors control was made by SRFU or other specialties after discharge.
Results
Data from forty-eight patients (mean age: 70.6 ± 8.7 years; 47.9% females) were collected. 27.5% were referred to SRFU after discharge. Antidiabetic treatment was changed in 48.7%. Among patients whose treatment was changed, add-on strategy was the most used way to switch it (63.2%). Patients referred to SRFU were more likely to undergo changes in treatment (81.8% vs 35.7%; $P=0.01$). A1C reductions were higher among patients under SRFU control at 6 and 1 year (−0.74% vs −0.69% and −0.92% vs −0.65%, respectively). Also, rates of new hospitalizations due to heart failure at 6 and 12 months (18.2% vs 21%; 0% vs 5.5%) and mortality by any cause (0% vs 13%; 0% vs 5.5%), were lower in SRFU group. Nevertheless, non-significant differences were observed between groups.
Conclusions
Our results show a non-significant trend toward to improvement of metabolic and cardiovascular outcomes among patients that were referred to SRFU after MI. These differences were more remarkable when follow-up time was longer. Though further studies with a larger number of patients are ongoing in our Hospital, we conclude that referrals to a SRFU should be recommended in these patients.

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EP212

Which are the male factors associated with female sexual dysfunction (FSD)?

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It has been generally assumed that partner's erectile dysfunction (ED), premature (PE) and delayed ejaculation (DE) play a significant role in determining Female sexual dysfunction (FSD). The present study aimed to evaluate the role of perceived male partner's sexual function and of the referred quality of relationship in determining FSD. A consecutive series of 156 heterosexual women consulting our outpatient clinic for FSD between January and December 2014 was retrospectively studied. All patients underwent a structured interview and filled out the Female Sexual Function Index (FSFI).
No significant association was observed between FSFI total score and cardiovascular risk factors or investigated metabolic parameters. When relational parameters were evaluated, FSFI total score decreased as a function of partner's age, conflicts within the couple, a relationship without cohabitation and the habit of engaging in intercourse to please the partner ($P<0.05$); FSFI total score increased as a function of frequency of intercourse, attempts to conceive and fertility-focused intercourse ($P<0.05$). FSFI total score showed a negative, stepwise correlation with partner's perceived hypoactive sexual desire (HSD) ($r=-0.327$; $P<0.0001$), whereas no significant correlation was found between FSFI and ED, PE or DE. In an age-adjusted model, partner's HSD was negatively related to FSFI total score (Wald = 9.196, $P=0.002$), and arousal (Wald = 7.893, $P=0.005$), lubrication (Wald = 5.042, $P=0.025$), orgasm (Wald = 9.293, $P=0.002$), satisfaction (Wald = 12.764, $P<0.0001$) and pain (Wald = 6.492, $P=0.011$) domains. Partner's HSD was also significantly associated with somatized anxiety, low frequency of intercourse, low partner's care for the patient's sexual pleasure and with a higher frequency of masturbation, even after adjusting for age ($P<0.05$). In patients not reporting any HSD, FSFI total score was significantly lower when their partner's libido was low ($P=0.041$); the correlation disappeared if the patient also experienced HSD.
In conclusion, the partner's performance during sexual intercourse, in terms of erectile function and ejaculatory times, does not seem to act as a primary contributing factor to FSD, as determined by FSFI scores; conversely, women's sexuality seems to be mostly impaired by the perceived reduction of their partner's sexual interest.

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EP213

Aerobic exercise increases catalase activity and decreased levels of leptin and TNFα in patients with liver disease

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Introduction
Both insulin resistance and oxidative stress are implicated in the pathophysiology of various diseases such as type 2 diabetes mellitus, atherosclerosis or liver disease. Furthermore, the uncoupling protein-1 (UCP1) is involved in induced thermogenesis, related to the pathogenesis of obesity and diabetes. The aim of this study was to assess the impact of aerobic exercise on the inflammatory profile in patients with chronic hepatitis C.
Methods
We designed an experimental prospective (before-after) study that included patients with chronic hepatitis C and insulin resistance but without associated metabolic syndrome. An individualized program of aerobic exercise (three sessions of 60-min/week) for 16 weeks was designed. Variables were determined (antioxidant markers and adipokines) before and after the intervention. Serum leptin and TNF-alpha concentrations were measured using commercial kits for ELISA (Immunotech, Coulter Corp., Westbrook, MA, USA). The catalase activity was inflammatory cytokines monitored with a commercial kit (Cayman Chemicals, Michigan USA).
Results
A total of 34 patients were included. The mean age was 46.8 ± 5 years and 22 were male (65%). The mean baseline BMI was 25.7 ± 3.5 kg/m^2 and excess weight of 6.17 ± 6.67 kg. Adherence to the exercise program was 88%. After 16 weeks of the exercise program, a significant increase in catalase enzyme levels (20.37 ± 1.32 vs 27.33 ± 1.94 mmol/min^{-1} per ml, $P=0.005$) and a decrease of leptin (14 500 vs 11 500 pg/ml, $P<0.05$) and TNFα (0.65 vs 0.05 pg/ml, $P<0.05$) levels were detected. On the other hand, the concentration of uncoupling protein-1 (UCP1) showed a statistically significant increase after exercise (305.2 vs 510.5, $P<0.05$).
Conclusion
In our series, the prescription of an individualized aerobic exercise program, controlled and monitored for 16 weeks, improved antioxidant status and decreased levels of proinflammatory cytokines and adipokines in patients with chronic liver disease and insulin resistance.

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EP214

Impact of overweight and obesity on cardiac diastolic function

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Introduction
Left ventricular diastolic dysfunction (LVDD) is a common cause of heart failure in obese patients. The aim of this study is to evaluate diastolic function and its relation to body mass index (BMI) in overweight and obese patients by using transthoracic echocardiography.
Material and method
A total of 133 cases were enrolled in the study. All anthropometric and laboratory measures were recorded. After measuring two-dimensional and M-mode echocardiographic variables, left and right ventricle diastolic functions were evaluated by conventional and tissue Doppler imaging. The patients with diabetes mellitus, hypertension and any kind of cardiovascular disease were excluded from the study.

Results
BMI was positively correlated with systolic and diastolic blood pressures and laboratory measures of HOMA-IR, low density lipoprotein (LDL) and proBNP. BMI was positively correlated with left atrium (LA) and left ventricul (LV) end-diastolic, end-systolic diameters, thickness of the wall of the LV, LA volume indices and LV mass indices ($P=0.000$). When tissue Doppler diastolic parameters were evaluated for right and left ventricul; BMI was negatively correlated with mitral septal annulus E' ($P=0.022$), and positively correlated with LV end-diastolic filling index E/e' ($P=0.005$), tricuspid annulus E' ($P=0.049$), tricuspid annulus A' ($P=0.006$), tricuspid annulus peak myocardial systolic velocity (Sa) ($P=0,004$). Pro-BNP was negatively correlated with mitral annulus E' ($P=0.007$) and positively correlated with left atrium and ventricular diameters ($P=0.027$ and 0.008 respectively), left atrium volume index ($P=0.000$) and E/e' ($P=0.029$).
Conclusion
Overweight and obesity have a negative impact on diastolic function as assessed by tissue Doppler imaging. Positive correlation between BMI and pro-BNP levels may call attention to potential value of pro-BNP as a marker of diastolic dysfunction.

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EP215

TNF related apoptosis inducing ligand (TRAIL) reduces reactive oxygen species production by human aortic endothelial cells exposed to inflammatory stimuli

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Introduction
Accumulating evidence suggests that one of the most significant contributors to endothelial dysfunction is increased oxidative stress. Excessive reactive oxygen species (ROS) generation can have injurious effects within the vasculature including elevated expression of adhesion molecules, stimulation of vascular smooth muscle cell proliferation, and promotion of endothelial cell apoptosis; events which culminate in the formation and progression of atherosclerotic plaque. Tumour necrosis factor related apoptosis inducing ligand (TRAIL), a member of the tumour necrosis factor (TNF) superfamily, has been shown to exhibit anti-atherosclerotic properties in animal studies. Preliminary studies from our own group, indicate that under pro-atherogenic oscillatory flow, TRAIL treatment of human aortic endothelial cells (HAECs) can shift net gene expression toward an 'atheroprotected' phenotype by up-regulating anti-oxidant genes. The aim of this study therefore was to confirm the anti-oxidant potential of TRAIL at a functional level, by investigating the effect of TRAIL on TNF-α and hyperglycaemia induced ROS production.
Methods
Primary human-derived HAECs were cultured in six-well plates and exposed to pro-oxidant conditions (TNF-α 100 ng/ml or Glucose 30 mmol, 24 h), in the presence and absence of Recombinant TRAIL (100 ng/ml, 24 h). Flow cytometry using dihydroethidium staining was utilised to measure ROS.
Results
TNF-α and hyperglycaemia significantly increased ROS production from HAECs, whilst TRAIL alone had no effect on ROS production. When co-cultured with TNF-α however, TRAIL significantly attenuated TNF-α induced ROS release ($n=3$, $P<0.05$). TRAIL also significantly attenuated hyperglycaemia induced ROS release ($n=3$, $P<0.05$).
Conclusion
TRAIL may impart protective effects on the vascular endothelium, in-part through reduction of oxidative stress. Though the anti-oxidant mechanism is unclear, this effect does not appear to be mediated by TNF-α antagonism.

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EP216

Primary aldosteronism and pregnancy

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Introduction
Primary aldosteronism (PA) may present in younger age and it may so complicate pregnancy if not diagnosed early. Our aim was to identify patients in whom PA was diagnosed after pregnancy and to seek for possible complications during pregnancy.
Design of methods
Retrospective analysis of patients with PA.
Results
We found nine patients with PA (age at diagnosis 31.9 ± 5 years, hypertension duration 5.9 ± 2.6 years) suffering from hypertension 2.6 ± 1.6 years before pregnancy (two patients had hypertension diagnosed during pregnancy). In seven cases, pregnancy was terminated with caesarean section and two patients delivered spontaneously. Preterm delivery occurred in three cases – the earliest one in the sixth month. In six cases, diagnosis of preeclampsia was made.
Subsequent diagnosis of PA (sometimes with a long delay (12 years)) was made on the basis of significantly low potassium values (two subjects suffered even from hypokalemic paralysis) and hypertension, elevated plasma/serum aldosterone and suppressed plasma renin activity or plasma renin. Eight subjects underwent laparoscopic adrenalectomy (in all cases, diagnosis of a cortical adenoma was made) and the last subjects was classified with bilateral hyperplasia according adrenal venous sampling. Operation normalized blood pressure in six subjects and improved significantly blood pressure control in remaining two subjects. One patient became pregnant after adrenalectomy and her pregnancy went uneventful.
Conclusion
The most frequent pregnancy-related complication of PA is preeclampsia. The best prevention of these complications is only early diagnosis of PA, in these particular hypertensive cases the awareness of hypokalemia.

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EP217

Hypertension in young patients: at what age should we explore?

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Introduction
Secondary high blood pressure is commonly diagnosed in young patients. In recent years, hypertension is increasing as well as the other components of metabolic syndrome such as obesity. The aim of this study was to determine the etiology of hypertension in patients aged <40 years old admitted in an endocrinology department.
Materials and methods
It was a retrospective study including 55 patients <40 years old hospitalized at the endocrinology department between 2003 and 2015 for exploration of a high blood pressure. Patients with cardiac or known renal failure were not enrolled. Epidemiological characteristics, clinical signs of secondary hypertension and biological data were recorded.
Results
The mean age at diagnosis of hypertension was 27.7 ± 7.4 years. Sex ratio (M/F) was 1.2. The mean duration of hypertension was 25.2 ± 43.1 months. 56.1% of patients had severe hypertension. There was a family history of hypertension in 72.7% of cases. Twenty percent patients had prediabetes or diabetes, 30.9% had dyslipemia and 81.8% had overweight. The triad of pheochromocytoma was observed in 18.1%. Cushing syndrome clinical signs were observed in 12.7%. Endocrine causes of hypertension were found in 25.5%: Cushing syndrome in 5.5%, pheochromocytoma in 5.5%, primary hyperaldosteronism in 14.5% (six cases of Conn syndrome and two cases of adrenal hyperplasia) and secondary hyperaldosteronism in 3.6%: One patient had an hypoplasia of thoracic aorta. Renal artery ultrasound was performed in 47.2% of cases. No renal artery stenosis was observed. The etiology of hypertension remained unknown in 70.9% of cases. The rate of secondary hypertension was no different between patients with overweight and those without overwieight ($P=0.11$).
Conclusion
Prevalence of secondary hypertension in our study was 29.1%. Primary hyperaldosteronism was the most frequent cause. Obesity should not dispense from the exploration of secondary hypertension in youth population.

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EP218

Comparison low-density lipoprotein cholesterol levels calcutation using the novel method by Martin vs the Friedewald equation in type 2 diabetic patients

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Introduction
LDL cholesterol (LDL-C) is usualy estimated using the Friedewald equation. This equation assumes a fixed factor of 5 for the ratio of triglycerides to very LPL cholesterol (TG:VLDL-C); however, the actual TG:VLDL-C ratio varies significantly across the range of triglyceride and cholesterol levels. A new method was proposed by Martin, S and co-workers using NHANES data. We aimed to evaluate the concordance Friedewald formula with the new method for LDL-C estimation from the standard lipid profile using an adjustable factor for the TG:VLDL-C ratio.
Design and settings
We used the results of consecutive clinical lipid profiles obtained from 2000 through 2015 from 40 339 patients of our outpatient clinic, at our hospital lab. The measurements were done mainly in type 2 diabetic – 66.1%. Females were 52% of cases cholesterol concentrations were directly measured after vertical spin density. LDL-C was measured if tryglicerides over 400 mg/dl and calculated by Friedewald formula if lower. Data were analysed in SPSS package v20.
Results
Diabetic patients had lower LCL-C levels than non diabetics (92 vs 101 mg/dl – $P<0.001$). Results of LCL-C are highly correlated in the all lipid profiles (93% $P<0.001$) but mean values are 108.3 vs 96.4 mg/dl using Friedewald formula vs the new method. Wilcokson rank test find significant differences between the 2 methods ($P<0.001$).
Conclusions and relevance
This novel method to estimate LDL-C using an adjustable factor for the TG:VLDL-C ratio produces significant lower values of LDL-C than the Friedewald equation. These findings require external validation, as well as assessment of their clinical importance. The implementation of the new method into clinical practice is particular relevant when triglycerides are higher than 400 mg/dl.

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EP219

The relationship between non-high density lipoprotein cholesterol and insuline resistance in obese patients

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Introduction
Correction of Insulin resistance (IR) and dyslipidemic conditions of obese patients is important for the prevention of cardiovascular disease (CVD). The aim of our study is to determine the relationship between IR and non-high-density lipoprotein cholesterol (non-HDL-C) in obese patients.
Material and methods
248 patients over the age of eighteen, non-pregnant, followed with a diagnosis of obesity but did not receive the treatment of metformin and statin are investigated retrospectively. Fasting glucose (FG), HbA1c, insulin, homeostasis model assessment of IR (HOMA-IR), LDL-C, triglycerides (TG), HDL-C, total cholesterol (TC) and non-HDL-C parameters of these patients were evaluated.
Results
Totally 248 patients (35 male (14.1%) – 213 female (85.9%) were included to study. When male and female patients are compared, significant differences were observed only for the parameters of HDL-C and TG ($P<0.05$). While it is found that HDL-C is higher in female group, TG is higher in male group. Intra-group comparisons reveal that there is a highly significant correlation between HOMA-IR and HDL-C ($P<0.01$). It is also observed that HOMA-IR and TG are highly correlated with each other among women ($P<0.01$). Among women it is also found that non-HDL-C is highly correlated both with FG and HbA1c ($P<0.01$).
Conclusion
When HOMA-IR as insulin resistance marker was found related with HDL-C and TG in women, the absence of this relation in men may be due to number of patients. However, the absence of correlation between HOMA-IR and non-HDL-C in male and female patients may be because of a more strong relationship between HOMA-IR and TG in early period. In addition to this, during this period the fact that non-HDL-C is highly correlated with both HbA1c and FG level may suggest that the importance of non-HDL-C in prediabetes and diabetes stages may increase.

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EP220

Comparison of serum thyroid stimulating hormone and anti-thyroid peroxidase antibody levels in euthyroid subjects with and without metabolic syndrome

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Objective
The present study aimed to evaluate thyroid stimulating hormone (TSH) levels and anti-thyroid peroxidase antibodies (anti-TPOab) in euthyroid subjects with metabolic syndrome (MetS) and to compare them with healthy subjects without MetS.
Design
Study included 173 subjects consisted of 96 subjects with MetS and 77 healthy controls. Gender, age, body mass index (BMI), waist circumfrence (WC), and detailed medical history of all participants were noted. Serum insulin, glucose, 'Homeostatic Model Assessment- Insulin Resistance' (HOMA-IR), total cholesterol (TC-HOL), low density lipoprotein (LDL-CHOL), high density lipoprotein (HDL-CHOL), triglyceride (TG), TSH, free T4, and anti-TPOab levels were obtained.
Results
TSH and anti-TPOab levels were significantly higher in the MetS group than control group ($P=0.048$ and $P=0.001$, respectively). A ROC curve for anti-TPOab to discriminate between patients with MetS and controls was determined at $\geq$16.4 IU/ml (sensitivity 89.58%; specificity 80.52%; positive predictive value 85.15%; negative predictive value 86.11%; $P=0.001$). Odds ratio for anti-TPOab $\geq$16.4 IU/ml between MetS and control group were 35 547 (95% CI 14 979–84 357).
Conclusions
Serum TSH and anti-TPOab levels were significantly higher in euthyroid subjects with MetS than those without MetS. Subjects with MetS who had anti-TPOab levels $\geq$16.4 IU/ml had 8-9-fold risk of having higher than normal BMI; sevenfold risk of having HT; 11-fold risk of having higher than normal HOMA-IR; 2-fold higher incidence of family history of CAD; and fourfold risk of having HL.
Keywords: metabolic syndrome, anti-thyroid peroxidase antibody, thyroid stimulating hormone, cut-off

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EP221

Effect of progesterone on intracellular calcium in mESC-derived cardiomyocytes

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Sex steroid hormones effect on the early embryo-development and regulate the calcium signaling in cardiac muscle. Progesterone (P4) has been reported to affect both blood pressure and other aspects of the cardiovascular system. To confirm the effect of P4 on early differentiation of mouse embryonic stem (mES) cells into cardiomyocytes, the hanging-drop method was performed to form embryoid bodies (EB). The mouse EBs (mEB) were suspended, attached onto six well plates and cultured in differentiation medium containing steroid-free FBS without LIF. P4 (10 nM) was applied at 2 days after attachment and media were replaced every 2 days. To assess the differentiation into cardiomyocytes, the presence of mesoderm markers such as Branchyury and cardiac-specific marker genes such as Tbx20 and Ctn1 were confirmed. In addition, the expression of sex steroid hormone-receptors, including PR, ER and AR, was confirmed. Interestingly, mRNA expression of AR and ER increased time-dependently during

differentiation into cardiomyocytes, while expression of PR exhibited the opposite pattern to that of the beating ratio. The beating ratio of the P4-treated group (60.45 ± 1.54%) decreased relative to that of the VE group (92.17 ± 2.98%) on day 12. Based on this response, the expression of contraction-related genes and the intracellular Ca^{2+} level was investigated. The expression of contraction-related genes such as Ryr2, Cam2, Trpv2 and Mlck3 was decreased in the P4-treated group relative to the VE and RU486 group. The protein expression of TRPV2 in P4-treated group also decreased. Subsequent measurement of the intracellular Ca^{2+} level by confocal analysis revealed decreased level in the P4-treated group. Moreover, the beating frequency of the EB population was significantly lower in the P4-treated group. These results suggest that P4 induced a decrease in intracellular Ca^{2+} level with reduced expression of Ca^{2+} channel and regulatory proteins, thereby causing a decrease in contracting cardiomyocytes with low beating frequency.

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EP222

Anti-thyroid antibodies as an additional risk factor for endothelial dysfunction in type 2 diabetic patients with subclinical hypothyroidism

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Aim
Recent studies have shown that immune responses contribute to atherosclerosis. The aim of this study was to investigate the relationship between carotid imt and the levels of anti-tpo in type 2 diabetic subjects with subclinical hypothyroidism (sch).
Subjects and methods
A total of 109 non-smoking diabetic subjects with sch were recruited for this study from June 2013 to May 2015. We used the analysis of variance to compare the differences of imt among the groups with different anti-tpo levels. Carotid imt was evaluated using high-resolution b-mode ultrasonography. Statistical analysis was performed by using spss 18 (P value <0.05 was considered significant).
Results
The mean age of the participants was 54.3 ± 5.06 years with diabetes duration 4.6 ± 3.21 years. A positive correlation was found between the mean of six segment carotid imt means and the levels of anti-tpo ($r=0.58$). Carotid imt levels were also significantly and positively associated with tsh, fpg and hba1c levels, whereas negatively with hdl-c. There were no statistically significant differences in the lipid profile and blood pressure levels between the groups with different anti-tpo levels.
Conclusion
In type 2 diabetic subjects with sch we found significant association between levels of anti-tpo and carotid imt. Measurement of thyroid antibodies can be useful risk factor for progression of carotid imt in type 2 diabetic subjects.

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EP223

A novel lipid tetrad index as predictor of premature coronary artery disease in diabetic patients

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Background
The aim of this study was to explore if evaluation of lipid risk factors like lipoprotein(a) (Lp(a)) and conventional lipid profile parameters can be a efficient predictor of the cardiovascular risk in the patients of diabetes.
Methods
Sixty individuals with angiographically proven premature CAD and 30 healthy individuals matched for age and sex were studied a tertiary health care center, New Delhi, India, over a period of 18 months. CAD patients were divided into two groups based on presence ($n=30$) [Group I] and absence ($n=30$) [Group II] of type 2 diabetes mellitus. The serum levels of Lp(a) were measured by ELISA and routine lipid profile (serum triglyceride, total cholesterol, HDL-C and LDL-C) was measured by automated analyzer. Angiographic clinical vessel scoring was also done for all the patients.
Results
Lp(a) levels for Group I was 40.26 ± 8.23 mg/dl, Group II was 40.81 ± 11.16 mg/dl respectively which was significantly (i.e. $P<0.01$) higher than the levels in healthy controls Lp(a) = 16.39 ± 5.71 mg/dl]. We found a significant increase in mean levels of total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C) and Triglyceride (TG) in cases than controls ($P<0.01$). In contrast high-density lipoprotein-cholesterol (HDL-C) values decreased. Non HDL-C was calculated using the equation = [total cholesterol (TC) − LDL-C]. Lipid Tetrad Index (LTI) and Atherogenic Index were also calculated for all patients. The Modified Lipid Tetrad Index that we propose was calculated using the equation MLTI = [non-HDL-C × triglycerides × Lp(a)/HDL-C]. On analyzing by cumulative probability plot the new modified Lipid Tetrad Index defined by us is able to discriminate case and control populations more precisely than the existing LTI and Atherogenic Index. The Modified Lipid Tetrad Index has a better sensitivity and specificity than the existing LTI and also has a better correlation with the angiographic vessel score in all patients.
Conclusion
The new proposed Modified Lipid Tetrad Index is a better marker and predictor of severity of premature CAD in diabetic patients from India, than the existing Lipid Tetrad Index and Atherogenic Index.

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EP224

Metabolic effects by H. pylori infection and eradication

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Introduction
H. pylori infection has been related with diseases such as type 2 diabetes and metabolic syndrome.
Objective
To evaluate changes in carbohydrates metabolism, lipid profile and intake regulating hormones induced by 75 g oral glucose tolerance test (OGTT), before and after antibiotic eradication treatment in patients colonized by H. pylori.
Materials and methods
A prospective study of 40 non-diabetics patients were performed. We analyzed clinical data, carbohydrate and lipid metabolim, and ghrelin and GLP1 levels before and after antibiotic eradication treatment.
Results
We studied 40 patients (60% women). Average age was 46.9 ± 2; 70% had family history of digestive disorders and 57.5% clinical history of gastrointestinal disease (12.5% gastroesophageal reflux disease and 12.5% peptic ulcer). After antibiotic treatment, we found a significant decrease in HbA1c ($P=0.014$), glucose at 60′ ($P=0.018$) and 120′ ($P=0.019$) post-OGTT, and a significant increase in HDL-cholesterol ($P=0.021$). There were significant changes in basal ghrelin levels ($P=0.05$). We did not find significant changes in anthropometrics parameters, blood pressure and C-peptide levels. We found some significant positive correlations between weight and BMI with C-peptide, basal glucose and insulin, glucose 120′ post-OGTT pre- and post-treatment; also between triglycerides with HbA1c, C-peptide, glucose and insulin 120′ post-OGTT pre-treatment; and between total-cholesterol with basal glucose and insulin pre and post-treatment. Triglycerides and HDL-cholesterol correlated negatively. We did not find significant correlations between ghrelin leves or GLP-1 with metabolic parameters pre- or post-treatment; 90% of patients completed correctly the treatment and 31.6% used ranitidine although 97.5% got H. pylori eradication after conventional antibiotic treatment.
Conclusions
1) H. pylori eradication improved carbohydrate and lipid metabolism. 2) Significant correlations between anthropometric measurements, carbohydrates and lipids metabolism before and after treatment were observed. 3) More than 95% of patients achieved H. pylori eradication with conventional antibiotic treatment.

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EP225

Testosterone therapy in female-to-male transsexuals: effects on body weight, blood pressure and lipid profile

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Introduction and objectives
A possible increase in blood pressure (BP) and other cardiovascular risk factors has been associated with testosterone treatment (TT) in female-to-male transsexuals (FMT). Nonetheless, the available evidence does not support an increase in CV morbidity or mortality. We set out to analyze the impact of TT on BP and lipid profile in a cohort of FMT patients.
Methodology
Retrospective observational study with no control group in a cohort of 34 FMT patients who started TT following a standard protocol, comparing clinical and routine laboratory data before and after 6–12 months.
Results
Age was 27 ± 6 years and BMI 26.7 ± 3.1 kg/m^2. As expected, treatment increased free testosterone levels and reduced 17-β-estradiol. BMI increased to 27.8 ± 3.4 kg/m^2 ($P < 0.001$). There were no significant changes in systolic BP (120.9 ± 9.9–120.6 ± 10.9 mmHg) and diastolic BP (82.4 ± 7.6–80.9 ± 8.1 mmHg), glycemia, creatinine and total cholesterol (TC), but HDL-cholesterol was significantly reduced (58.9 ± 12.9–54.7 ± 13.6 mg/dl, $P < 0.001$) while LDL-cholesterol (99.9 ± 23.9–103.5 ± 23.0 mg/dl, $P = 0.030$) and triglycerides (166.6 ± 37.8–178.1 ± 45.2 mg/dl, $P < 0.001$) were increased. There were no new-onset hypertension cases.
Conclusions
Our study does not support the BP increase reported in some series. We found, however an increased BMI. In the literature, TT is associated with increased muscle mass but not adiposity, thus we cannot infer an increased cardiovascular risk. Regrettably we do not have impedanciometry data to elucidate this point. There is a mild but definite deterioration of the lipid profile with reduced HDL-cholesterol and increased LDL-cholesterol and triglycerides. That may be in part attributed to reduced levels of 17-β-estradiol rather than a direct action of testosterone on lipid metabolism. This is however considered as a common adverse effect of TT.

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EP226

Lipid accumulation product (LAP) and waist circumference to height ratio (WHtR) associated with free androgen index but not with serum testosterone and androstendione in women with PCOS

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Introduction
Polycystic ovary syndrome (PCOS) is associated with metabolic disorders such as insulin resistance, hyperinsulinemia, dyslipidemia and central obesity which increase the risk of cardiovascular diseases (CVD). Lipid accumulation product (LAP) and waist circumference to height ratio (WHtR) are novel CVD risk predictors based on the assessment of waist circumference, height and serum triglycerides. The aim of our study was to evaluate the LAP and WHtR associations with hyperandrogenemia in women with PCOS.
Materials
The study group consists of 161 women with PCOS diagnosed according to the Rotterdam criteria aged 24.7 ± 4.9. We measured serum testosterone, androstendione, sex hormone binding globulin (SHBG), lipid profile by commercial kits. Free androgen index (FAI) was calculated by standard formula. LAP cut-off value was 34.5, and for WHtR was 0.5. Study group was divided into two subgroups according to FAI value ≥ 5.0 and separately into three subgroups according to serum testosterone and androstendione concentrations.
Results
Women with PCOS and FAI over 5.0 had significantly higher LAP values than women with FAI below 5 (84.75% vs 15.25% respectively, $P < 0.005$), OR = 5.787, which suggests that FAI value > 5 is associated with fivefold increased risk of high LAP values. Similarly, PCOS women with FAI > 5 had higher WHtR, which suggests that increased FAI value is associated with higher WHtR (OR–3.55, $P < 0.005$). Such associations were not observed in case of subgroups divided according to androstendione and testosterone concentrations – WHtR and LAP were comparable. LAP and WHtR were significantly negatively correlated with SHBG concentration and positively with FAI values, but not with serum testosterone and androstendione levels.
Conclusions
Hyperandrogenemia expressed as FAI ≥ 5.0 is associated with significantly higher values of novel CVD risk predictors – LAP and WHtR in women with PCOS. Serum SHBG level as well as FAI value are good predictors of CVD risk in women with PCOS.

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EP227

Higher than expected prevalence of the aortic dilation in Turner syndrome in Lithuanian population

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Introduction
Aortic dilation (AD) is the life threating complication of Turner syndrome (TS). The reported prevalence of AD in TS various between 12 and 39%. Factors predicting enlargement of diameter of aorta (DA) are still under investigation.
Aim
To assess the prevalence of AD in TS in Lithuanian population, to evaluate the possible predictors of AD development.
Methods
Forty-three patients with TS aged ≥ 18 year were enrolled into the prospective cross-sectional study. Cardioechoscopy was used to evaluate DA. DA was adjusted for body surface area. AD was defined as DA > 2.0 cm/m^2. Age, congenital cardiovascular disorders (CCD), karyotype, metabolic parameters (BMI, HOMA index), heart ratio (HR), blood pressure (BP), Estrogens (E), Testosterone (T) levels duration of Growth Hormone (GH) and E use, E initiation time were evaluated in the relation to AD.
Results
The dilation of the root of aorta (ADR) was reported in 37.2% ($n = 16$) of the cases, the dilation of ascending (ADA) aorta was observed in 31% ($n = 13$). When summarized ADR and ADA the prevalence of AD increased up to 48.8% ($n = 21$).
The largest diameter of the root of aorta (DAR) had strong negative correlation with BMI ($r = -0.7$, $P < 0.001$), HOMA index ($r = -0.408$, $P = 0.009$), E initiation age ($r = -0.33$, $P = 0.031$). DAR correlated with HR ($r = 0.37$, $P = 0.014$), duration to E use ($r = 0.347$, $P = 0.023$), T level ($r = -0.34$, $P = 0.028$).
The largest diameter of ascending aorta correlated with the duration of GH use ($r = 0.406$, $P = 0.009$), and T level ($r = -0.38$, $P = 0.014$).
The frequency of AD did not differ between the classic (45, X0) and nonclassic karyotype (non-45, X0) or the presence of CCD. There was no relationship between BP, age and DA.
Conclusion
The prevalence of AD in TS in Lithuania was higher than reported in other studies. HOMA index correlation with AD was identified for the first time.

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EP228

Hypertension and related cardiovascular diseases: a new role for low levels of parathyroid hormone

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Hypertension or elevated arterial blood pressure (BP) is the most common cause of cardiovascular diseases (CVDs). The arterial BP is regulated by

renin-angiotensin-aldosterone system (RAAS), whereas dysfunctional RAAS may lead to development of hypertension and associated CVDs. Parathyroid hormone (PTH) secreted by parathyroid glands regulates RAAS by directly stimulating aldosterone synthesis in zona glomerulosa cells, which leads to development of hypertension. Conversely, RAAS controls PTH secretion; in high dietary salt intake aldosterone promotes reabsorption of sodium and increases calcium excretion in renal distal tubules followed by PTH secretion. PTH is an independent cardiovascular risk factor, contributing to cardiovascular damage via binding to PTH receptors on vascular smooth muscle cells and cardiomyocytes. The present study examined the role of PTH in development of hypertension and consequent CVDs. Hundred hypertensive CVD patients of both sexes and hundred healthy age-matched controls were investigated. Blood samples were collected and plasma PTH concentrations were measured using ECLIA system. Of 15 patients treated with RAAS inhibitors (RAASi), PTH concentrations were low in 12 and within normal range in three patients. Among 26 patients under non-RAASi treatment, PTH concentrations were low in 23 and normal in three patients. Of 33 patients given combinations of RAASi and non-RAASi, PTH concentrations were low in 27 and normal in six patients. In 26 untreated patients, PTH concentrations were low in 22 and normal in four patients. Contrary to earlier reports, PTH concentrations were below normal range in 84% patients, whereas PTH concentrations were within normal range in 16% patients, irrespective of any or no treatment. The majority of patients was married, had exercise free lifestyle with no specific diet plan, belonged to low socioeconomic status, fell in the obese category and had family history of CVDs. In conclusion, our hypertensive cardiovascular patients had either low or normal values of PTH.

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EP229

Role of additional risk factors of cardiovascular disease in men with type 2 diabetes and obesity

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Late identification and inadequate assessment of cardiovascular risk factors are being considered as the main cause of high mortality in men with type 2 diabetes mellitus (T2DM).

Aim

To analyze the carbohydrate metabolism, levels of testosterone, proinflammatory cytokines in patients with T2DM and obesity.

Methods

We examined 123 men with T2DM and obesity (mean age – 53.8±6.8). Parameters of carbohydrate metabolism, total testosterone (T), leptin, C-reactive protein (CRP), e-selectin were analyzed.

Patients were divided into four groups: the 1st group included 41 patients with BMI 25–29.9 kg/m^2, the 2nd group – 51 patients with BMI 30–34.9 kg/m^2, the 3rd group – 23 patients with BMI 35–39.9 kg/m^2, the 4th group – 8 patients with BMI higher than 40 kg/m^2.

Data were analyzed using Mann–Whitney *U*-test for two independent groups.

Results

Statistically significant differences in the parameters of carbohydrate metabolism between groups were not found. The levels of T decreased as the increasing of BMI. Leptin level in the 1st group was 7.16[4.89; 19.7] ng/ml, in the 2nd – 11.13[7.75; 14.88] ng/ml, in the 3rd – 16.8[10.86; 27.59] ng/ml, and in the 4th – 27.68[20.15; 36.41] ng/ml ($P<0.005$). The CRP concentrations were statistically different in the 1st (4.49[2.06; 10.6] mg/l) and 4th (11.7[9.04, 13.95] mg/l) groups ($P=0.006$). The level of e-selectin in the 1st group was twice lower than in 4th (41.16[32.03; 64.77] ng/ml vs 81.2[46.1; 123.65] ng/ml) ($P=0.02$).

Conclusion

The excessive accumulation of adipose tissue leads to decreasing of T levels in men with T2DM. Increasing of leptin and CRP concentrations indicates the existence of systemic inflammatory process, which could be considered as an additional risk factor for cardiovascular disease in patients with T2DM.

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EP230

A systematic review and meta-analysis of interventions for the treatment of chronic non-hypovolaemic hypotonic hyponatraemia

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Objectives

International and national guidelines on the treatment of chronic non-hypovolaemic hypotonic hyponatraemia differ widely. Using methods embodied in the Cochrane Handbook, a systematic review and meta-analysis was conducted to investigate the efficacy and safety of interventions for this condition.

Methods

Following registration of the review protocol with PROSPERO (CRD42015016670), systematic literature searches were conducted to identify randomised or quasi-randomised controlled trials comparing any degree of fluid restriction or any drug treatment with the aim of increasing serum sodium concentration in patients with chronic non-hypovolaemic hypotonic hyponatraemia. Where possible and appropriate, outcome data were combined in a meta-analysis.

Results

45 716 records (i.e. bibliographic references) were identified from the searches and 18 trials (assessing conivaptan, lixivaptan, tolvaptan and satavaptan) met the eligibility criteria. No RCT evidence was identified for effectiveness of treatments other than for the 'vaptans' (listed above) for hyponatraemia. Results suggest that all four vaptans significantly improve serum sodium concentration. Lixivaptan, tolvaptan and satavaptan were associated with greater rates of response versus placebo. There was no evidence of a difference between any of the vaptans compared with placebo for mortality, discontinuation and rates of hypernatraemia.

Conclusions

Vaptans demonstrated superiority over placebo for outcomes relating to serum sodium correction. Few studies measured health-related quality of life (QoL) using a range of different instruments and showed no evidence that vaptans negatively impact QoL. For all vaptans, cases of overcorrection were rare. With the exception of vaptans, no RCT evidence was identified in relation to the alternative strategies commonly employed including urea, mannitol, loop diuretics, corticosteroids, demeclocycline, lithium and phenytoin.

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EP231

Predictive factors of the metabolic syndrome in the obstructive sleep apnea hypopnea syndrome

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Introduction

The metabolic syndrome (MS) is a frequent complication of the obstructive sleep apnea hypopnea syndrome (OSAHS). Its predictive factors have to be known by the doctors setting in charge patients with OSAHS. The aim of this study was to determine the prevalence of the MS and its predictive factors in Tunisian patients with OSAHS.

Methods

A retrospective study including 181 patients with OSAHS from the respiratory D department at the Abderrahmane Mami Ariana hospital Tunisia, between January 2010 and December 2014. Metabolic syndrome was defined according to the International Diabetes Federation criteria of 2005. We looked for the MS related factors by univariate then multivariate analysis.

Results

The prevalence of the MS was 68%. The frequency of the MS was highest between 56 and 65 years. Compared to the apneic patients without MS, those with MS were older (55.9±12.82 years vs 51±15.27 years), more frequently women (61% vs 58.6%), and a lower frequency of postmenopausal women (76% vs 80%). But there was no statistical difference for those parameters. The MS was more frequent in patients with a history of hypertension ($P<0.05$), type 2 diabetes ($P<0.0001$) and dyslipidemia ($P=0.001$). Apneic patients with MS had more daytime sleepiness ($P=0.04$), an epworth score greater than or equal to ten was more observed (71.4% vs 28.6%; $P=0.034$), an attention disorders ($P=0.006$) and a higher body mass index (38.02±6.45 kg/m2 vs 35.85±7.75 kg/m2; $P=0.05$). The MS was more frequent in patients with a pathological Oto-rhino-laryngology examination (65.9% vs 46.6%; $P=0.014$). By studying the impact of the severity of OSAHS on the occurrence of MS, we found no statistically significant difference.

Conclusion
The prevalence of MS is high in patients with OSAHS. Its occurrence does not correlate with the severity of OSAHS.

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EP232

Vascular calcification – Impact of PRRG1-4

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Pathophysiological calcification in the vasculature favours cardio- and cerebrovascular diseases. In patients with chronic kidney disease vitamin K metabolites are associated with decreased vascular calcification.
We investigated the expression of the vitamin K dependent proteins PRRG1-4 in vessels and bone to identify differences in expression pattern during atherosclerosis (AS) stages and compare the two tissue profiles.
Gene expression levels of PRRG1-4 were examined with predesigned TaqMan assays on a LC480 system in vessels (external iliac artery and aorta) and bone of 26 organ donors. Relative Cp values were obtained by division with beta actin.
Determination of calcification stages was done histologically: no changes: unaffected vessels, intima thickening: more than onefold intima thickening without calcification, intima calcification: one or more calcification spots.
Gene expression of PRRG1 decreased in bone compared to vessels in atherosclerosis ($P=0.001$).
In vessels gene expression of PRRG1, 3 and 4 were decreased in atherosclerosis compared to normal state ($P=0.002$, $P=0.011$, $P=0.011$). In bone gene expression of PRRG1-4 did not change when atherosclerotic vessels were present.
Looking at three stages of atherosclerosis, no differences in gene expression of PRRG1-4 are seen in intima thickening, in intima calcification PRRG1 ($P=0.001$) show differences in gene expression in bone and vessels.
In vessels PRRG1 ($P=0.013$), 3 ($P=0.048$) and 4 ($P=0.049$) gene expression decreased during intima thickening and keeps low in the calcification stage. In bone gene expression of PRRG1-4 did not change during AS progression.
Gene expression of vitamin K dependent proteins changes during calcification of the vessel wall implicating a more complex role of vitamin K dependent proteins in vascular calcification than previously known.

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EP233

Relation of apelin with duration of diabetes in hypertension patients with type 2 diabetes

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Introduction
Apelin is one of the cardiovascular factors, adipokin, which plays an important role not only in the pathogenesis of hypertension, but also of type 2 diabetes (T2D). The aim of the study was to assess apelin levels in blood serum and investigate its relationship with duration of diabetes in hypertension patients with T2D.
Methods
The study involved 63 hypertension patients grades 2–3 with T2D (32 men and 31 women) aged 43 to 70. Depending on the duration of diabetes three groups of patients were formed: 1. patients with T2D duration of 1 year (24%), 2. patients with T2D duration of 1–5 years (44%), 3. patients with T2D duration of more than 5 years (32%). The blood level of apelin was tested using an ELISA. The control group consisted of 14 practically healthy people.
Results
The levels of apelin in blood in the hypertension patients T2DM were significantly lower compared to healthy volunteers – 0.882(0.788; 0.924) ng/ml vs 1.097(0.944; 1.171) ng/ml, $P<0.01$. Among patients with T2D duration of 1 year apelin levels were 0.926(0.871; 0.948) ng/ml ($P<0.01$ vs control group), in patients with T2D duration over 5 years – 0.883(0.801; 0.911) ng/ml ($P<0.001$ versus control group), in patients with T2D duration of more than 5 years – 0.855(0.736; 0.863) ng/ml ($P<0,001$ vs control group). Patients with T2D duration of more than 5 years had significantly lower blood levels of apelin than in patients with T2D duration of 1 year – 0.855(0.736; 0.863) ng/ml vs 0.926(0.871; 0.948) ng/ml, $P<0.05$.
Conclusion
In hypertension patients with T2D blood levels of apelin were lower than in healthy subjects. Patients with long duration of diabetes (over 5 years) had significant reduction of apelin compared to patients with T2D duration of 1 year. This may indicate deepening of disorders of apelin production with increasing duration of T2D.

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EP234

Erythropoietin therapy and the cardiovascular outcome in cardio-renal syndrome patients

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Background
Kidney diseases and cardiac diseases can affect each other. Patient with renal failure have many cardiac problems specially heart failure, anemia of CRF is resistant to treatment with iron or even blood transfusion and erythropoietin therapy gives good results as the failing kidney can not synthesize it
The previous published data showed that EPO treatment in patients with cardiorenal syndrome (CRS) anemia led to reverse ventricular remodeling together with systolic function improvement. These changes were supported by a fall in BNP, its plasma lowering might indirectly signal an improvement in cardiac function and outcome in patients with CRS in whom the anemia is corrected by EPO.
Aim of the work
To investigate the value of erythropoietin therapy in the treatment of CRS patients with anemia and to evaluate the relationship between clinical, echocardiography and serum BNP levels in those patients in comparison with the standard therapy as iron and blood transfusion.
Patients & methods
The prospective study included 30 chronic renal failure patients under dialysis who are presented with anemic heart failure diagnosed according to New York Heart Association (NYHA) classification which was proved by echocardiographic finding (EF-FS). Plasma BNP was measured at the beginning and at the end of the study after three months on erythropoietin therapy. patients were divided into (Group 1) was treated with erythropoietin and (Group 2) was receiving standard treatment (Group 2).
Results
(Group 1) on erythropoietin therapy got significant decrease in BNP level by 33.8%, vs only 17.5% in (Group 2) on traditional therapy like blood transfusion, iron got and significant increase in the EF by 6.2% and FS by 3.6% in Group -1 vs significant decreased EF% by 9.7% and FS by 3.2% in Group -2 patients and the results were statistically significant ($P>0.05$).

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EP235

A retrospective observational-cohort study of the relationship between reactive hypoglycaemia to postural orthostatic tachycardia syndrome (PoTS)

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Postural orthostatic tachycardia syndrome (PoTS) occurs as a consequence of the abnormal functioning of the autonomic nervous system (dysautonomia). Despite the many associated conditions, the assessment and relationship to reactive hypoglycaemia has not been explored in the clinical literature.
The purpose of this retrospective observational-cohort study was to identify relationships between the physical and biochemical characteristics in potential carbohydrate metabolic disorders in individuals diagnosed with PoTS. This study used a standard prolonged oral glucose tolerance test (POGTT) over 5 hours.
Seventeen individuals were tested, with a mean age of 27.23 years; one patient was unable to complete the test due to an intense and significant response to the sugar load; 41% achieved peak glucose levels at 30 minutes and 57% attained nadir glucose (ranges: 1.8–3.4 mmol/L) between 210–240 minutes. Fasting insulin levels were noted in 30% of individuals, cortisol levels at baseline were

adequate and unremarkable. Joint hypermobility (29%), Inappropriate Sinus Tachycardia (31%) and Chronic Fatigue (22%) were additional associated conditions represented within the study group.
The data collected from this small study suggests a strong relationship between PoTS and carbohydrate metabolic dysfunction. We observed that patients exhibited a biphasic response with symptoms related to the both the nadir glucose and the large changes in blood glucose that were independent of the recorded glucose level. Significant symptoms occurred despite only 60% achieving a nadir glucose of 3.0 mmol/L; with a considerable number of these patients exhibiting a substantial improvement in symptoms with dietary changes to address reactive hypoglycaemia. Our study is hampered by the small number and homogeneity of our participants; however our results underpin the recommendations of a low carbohydrate diet with the consumption of meals every 2–3 hours for the stabilisation of blood glucose values and an improvement to symptoms.

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EP236

Effects of statins on lipid and carbohydrate metabolism in patient with type 2 diabetes and cardiovascular diseases

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Patients with diabetes mellitus (DM) type 2 is a group of high cardiovascular risk. The incidence of coronary heart disease in their 2–4 times higher than in the population without diabetes, 80% of cases of diabetes combined with hypertension. At the same time any change in lipid metabolism leads to increased cardiovascular risk in patients with type 2 diabetes. Statins is first-line drugs in patients with dyslipidemia.
Materials and methods
The study involved 15 patients with type 2 diabetes and dyslipidemia in mean age 59.8±1.03 years, among them, 11 women and four male. All patients was prescribed statins in mean dose 4 mg per day for 3 month. During the study were determined the levels of glycated hemoglobin (HbA1c) and lipid status before and after treatment.
Results
Analyzing the results obtained in the groups of patients a significant decrease in levels of total cholesterol, low-density lipoprotein. Triglyceride levels decreased to normal range after 3 months. Statistically significant increase in glycated hemoglobin was not confirmed.

	Total cholesterol	Triglycer-ides	Low-density lipoprotein	Very low density lipopro-teins	High-density lipoprotein	HbA1c, %
Before treatment ($n=15$)	5.64±0.2	1.77±0.2	3.73±0.2	0.51±0.05	1.49±0.08	7.39±0.4
After treatment ($n=15$)	4.38±0.2*	1.65±0.2	2.53±0.2*	0.51±0.06	1.48±0.08	7.54±0.3

*Significant difference between the indices before and after treatment ($P<0.05$).

Conclusions
Application of statin leads to the likely reduction in levels of total cholesterol, low density lipoprotein, indicating that effective treatment of dyslipidaemia in patients with type 2 diabetes. Statistically significant effect on glycated hemoglobin was not observed.

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EP237

Fixed combination features in management of Hypertensive patients with diabetes, dyslipidemia and subclinical hypothyroidism

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Objective
A subclinical hypothyroidism (SH) is the independent factor of the risk of cardiovascular diseases. The aim is to learn the possibility of optimization of the standard treatment of lipid and carbohydrate disoders, antihypertensive treatment of the levothyroxine replacement therapy (LRT) for women with metabolic syndrome (MS) and SH.
Methods
137 women: 1gr.-68pts with MS, SH and with the LRT use; 2gr.-69pts with MS and without LRT use. Body mass index, echocardiography, fast levels of TSH, freeT4, freeT3, glucose, insulin, lipids, ambulatory blood pressure monitoring were determined. The insulin resistance was diagnosed at increase of the Homa-index. All of the patients got 10 mg of atorvastatin, 10 mg of lisinopril (ACE Inhibitors), metformin 1500 mg per day and patients of 1 gr. got additionally LRT in the dose of 50 mg per day. Patients were observed at the beginning and in 6 months of treatment.
Results
In 6 months the authentically large serum levels of total cholesterol (TC5.4±0.5 mmol/l) and low-density lipoprotein (LDL3.0±0.2 mmol/l) cholesterol in 2 gr. remained as at the beginning of the research. This pattern of lipid abnormalities for women with MS, SH is important because it is a risk factor for atherosclerotic cardiovascular disease. The Homa-index 3.0±0.2, blood pressure monitoring 143/85 mm Hg remained elevated. In 6 months the women with MS, SH and LRT use of the 1 gr. demonstrated the reliable decline, the best decline of all indicators: TC4.5±0.4 mmol/l, LDL2.0±0.3 mmol/l, glucose, Homa-index 2.2±0.3, ambulatory blood pressure monitoring 130/80 mm Hg.
Conclusions
The therapy of atorvastatin, lisinopril, metformin for women with MS, SH during 6 months is insufficient for the achievement of the target levels of TC, LDL, glucose, Homa-index, ambulatory blood pressure monitoring while setting of the combined therapy of LRT use, optimizes efficiency of lipid lowering therapy allowing to attain the normal levels of lipids without the increase of dose of statin and to decrease displays of insulin resistance and to improve antihypertensive treatment.

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EP238

Dyslipidemia in young women with polycystic ovary syndrome

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Introduction and aims
Polycystic ovary syndrome (PCOS) is a frequent endocrinopathy among with young women. It is known that insulin resistance is encountered in the vast majority of the women with PCOS and hence the risk of type 2 diabetes mellitus and coronary artery disease are increased. These cardiac and metabolic risk increments may also associated with hyperandrogenemia and dyslipidemia. The metabolic changes of lipid profiles in young women with PCOS are not completely understood. The aim of this study is to evaluate changes of lipid profile in both of patients with young women with PCOS.
Materials and methods
Thirty-six young women with PCOS (mean age: 23.4±4.6 year and mean body mass index (BMI): 23.8±4.8 kg/m^2), and 32 healthy normoovulatory age- and BMI-matched women (mean age 23.4±4.6 years; BMI: 22.1±2.8 kg/m^2) were included in our study. The diagnosis of PCOS was made based on Rotterdam diagnostic criteria. The BMI for all patients was calculated by the formula: [body weight (kg)/height (m)^2]. The waist circumference (WC) was measured. All blood samples were taken between 08:00 and 10:00 am following 8 hour fasting period. All hormonal and biochemical analysis were performed by automatic analyzer.
Results
The waist circumference in the PCOS and control groups were 80.6±7.3 and 77.5±2.0 cm, respectively. There was a statistically significant difference between the PCOS and control group in terms of waist circumference ($P=0.018$).
The glucose, total cholesterol (C), HDL-C, LDL-C and TG levels in PCOS group were 89.9±11.3 mg/dl, 177.2±26.3 mg/dl, 54.8±12.3 mg/dl, 105.0±23.5 mg/dl and 110.8±42.3 mg/dl respectively whereas the corresponding values in the control group were 86.1±12 mg/dl, 161.2±30.6 mg/dl, 55.9±12.9 mg/dl, 94.3±24.5 mg/dl and 81.8±39.9 mg/dl, respectively. The differences in glucose, HDL-C, LDL-C levels between PCOS and the control groups were not found to be statistically significant whereas total cholesterol ($P=0.02$) and triglyceride ($P=0.006$) levels were significantly different from control subjects. There were not any correlations between WC and serum lipid levels such as total cholesterol, HDL-C, LDL-C and triglyceride.
Conclusions
According to our study, elevated total cholesterol and triglyceride levels were found in young women with PCOS. These changes of lipid levels could be lead to predispose subclinical atherosclerosis in young women with PCOS.

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EP239

The cardiovascular complications and risk factors in cardiac patients with type 2 diabetes

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The purpose
To investigate the prevalence and the relationship between cardiovascular complications (CVC) and risk factors (RF) in patients with essential hypertension (EH) and coronary heart disease (CHD) in combination with diabetes mellitus type 2 (DM-2).
Materials and methods
A retrospective analysis of case histories of 79 patients with cardiac profile (37 of them women, with an average patient age – 59.6 ± 6.2 years) with hypertension stage II – III (hypertension duration - 8.9 ± 3.2 years) and chronic forms of CHD (CHD duration – 9.7 ± 2.4 years) with concomitant DM-2 (DM-2 duration – 6.8 ± 1.6 years). Please observe the complications associated with diabetes, the level of psychosocial stress to conduct the survey on a scale Reader.
Results
In the studied group of heart rhythm disorder (arrhythmia extrasystolic and atrial fibrillation) were significantly more ($P<0.05$) occurred in women; males were more individuals with overweight (respectively 62% of males and 48% females). Atherogenic hyperlipidemia (AHL) was observed in 72% of women and 85% men. Myocardial infarction (MI) associated with the AHL and the violation of the compensation DM-2 (elevated glycosylated hemoglobin (HbA1c) in average $8.14 \pm 1.23\%$) and is more common in men than in women (18% and 8%). The connection AHL non-compliance with diet, irregular meals, and stress levels on the scale of the Reader (95% CI: 0.016 – 0.038; $P<0.001$). A negative correlation was between stress levels and body weight ($r=-0.42$); positive relationship – between stress, the incidence of MI and frequent infectious diseases ($r=0.54$). Manifestations of CVC were less pronounced in patients with an active lifestyle and in patients who had no bad habits ($P=0.01$).
Conclusions
The results of the analysis indicate that patients with hypertension and CHD with DM- 2 have more RF and CVC. Accompanying illnesses are very common in these patients, and modifiable risk factors, including hypertension, DM-2? Psychosocial stress should be considered as one of the main directions for the best results from the treatment and prevention of CVC.

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EP240

Metabolic syndrome as the result of the inversion of the cycle 'day/night'

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Background
The pathophysiological base of metabolic syndrome is insulin resistance. According to Scott E.M., Grant P.J., insulin resistance is supposed to be formed during the evolution and connected by circadian rhythms. Melatonin is synchronizer of circadian rhythms. The modern lifestyle leads to the breach of melatonin synthesis because of absence of season changes in the length of a light day due to the using of artificial lighting.
Aim
The aim was studied influence of melatonin on the development of MS in inversion of the cycle 'day/night'.
Design
Group 'A' ($n=25$), patients with MetS (the National Cholesterol Education Programs Adult Treatment Panel) and inversion of the cycle 'day/night' (at least two night shift a week for 6 and more years), group 'C' ($n=23$), healthy people, working in day shifts. Blood pressure (BP) has been monitored for 24 years. It is determined waist circumference (WC), high-density lipoproteins (HDL) fasting triglycerides (TG), fasting glucose. The melatonin secretion has been determined according to excretion 6-sulfatoxymelatonin (MT6S) in urine.
Results
Total MT6S in both groups was equal, $P=0.077$. MT6S at 0400 h in group 'A' (25.3 95% CI: 17.8–32.8 ng/ml) was less $P<0.014$. Night MT6S in group 'A' (10.2 95% CI: 7.3–13 ng/ml) was higher $P<0.001$. MT6S at 0400 h was connected with BP($r=-0.34$), TG ($r=-0.34$), HDL ($r=0.26$), glucose ($r=-0.38$), $P<0.05$. Correlation has been determined between the day MT6S and WC ($r=-0.28$, $P<0.05$). When the peak secretion of melatonin decreases, it is determined increasing the risk of abdominal obesity (OR 1.8, 95% CI: 0.8–3.7; $P<0.05$), hypertension OR 1.6 (95% CI: 0.8–3.4; $P<0,05$) risk of nocturnal hypertension (OR 1.6, 95% CI: 0.8–3.4; $P<0.05$, hypertriglycerides (OR 1.4, 95% CI: 0.7–2.1; $P<0.05$), HDL decreasing (OR 1.7, 95% CI 0.9–2.6, $P<0.05$)
Conclusions
During the long inversion of the cycle 'day/night', disturbance of melatonin secretion leads to the development of metabolic syndrome.

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EP241

Detection of subclinical diabetic autonomic neuropathy by reflex cardiovascular testing

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Background
Diabetic autonomic neuropathy (DAN) is among the least recognized and understood complication of diabetes despite its significant negative impact on survival and quality of life in people with diabetes. Diabetic neuropathies including cardiac autonomic neuropathy (CAN), are a common chronic complication of type 1 and Type 2 diabetes and confer a high morbidity and mortality to diabetic pateints. The reported prevalence of CAN varies greatly depending on the criteria used to identify CAN and the population studied. CAN is ultimately the result of complex interactions among degree of glycemic control, disease duration and vascular risk factors. CAN encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics and is associated with a high risk of cardiac arrhythmias, sudden death, (possibly related to silent myocardial ischemia) and large costs to the welfare system. Clinical symptoms of autonomic neuropathy generally do not occur until long after the onset of diabetes. Subclinical autonomic dysfunction, however, can occur within a year of diagnosis in type 2 diabetic patients and within 2 years in type 1 diabetic patients.
Objective
Possibility of the use of non-invasive cardiovascular tests for early detection of subclinical autonomic neuropathy in type 2 diabetic patients.
Study design
This study included 40 type 2 diabetic male patients (from 30 to 70 years old) with new onset or longstanding diabetes.
Results
20 (50%) diabetic patients had one abnormal test and 10 (25%) diabetic patients had two abnormal reflex cardiovascular tests. Cardiovascular tests were affected by age, higher body mass index, glucose control and diabetes duration.
Conclusion
Reflex cardiovascular tests can be used for the early screening of cardiovascular autonomic neuropathy before more sophisticated and specific tests.
Keywords: DAN and reflex cardiovascular tests

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EP242

Dietary intakes in relation to carotid intima-media thickness in subjects with subclinical atherosclerosis

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Demonstrating a relationship between diet and atherosclerosis should provide an opportunity for potential risk reduction at an early stage of the known long disease process instead of the need to intervene at the symptomatic disease stage. Thus, we aimed to evaluate the relationship between levels of nutrients intake as determined by food frequency questionnaire (FFQ) with the degree of atherosclerotic lesions as measured by carotid intima-medial ratio (CIMT).
One hundred eighty nine patients, aged between 40–78 years, were randomly recruited from the internal medicine clinics at King Abdulaziz University Hospital in Jeddah, Saudi Arabia. Dietary intake data were collected by a 92 item, semi-quantitative FFQ designed to assess average food intake over the previous 12 months. Macronutrient intakes were adjusted for total energy intake using the nutrient residual method and were also presented as the percentage of total energy intake (nutrient density). Common, internal and external carotid arteries on both sides were scanned and the presence of plaques was noted using high resolution B-mode ultrasonography. The mean values of maximum left and right CIMT were determined. The presence of atherosclerotic plaque was defined as any stenosis in either the right or left carotid artery.

Data are presented as mean ± S.E.M. The associations between CIMT and dietary intake levels were examined by univariate analysis while adjusting for potential confounders. All statistical analysis was conducted using the SPSS 21.0 statistical packages, and statistical significance was set at $P<0.05$. All P values were two-tailed.
Our results suggest that dietary intake levels might affect the risk of subclinical atherosclerosis. Significant findings were consistent with dietary recommendations and lifestyle intervention. An aggressive cardiovascular risk factor modification exerted early on in life might have a potential to reduce the risk of atherosclerosis and the incidence of heart attack at later stages.

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EP243

Comparison of hypertriglyceridemic and normotriglyceridemic patients in Konya and in the surrounding area in Turkey

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Methods
This study, was a cross-sectional survey. Sampling design was based upon multistage probability sampling. Patient with diabetes, hypertension, cardiovascular diseases and any other diseases were excluded from the study. Age and gender were noted. Heights, weights and waist circumference (WC) were measured. BMI was calculated. Blood pressure (BP) was measured. Fasting thyrigliseride levels were evaluated. Patients were divided into two groups according to their triglyceride levels (TG <150 mg/dl and TG >150 mg/dl.
Results
344 participants were screened for the study, 224 of them had normotriglyceridemia, 120 of them had hypertriglyceridemia. 38.5% of participants were male, and 61.5% was female. Mean age was 48.76 ± 14.08 years. Mean values were; WC 91.14 ± 13.54 cm, BMI 28.42 ± 5.87 kg/m^2,systolic BP 131.74 ± 25.62 mm/Hg, diastolic BP 81.05 ± 15.17 mm/Hg in normotriglyceridemia group. Mean values were; WC 94.85 ± 11.83 cm, BMI 29.02 ± 5.15 kg/m^2, systolic BP 140.08 ± 23.65 mm/Hg, diastolic BP 87.46 ± 16.89 mm/Hg in hypertriglyceridemia group. Except BMI the other variables were significantly higher in the hypertriglyceridemia group ($P<0.04$). BMI was similar in each groups.
Conclusion
Present study showed that without any comorbidities hyperthyrigliceridemia was a risk factor of hypertension. High BP, increased WC, hypertrigliceridemia were ATP III metabolic syndrome criterias. Metabolic syndrome is associated with increased risk for cardiovascular disease.

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EP244

Cardiovascular safety; which antidiabetic agent will be your choice in patients, who have coexisting cardiovascular disease?

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Three eagerly awaited large, randomised, controlled cardiovascular safety trials with new antidiabetic drugs have recently been completed. The results of these studies are of wide interest to the diabetes and cardiology clinical scientific communities, and the results have been presented at diabetes and cardiology scientific meetings. These have studied drugs in each of the new classes of antidiabetic drugs: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor; lixisenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist; and empagliflozin, a sodium-glucose co-transporter-2 (SGLT2) inhibitor.
The impressive reduction in total mortality that was seen with empagliflozin in the EMPA-REG OUTCOME trial will lead to a change in the management of this challenging group of patients, who have existing cardiovascular disease and may be uncontrolled on insulin therapy, and initially the increased use of empagliflozin should be focused on this group. As there are currently no data to support a similar benefit with dapagliflozin or canagliflozin it is likely that empagliflozin will quickly become the most prescribed drug in this class.
Three studies have now demonstrated no cardiovascular benefits with DPP-4 inhibitors and GLP-1 receptor agonist, and although these drugs are well tolerated. From a patient perspective empagliflozin was also well tolerated and reduced weight. The prescribing of DPP-4 inhibitors may well decline in favour of empagliflozin. Writers of guidelines will need to consider revision of guidelines based on the results of these studies, and in time empagliflozin could become the favoured secondline therapy after metformin.

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EP245

Stress hyperglycemia in acute coronary syndrome and pulmonary disease

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In a large sample of elderly patients with acute myocardial infarction, higher glucose levels were associated with a greater risk of 30-day mortality in patients with diabetes compared to patients without diabetes. In addition to previous hypothesis for mechanism of harm, recent studies have concluded that stress hyperglycaemia is an independent predictor of left ventricular remodelling after anterior myocardial infarction and may also contribute to arrhythmias.
There has also been a recent focus on biomarkers and tools to predict the risk of stress hyperglycaemia, future diabetes and outcomes from intervention. Higher cortisol levels have been found to be predictive of the onset of stress hyperglycaemia as well as of subsequent normalisation of blood glucose levels. In the case of the latter it is suggested that higher cortisol levels reflect stress-precipitated hyperglycaemia whereas lower cortisol levels suggest 'underlying glucose intolerance' as the most likely explanation for hyperglycaemia.
HbA1c has also been studied with varying results. One study found that hyperglycaemia and non-elevated HbA1c was associated with a poor prognosis following acute myocardial infarction whereas another study did not find any association between mortality and HbA1c.
Another recent field of interest has been hperglycemia in setting of pulmonary disease. Stress hyperglycaemia is seen in up to 50% of patients hospitalised with exacerbations of chronic obstructive pulmonary disease and each 1 mmol/l increase in blood glucose has been shown to increase the absolute risk of death or prolonged hospital stay by 15%. Prospective studies are currently underway to determine whether blood glucose control can improve chronic obstructive pulmonary disease exacerbation outcomes. A similar picture has been identified with pneumonia.

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Clinical case reports – Pituitary/Adrenal

EP246

Five years of growth hormone therapy in children born small for gestational age

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Introduction
Growth hormone (rhGH) is an effective treatment for short children born small for gestational age (SGA) who fail to demonstrate catch-up growth by 2–4 years of age. This children usually do not have classical GH deficiency, but either low GH secretion or reduced sensitivity to GH. The goals of therapy are to achieve a normal height in early childhood and an adult height within the normal target range.
Objectives
Evaluation of efficacity and safety profile in the first 5 years of rhGH treatment in ten SGA children.
Methods
The study enrolled ten SGA children (six boys, four girls). All patients were given a mean dose of 0.035 mg/kg per day and followed for a period of minimum 5years (mean 5.68 years).

Results
The mean height expressed in s.d. raised from −2.43 at diagnosis to +0.28 after 5 years. In the first 5 years of therapy there were no cases of diabetes mellitus or impaired glucose tolerance, two patients (20%) presented impaired fasting glucose, one patient (10%) developed hypothyroidism and four patients (40%) presented transitory subclinical hypothyroidism. Mean IGF1 values were higher than normal range, but not exceeding +2DS.

Table 1 Data from the first 5 years of rhGH therapy.

Parameter	Baseline	1 year	2 years	3 years	4 years	5 years
Chronological age (years)	6.29	7.29	8.29	9.29	10.29	11.29
Bone age (years)	4.05	4.75	5.56	7.15	9.3	11.05
Mean IGF-1 values (ng/ml and s.d.)	77.5 (+0.24)	305.38 (+1.49)	258.71 (+1.54)	329.85 (+1.26)	412.44 (+1.47)	476.55 (+1.85)
Height (s.d.)	−2.43	−1.37	−0.91	−0.68	−0.43	+0.28
Growth velocity (cm/year)	–	11.76	9.24	8.16	7.68	6.24

Conclusions
GH therapy is reasonably safe and effective in increasing linear growth in children born SGA who fail to have catch-up growth. Maximum height velocity was registered in the first year of treatment, 11.76 cm/year. and declined in time. No adverse events. Overall, GH treatment was safe and well tolerated.

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EP247

Pituitary adenoma associated with pheochromocytoma/paraganglioma

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Background
Pituitary adenomas (PA) and pheochromocytomas/paraganglioma (pheo/PGL) can occur in the same patient due to coincidence or of shared pathogenesis. There is evidence that, at least in some cases, classical pheo/PGL predisposing genes, may also play a role in pituitary tumorigenesis. A new condition called 'the three P Association' (3PAs) for the combination of PA with pheo/PGL has been recently described in patients with or without succinate dehydrogenase (SDHx) germline mutations.
Aim
To report our experience on 3PAs in three patients. Case 1: A 54-year-old male patient with bilateral pheochromocytoma underwent bilateral adrenalectomy. Three years later he was diagnosed with growth hormone-secreting pituitary adenoma that was completely resected after transsphenoidal surgery. Genetic screening for pheo/PGL genes (RET, VHL, SDHB and SDHD) were negative (including sequencing and gross delection analysis). Case 2: A 38-year-old-female patient was initially seen for macroprolactinoma and chronically treated with dopamine agonist. Four years later the patient was diagnosed with multiple PGL (cervical and unresectable mediastinal PGL), currently under somatostatin analogue therapy. Her brother was operated for PGL and gene study revealed a SDHB exon 1 deletion (genetic disorder associated with familial PGL type 4). This genetic rearrangement was also detected in her mother and sister. Case 3: A 55-year-old female patient was diagnosed with a right pheochromocytoma. She underwent right adrenalectomy. Five years later she was diagnosed with GH-secreting pituitary microadenoma and treated with transsphenoidal surgery. She was also diagnosed with primary hyperparathyroidism without surgical criteria. Genetic study for MEN 1, RET and VHL was negative.
Conclusion
The association of PA and pheo/PGL is an exceptional event, but recent insights provide strong evidence that PA can develop in patients with pheo/PGL or germline SDHx subunit mutations. Genetic testing should be considered in all patients or families with 3PAs.

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EP248

Kallmann syndrome and ichthiosis. A case of contiguous gene deletion syndrome

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Introduction
Kallmann Syndrome (KS) is a genetically heterogeneous disease characterised by hypogonadotrophic hypogonadism with anosmia or hyposmia. It can be associated with X-linked ichthyosis (XLI) in a contiguous gene syndrome related to a Xp22.3 region deletion, which include KAL1 and STS genes.
Case report
We report a case of a 32-year-old male with ichthyosis referred for evaluation of high height (2.07 m), overweight (BMI 29.6 kg/m^2) and microgenitalia.
He had absence of secondary sexual characters. Baseline plasma levels of testosterone were 0.12 ng/ml (2.49–8.36), FSH 0.25 mUI 7 ml (1.5–12.4) and LH <0.1 mUI/ml (1.7–8.6). Prolactin levels were 7.67 ng/ml (4.04–15.2). MRI showed hypoplastic hypophysis, ultrasound showed small testes and a bone densitometry revealed osteoporosis (spine *T* score −3.55). Karyotype was 46 XY. He was diagnosed of hypogonadotrophic hypogonadism associated to ichthyosis. Genomic DNA samples were extracted. A microarray-based comparative genomic hybridisation test (aCGH) was performed. The result was a pathogenic copy number DNA variant: arr(hg19)Xp22.32p22.31 (4 699 972–9 427 600)xo which contains 12 genes: NLGN4X, VCX3A, HDHD1, STS, VCX, PNPLA4, MIR651, VCX2, VCX3B, KAL1, FAM9A, FAM9B. Among these genes, STS is responsible for XLI and KAL 1 gene is responsible for the X-linked form of KS. Further studies revealed that the deletion was inherited from his mother. Females with similar Xp22 deletions are phenotypically normal except for short stature, because they need only one copy of this region to be normal.
He started intramuscular testosterone undecanoate supplementation in progressive doses to achieve secondary sexual character development and continued with substitutive treatment. Three years later bone densitometry improved (spine *T* score −2.78 s.d.).
Conclusion
KS is a genetically heterogeneous disease that can be associated with other diseases in a contiguous gene syndrome. New genomic tests provide a better understanding and knowledge of genetic diseases, diagnosis and management. Special attention has to be drawn to complications like osteoporosis, infertility and testis cancer.

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EP249

Spinal metastasis in childhood-onset craniopharyngioma: Case report, review of the literature and experiences in the German childhood-onset craniopharyngioma registry

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Background
Remote recurrence and metastasis are unusual complications in childhood-onset adamantinomatous craniopharyngioma mainly occurring either along a previous surgical route or by seeding via cerebrospinal fluid.
Case description
An 11-year-old female patient initially presented with headache and neck pain as well as nausea over the course of 2 months. A sellar/suprasellar mass (4.0 cm× 4.0 cm 5.0 cm) was detected on magnetic resonance imaging (MRI). Initial surgery resulted in complete resection (CR) based on intraoperative microscopic inspection. CR was confirmed by postoperative MRI. The tumor was histologically determined to be an adamantinomatous craniopharyngioma. Seven years after initial CR, the patient presented with back pain spreading to the ventral side of the upper legs as well as a loss of strength. MRI showed a spinal neoplasm at the level of T12/L1 without any sign of local sellar/suprasellar recurrence. The patient underwent a spinal tumor resection without complications. Histological analysis confirmed the spinal tumor to be a metastasis of the initial adamantinomatous craniopharyngioma. Clinical complaints due to the

spinal metastasis ceased after CR. Currently, the patient is in complete remission 9 years after CR of the sellar/suprasellar craniopharyngioma and 2 years after CR of a spinal metastasis of craniopharyngioma.
Only one case of an adult patient with spinal metastasis of an adamantinomatous craniopharyngioma has been reported in the literature up to now. Our case represents the first case of childhood-onset craniopharyngioma with spinal metastasis in the total cohort of 582 patients, recruited prospectively in the German childhood craniopharyngioma registry.
Conclusions
We report the first case of remote spinal recurrence of a childhood-onset adamantinomatous craniopharyngioma. Spinal metastasis is a very rare complication in childhood-onset craniopharyngioma and should be considered in long-term follow-up of childhood-onset craniopharyngioma patients with peripheral neurological complaints and symptoms.

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EP250

Capecitabine and temozolomide (CAPTEM) treatment of atypical macrocorticotropinoma in a patient with Nelson's syndrome

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Introduction
Atypical pituitary adenomas are often characterized by rapid growth and massive invasion of the surrounding structures. Usually, they are associated with poor prognosis and high recurrence rate due to resistance to conventional therapies. When surgery and radiation are ineffective, alternative therapies remain the last line treatment. Lately, a novel chemotherapy with capecitabine and temozolomide was proposed as a highly effective and extending the life of the patient procedure in refractory corticotroph pituitary tumors.
Aim
Aim of study was to present an effectiveness of CAPTEM in atypical corticotropinoma in a patient with Nelson's syndrome.
Case report
56-year-old male with Cushing's disease established 10 years earlier. During the first MRI $10\times9\times8$ mm pituitary adenoma was detected. Initially the patient underwent three subtotal selective transsphenoidal adenomectomies (2005, 2007, 2009). A postoperative pathologic exploration revealed a densely granulated corticotroph cell adenoma with MIB-1 index $>10\%$ and MGMT $(-)$. Due to a re-growth of the tumor, the patient underwent consecutive stereotactic radiotherapy (9Gy) and received cabergoline for 19 months. Afterwards, because of intractable complications of hypercortisolism, as well as previous treatment failures, a total bilateral adrenalectomy was performed as a lifesaving procedure. Subsequently, the patient developed Nelson's syndrome with intense skin hyperpigmentation and aggressive pituitary tumor progression. In 2011 transcranial neurosurgery and tomotherapy (45Gy) were applied. Due to next re-growth of the tumor with its expansion to cavernous sinuses and suprasellar region with a compression of the optic chiasm, and exhaustion of all conventional therapeutic options, the patient was admitted to our department for qualification to TMZ. Two cycles of TMZ (150 mg/m^2) for 5 days were applied and because of the progression of eye damage CAPTEM was introduced. After four cycles hormonal and imaging stabilizations are observed.
Conclusion
CAPTEM can be an effective treatment option in atypical adenomas in Nelson's syndrome.

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EP251

21-hydroxylase deficiency presenting as bilateral adrenal masses in the sixth decade of life in a phenotypically male but genetically female patient

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Introduction
21-hydroxylase deficiency (21-OHD) is a common inherited disorder accounting for 90–95% of congenital adrenal hyperplasia (CAH) cases. Some cases may be diagnosed in adulthood after the incidental discovery of adrenal masses on computerized tomography (CT).
Case report
A 59-year-old male was investigated for incidentally discovered bilateral adrenal masses in an abdomen CT scan, measuring 5 cm on the right and 8 cm on the left adrenal. At birth he had a phallus and partial fusion of the labioscrotal folds and was diagnosed with bilateral cryptorchidism and hypospadias. He was raised as a man. At the age of 15 the patient menstruated and karyotype testing revealed the XX cromosomal sex. He underwent multiple operations for the creation of a scrotum and the restoration of hypospadias. The uterus and ovaries were removed and prosthetic testes were placed in the scrotum. He was not receiving any cortisone supplementation. On physical examination he had a male appearance with sparse beard male-type baldness, height was 138 cm and weight 73 kg. He had gynecomastia and a 5 cm phallus with prosthetic testes. Testosterone was 7.8 ng/ml (nr for women 0.07–0.65), S-DHEA 420 μg/dl (22–263), E_2 144 pg/ml (5.7–102), ACTH 80.5 pg/ml (7.3–63.3), PRA 3.6 ng/ml per min (0.5–1.9), aldosterone 450 pg/ml (66–173), and on Synacthen test: 17OHP $0'$ 92 ng/ml, $30'$ 139, $60'$ 226 and cortisole $0'$ 199 nmol/l, $30'$ 242, $60'$ 285. Genetic testing of the 21-hydroxylase gene revealed a compound heterozygoticity for the mutations I172N and Q318X. Following left adrenalectomy histology revealed a diffusely hyperplastic adrenal cortical zone, measuring in total $12\times8\times4$ cm with regions of myelolipoma transformation.
Conclusions
Long standing, untreated classic virilizing form of CAH may lead to extensive hyperplasia of the adrenal cortex. It is prudent to measure 17OHPG in cases with massive adrenal enlargement.

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EP252

Acute myeloid leukemia presenting with panhypopituitarism and diabetes insipidus

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Introduction
Acute myeloid leukemia infiltrates the CNS in up to 50% of cases. In contrast, the infiltration of the pituitary gland by leukemia cells is unusual. To date, AML presenting with central diabetes insipidus (CDI) has been rarely reported. Here, we present a patient with AML (subtype clasification is proceeding) presenting with panhypopituitarism and CDI.
Case report
A 37-years-old man, with no significant past medical history, presented to Emergency department with complaint of high fever. Laboratory tests revealed increased CRP, ESR, serum sodium was 157 mEq/l and free cortizol was 3 μg/dl. Patient diagnosed as panhypopituitarism according to the pituitary hormones values (TSH:0.04 μIU/ml (0.2–4.2), ft_4: 0.801 ng/dl (0.99–1.65), kortizol: 3.21 μg/dl, ACTH: 12.3 pg/ml). On the mri scan, FLAIR image shows hyperintense lesions in bilateral hypothalamic areas probable due to leukemic infiltration and mri spectroscopy reveals high cho/cr and cho/naa ratios. Patient admitted the endocrinology clinic and hyponatremic IV hydration (%0.45 saline and %5 dextroz) was given in order. After correction of hypernatremia and dehydration, water deprivation test showed worsening of hypernatremia (sodium: 156 mEq/l), and serum osmolality test showed hyperosmolality (320 mosm/kg) with inappropriate low urine osmolality (170 mOsm/kg). Patient was treated with prednizolon, desmopression and $levoT_4$ sodium for panhypopituitarism. On the third day of admission, The laboratory studies showed neutropenia (white blood cell 2.6 k/μl), macrocytic anaemia (Hemoglobin 10.2 μg/dl, MCV 131.7 fl),and mild thrombocytosis. A diagnosis of myeloid leukemia was confirmed after examination of a peripheral blood and bone marrow aspiration (the genetic analysis is proceeding).
Conclusion
In conclusion, this is the first case of reporting coexistance of AML, CDI, panhypopituitarism and hypothalamic lesions probable due to leukemic infiltration.

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EP253

Adrenal insufficiency precipitated by Graves' hyperthyroidism in a patient on megestrol acetate treatment

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Introduction
Megestrol acetate (MA) is commonly used to promote weight gain in patients with HIV infection. Adrenal insufficiency (AI) has been reported as an adverse effect of MA but this association is not frequently recognized in clinical practice and only few cases develop symptoms of AI. We describe a case of symptomatic AI precipitated by Graves' hyperthyroidism in a HIV patient on long-term MA treatment.
Case report
A 44-year-old man with HIV-infection, followed in Infectious Diseases Unit since 1999, was admitted at hospital by weight loss, tremor and tachycardia. Thyroid function study revealed autoimmune hyperthyroidism (TSH: 0.01 μUI/ml; FT4: 4.88 ng/dl and positive TSH receptor antibody). Therapy with methimazole was started. He was taking 240 mg of MA daily irregularly for more than 11 years and discontinued MA for long time periods, but he never developed symptoms of AI. One month after discharge, he developed diarrhoea, abdominal pain, hypotension and asthenia. Laboratory analysis found hyponatremia and hyperkalemia and thyroid function still remained uncontrolled (elevated FT4 and undetectable TSH). Serum cortisol was 1.1 μg/dl and after cosyntropin stimulation, were 7.6 and 10.7 μg/dl at 30′ and 60′, respectively. The adrenocorticotropic hormone level was <5 pg/ml (normal, 5–50 pg/ml) and adrenal antibodies were negative. MA was discontinued and steroid replacement was initiated. The symptoms disappeared and the patient improved progressively. During follow-up, corticoids dose was progressively decreased to discontinuation, and radioactive iodine was prescribed to control hyperthyroidism. One year later, cortisol and ACTH levels were normal without need for corticoids.
Conclusions
To the best of our knowledge, it has not been reported that Graves' hyperthyroidism causes a symptomatic AI in patients with unrecognized or subclinical adrenocortical disease associated with MA treatment. Clinicians should be alert to the possibility of development of AI in patients taking MA, particularly if a stress situation is present.

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EP254

Bilateral adrenal mass mimicking adrenocortical carcinoma

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Introduction
Bilateral adrenal mass presents a unique diagnostic challenge and carries additional risk of being metastasis. The differential diagnosis of bilateral adrenal mass include primary or secondary neoplastic disorders (adrenocortical carcinoma, lymphoma, metastases), pheochromocytoma, longstanding congenital adrenal hyperplasia and macronodular adrenal hyperplasia, infections such as tuberculosis, histoplasmosis and blastomycosis.
Case
Thirty-five year-old male presented with weight loss, fever, emesis and headache. Laboratory findings showed hyperkalemia, hyponatremia, low cortisol serum levels and significantly elevated ACTH, CRP serum levels and ESR. Glucocorticoid treatment was initiated immediately. For evaluation of etiology of severe weight loss, CT disclosed bilateral adrenal mass, milimetric pulmonary nodules and cerebral-cerebellar nodulary lesions. Upon investigation, the patient complained testicular pain and swelling, and physical examination illustrated testicular mass ultrasound revealed epididimal thickening, heterogeneity and ductal hypoechoic nodulary lesions. For differential diagnosis, PET CT scan was performed and high adrenal mass uptakes (SUVmax:18,4)compatible with malignancies was detected. In the search for a definitive diagnosis, between metastatic adrenal carcinoma, metastatic carcinoma of unknown origin (lung, malignant melanoma etc.) and infectious causes, ultrasound guided fine needle aspiration biopsy of the adrenal mass was carried out. Histopathological examination demonstrated necrotizing granulomatous inflammation consistent with tuberculosis. Anti-tuberculosis treatment was started as soon as possible and the patient had a remarkable recovery through several months.
Conclusions
The most common causes of Addison's disease are idiopathic adrenal atrophy and adrenal tuberculosis. Globally, Tuberculosis prevalence decreases and it is reported that TB prevalence in 2015 was 42% lower than it used to be in 1990. However, tuberculosis is still an important health problem. Adrenal tuberculosis should be taken into consideration when adrenal failure and bilateral adrenal involvement is detected.

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EP255

Iatrogenic cushing syndrome and acute adrenal insufficiency due to the association of inhaled corticosteroids and ritonavir

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Introduction
Hepatic metabolism of inhaled corticosteroids (ICS) takes place via cytochrome P450 3A4. Nevertheless, it can be decreased by enzyme inhibitors such as itraconazole or ritonavir, thus leading to an increase in the bioavailability of ICS. This can result in an accumulation of the steroid drug and a cushing's syndrome.
Case report
We present the case of a 48 year old woman with human immunodeficiency virus (HIV) infection on highly active antiretroviral therapy that included ritonavir. Inhaled fluticasone was added to her treatment of severe chronic asthma. Two years later, she was admitted to the Intensive Care Unit due to a massive upper gastrointestinal bleeding secondary to an erosive gastritis, which required support with vasoactive drugs during 72 h. However, 1 week after her admission, the patient started to present hypoglycemias and hypotension, accompanied by intense astenia and weakness of the inferior limbs. Adrenal insufficiency was suspected. The Physical exam showed a cushingoid appearance. Blood tests were carried out, showing normal renal and liver functions and ions. Her morning serum cortisol concentration was 3.0 μg/dl (5–17 μg/dl) and morning Adrenocorticotropic hormone (ACTH) was 6.7 pg/ml (<46 pg/ml)). A craneal CT was done in order to rule out structural disease (MRI could not be done due to the morbid obesity of the patient) and it was normal. Therefore, final diagnosis was iatrogenic Cushing's syndrome and acute adrenal insufficiency due to the association of inhaled corticosteroids with ritonavir.
Conclusion
This case emphasizes the need for pharmacovigilance when managing patients on complex drug regimens for physicians treating HIV infected patients.

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EP256

Atypical X-linked adult adrenoleukodystrophy with cerebellar and brainstem involvement – a case report

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Background
X-linked adrenoleukodystrophy (ALD) is a peroxisomal disorder of beta-oxidation that results in accumulation of very long chain fatty acids (VLCFAs) in various tissues. The clinical phenotype of X-ALD in adults is variable and involves adrenal, gonadal and nervous system dysfunction (adrenomyeloneuropathy, AMN). Patients with AMN typically develop spastic paraparesis due to progressive degeneration of the cerebral white matter.
Objective
To report a case of a rare adult-onset cerebello-brainstem presentation of a sporadic ALD with sparing of the occipito-parietal lobes and autonomic dysfunction which resembles multi-system atrophy.
Case report
We report the case of a 33 year old man with Addison's disease since his early twenties and a 2-year history of progressive neurological deterioration preceded by a psychiatric bout with mania and psychosis. The neurological presentation started as a slowly progressive gait ataxia, unsteadiness and the need for walking support. Speech was poor and dysarthric and uninhibited behaviour was occasionally present. After 2 years of follow-up, generalized ataxia was

accompanied by atypical parkinsonism, urinary disturbances and spastic paraparesis with inability to walk. The brain MRI showed a marked cerebellar and midbrain atrophy with bilateral demyelination of the long tracts and hypotrophy of dorsal columns of the spinal cord, the latter being highly suggestive for AMN. Of note, the occipito-parietal parenchyma was spared. A differential diagnosis of this nervous system involvement in the context of Addison's disease is discussed.

Conclusion

Up to 60% of adolescent and young adult men with ADL/AMN have no or few neurologic abnormalities at the time of diagnosis of adrenal insufficiency. The cerebello-brainstem form of AMN can be a rare presentation of ALD. ADL/AMN should be considered in any boy or young man with adrenal insufficiency and neurological signs, albeit atypical.

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EP257

Hypogonadotropic hypogonadism in human immunodeficiency virus infected men: uncommonly low testosterone levels

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Introduction

Hypogonadism is common and occurs prematurely in human immunodeficiency virus (HIV)-infected men, being hypogonadotropic hypogonadism (HH) more frequent. However, HH with very low testosterone has not been described. We present three HIV-infected men with severe HH and normal pubertal development.

Case report

Three HIV-infected men, with HIV-1 diagnosis at the ages of 22, 34 and 35 years. Two of them had depressive syndrome, one treated with escitalopram and the other with mirtazapine. The one diagnosed with HIV when he was 22 started antiretroviral drugs (protease inhibitor and reverse-transcriptase inhibitors) at the age of 25 and seven years later complained of decreased libido, unejaculation and erectile dysfunction. The second one presented with decreased libido, unejaculation and hair loss in androgen-dependent areas 6 months after the HIV diagnosis. The third started antiretroviral drugs (reverse-transcriptase inhibitors) at the time of HIV diagnosis and 1 year later referred anejaculation and decreased libido. Laboratory tests revealed HH in all of them (FSH 1.48 and 0.7 U/l; LH 0.46, <0.12 and <0.07 U/l; total testosterone 24.2, <10 and 37 ng/dl and free testosterone 0.66 and 0.46 pg/ml). Prolactin, estradiol, the other pituitary axis and the sellar and head computed tomography scan were normal. All had normal CD4 count at the time of HH diagnosis. They started testosterone replacement therapy, with testosterone normalization and symptoms improvement.

Conclusions

Causes of HH in HIV-infected men include undernutrition, severe illness, drugs (psychotropics, opiates, megestrol acetate or steroids), pituitary dysfunction and co-morbid conditions, as antibody to hepatitis C virus seropositivity and injection drug use. Despite having none of these features (except two patients that were treated with low-dose psychotropics), our patients had HH with uncommonly low testosterone. This suggests that a different mechanism could contribute to severe HH in HIV-infected men. Screening for hypogonadism in all HIV-infected men might help to understand its etiology.

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EP258

Thyrotoxicosis leading to adrenal crises reveals primary bilateral adrenal lymphoma – case report

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Introduction

Amiodarone use may be associated with secondary severe organ dysfunction. Thyrotoxicosis develops in 15% cases. Primary bilateral adrenal lymphoma is a rare malignancy. If frequently presents bilaterally and with symptoms of adrenal insufficiency. Symptomatology for both conditions is nonspecific, especially in the elderly, and a high suspicion index is necessary for appropriate diagnosis.

Case report

A 78 year old female presented to the emergency department due to confusion, nausea and vomiting. She had history of Diabetes Mellitus, Hypertension and atrial fibrillation. She had been recently treated for urinary infection associated with vomiting and acute hypochloremic hyponatemia. Leucocyturia persisted and due to TSH 0.01 μU/ml, fT4 68 (10–18) pmol/l, fT3 6.34 (4–8) pmol/l, the patient was admitted to the Endocrinology ward. Further evaluation supported amiodarone-induced type 2 thyroiditis. Despite appropriate therapy, thyroid function further aggravated. She synchronously developed a septic state associated with nosocomial pneumonia. Hemodynamic instability, hyponatremia, hypoglycemia and vomiting raised the suspicion of concomitant adrenocortical insufficiency. Fluid resuscitation and hydrocortisone led to clinical improvement, with high dose glucocorticoid requirements. Adrenal insufficiency was admitted. Abdominal echography showed right and left justa-renal heterogeneous solid nodules (6.6 and 7 cm respectively) and left pleural effusion. Fluid analyses was negative for malignant cells. Thoracoabdominal contrasted-tomography suggested an endobronchic primary, also suspected during bronchofibroscopy, with hepatic and adrenal secondary deposits. The left mass compressed the ureter and seemed to penetrate the kidney and vascular structures. 24 h-Urinary metanephirnes were normal but the adrenals were not accessible to biopsy. After a period of seemingly favourable evolution the patient died. Autopsy confirmed primary adrenal non-hodgkin lymphoma.

Conclusion

Primary adrenal lymphoma is a rare cause of adrenal insufficiency but progression is often fast and fatal. This entity must integrate the differential diagnosis, especially in the elderly patient.

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EP259

Multiple endocrine dysfunctions in a patient with secondary hemochromatosis

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Introduction

Hemochromatosis is a disorder caused by an excess of iron deposition in the parenchymal cells that leads to organ dysfunction. In patients with secondary hemochromatosis due to multiple blood transfusions, endocrinopathies such as diabetes mellitus, hypopituitarism frequently develop.

Herein we report the case of a patient with B-thalassemia major who developed diabetes mellitus, hypopituitarism and primary hypoparathyroidism due to secondary hemochromatosis.

Case report

A 27-year-old male patient was diagnosed at the age of 4 years with hemochromatosis secondary to multiple transfusions for B-thalassemia major. At the age of 19 years, he developed diabetes mellitus and hypopituitarism with hypogonadotropic hypogonadism and corticotropin deficiency. MRI showed hemosiderin deposits in anterior pituitary gland.

He received insulin, hydrocortisone and testosterone enanthate. One year later, he was diagnosed as having iron-overload cardiomyopathy and hepatic cirrhosis.

At the age of 27 years, the patient presented with a weakness. On physical examination, he had a body weight of 56 kg, a body mass index of 17.2 kg/m^2, a blood pressure of 90/60 mmHg and a pulse rate of 75 per mn. Laboratory tests indicated a central hypothyroidism with a TSH of 3.94 μIU/ml and FT4 of 0.66 ng/ml and a hypoparathyroidism with hypocalcemia (corrected calcemia of 2.05 mmol/l), hyperphosphatemia (1.91 mmol/l) and low PTH level (13.3 pg/ml). He was treated with levothyroxine and 1 α hydroxyvitamin D3.

Conclusion

Patients with secondary hemochromatosis due to repeated transfusions may develop irreversible multiple endocrine failures. Therefore, a regular use of chelation therapy and a follow up with repeated screening examinations are necessary in patients with multiple transfusions.

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EP260

Severe hyperkalemia and unmasking of renal disease following adrenalectomy for aldosteronoma

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Severe hyperkalemia post adrenalectomy is documented in the literature but not actively sought after in high risk post-operative patients.
Case
Fifty-one year old woman with a 12 year history of hypertension and hypokalemia. Her BP was controlled with amlodipine 10 mg OD. Serum aldosterone was 2832 pmol/l with undetectable renin activity leading to aldosterone to renin ratio (ARR) >28 000 pmol/l per ng/ml per h. Creatinine was 75 μmol/l with eGFR of 85 ml/min. CT showed a 3.5 cm low density left adrenal mass and adrenal vein sampling confirmed left lateralization. She underwent left adrenalectomy. At the time of discharge serum creatinine was 71 umol/l, with potassium of 3.8 and eGFR of 85 ml/min. Her serum aldosterone was <70 pmol/l and renin activity of 0.36 ng/ml per h yielding ARR <194. She was readmitted after 3 months with potassium of 6.7 and serum creatinine of 154. She was started on fludrocortisone and her creatinine dropped to 123 with improvement in potassium of 5.2. On discontinuing fludrocortisone after 4 months her serum creatinine rose again and reached a new baseline level of 180 mmol/l, eGFR 28 ml/min.
Discussion
While overt pre-existing renal impairment may be a strong factor in predicting post-operative hyperkalemia. Evidence suggests that PA itself may induce a hyper-filtration injury that may mask renal impairment until the operative reversal of the phenomenon.
Conclusion
Hyperkalemia screening should be actively considered in high risk patients. Older age (>53), longer duration of hypertension (>10 years), impaired pre-op (<58 ml/min) and post-op GFR and higher levels of pre-op aldosterone and are all known risk factors. The long term cure of primary hyperaldosteronism and hypertension is expected to yield renal benefits but development of irreversible post adrenalectomy renal impairment after a long duration of hypertension may argue for earlier consideration of a PA diagnosis in hypertensive populations.

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Hypopituitarism in a phenotypically Turner-like female with 45X/46 XY karyotype

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Introduction
Mixed gonadal dysgenesis with 45X/46XY mosaicism is considered to be a rare disorder of sex development. This condition is characterized by a phenotypically very heterogeneous clinical presentation. In fact, the individuals with 45X/46XY mosaicism ranged from phenotypically normal men with azoospermia, going through individuals with genital ambiguity, to women with Turner syndrome.
Herein, we describe a phenotypically Turner-like female with 45X/46XY mosaicism with coexisting hypopituitarism.
Case report
A 20-year-old female patient was referred to our department for short stature and primary amenorrhea. On examination, she had a body weight of 44 kg, a height of 138 cm (<−4S.D.), a body mass index of 23.1 kg/m^2, a round face with a low posterior hairlines and multiple cutaneous nevi. She had a female phenotype with female external genitalia (Tanner stage: B3 P2 A1). Her bone age was delayed. Laboratory tests revealed a hypergonadotropic hypogonadism (FSH= 115 mIU/ml, LH=38.33 mIU/ml, oestradiol <9 pg/ml), a normal thyroid function and a normal prolactin level. L dopa stimulating test showed growth hormone deficiency (peak GH=3.89 ng/ml) and insulin-induced hypoglycemia test confirmed GH and corticotropin deficiency.
Pelvic ultrasonography and MRI scan showed a hypoplastic uterus with no visualized ovaries. Pituitary MRI scan was normal. Echocardiography and renal sonography revealed no abnormalities. Cytogenetic analysis of peripheral blood revealed a karyotype with mos 45, X (18%)/46, XY (82%).
Patient was put on hormone replacement therapy. Laparoscopy showed apparently complete Müllerian structure with streak gonads. Bilateral prophylactic gonadectomy was performed.
Conclusion
The coexisting of Turner syndrome and hypopituitarism has rarely been reported. GH deficiency should be considered when the short stature is lower than that usually found in Turner syndrome.

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EP262

Left adrenal Ectopic cushing syndrome even more challenging

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Background
The Ectopic ACTH Syndromes (EAS) often associated with severe hypercortisolism are really a challenge.
Case presentation
We report the case of a 48-year-old woman, newly diagnosed with hypertension, hypokalemia despite renin-angiotensin blockers intake, and complaints of intense fatigue, muscular weakness, and easy bruising, which worse in four months. EAS was biochemically confirmed, but two urinary catecholamines collection were negatives despite a left adrenal topography in all image studies included MIBG was found. The patient dramatically worse after lanreotide treatment, we hypothesize, the lack of response to somatostatin analogues could be explained because of the extremely high hypercortisolism that downregulate somatostatin receptor type 2 expression, so after ketoconazole therapy and cortisol normalization, we repeat SSRS scan, but we do not find any change. Finally adrenal left gland and an associated extra adrenal ganglioneuroma were removed. Surprisingly only the adrenal gland had significant staining of ACTH. After removal, blood pressure was normalized without pills, hypercortisolemic parameters and the clinical symptoms were resolved.
Conclusion
We highlight surgery, if is feasible, in EAS, is ever the best choice and can be curative. Regarding pharmacological options we emphasized glucocorticoids can decrease the somatostatin receptor type 2, expression in tumor, with diagnostic and treatment implications. Finally we propose ^{68}Gallium-SSTR-PET/CT, and pasireotide with somatostatin receptor type 5 affinity, could be better diagnostic and treatment alternatives in patients with very high cortisol levels.

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EP263

Cushing's disease – medical chameleon – case report of the patient with cyclic, ACTH-dependent Cushing's syndrome due to atypical pituitary macroadenoma

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Introduction
ACTH-secreting macroadenomas account for about 4–10% of Cushing's disease and are often resistant to surgical treatment and radiotherapy. The aim of the study was to present diagnostic and therapeutic difficulties in a case of cyclic recurrent ACTH-dependent Cushing's syndrome due to atypical pituitary adenoma.
Case report
50-year-old man with visceral obesity was referred to hospital because of poor control of diabetes and high blood pressure. On the basis of clinical symptoms and severe hypokaliemia hypercortisolemia was suspected and laboratory test were performed. They confirmed ACTH-dependent Cushing's syndrome (plasma cortisol=46.6 μg/dl (range 4.3–22.4); ACTH=176 pg/ml (4.7–48.6); urine daily cortisol excretion=15 870 μg (range 285–213.7)]. Further investigations did not show any pathology of the pituitary or another tumor responsible for ectopic ACTH syndrome. Between 08.2007 and 03.2008 the patient received inhibitors of steroidogenesis. The loose of weight (30 kg), normalization of cortisol level and significant improvement of patient's well-being were observed. The treatment has been withdrawn. During further follow-up of the patient there were periodically repeated periods of moderate subclinical hypercortisolemia, observed mainly in spring and autumn. In spring 2013, significant clinical and laboratory signs of hypercortisolemia appeared and MRI revealed pituitary macroadenoma (15×13×15 mm). In 09.2013 the patient underwent transsphenoidal surgery (atypical sparsely granulated coricotroph adenoma, ACTH (+), MIB1>20%). Postoperative MRI did not show tumor remnant, but moderate hypercortisolemia was present. The patient was disqualified from a second surgery, in 04.2015 he

received stereotactic radiotherapy. Since November 2015 the patient is being treated with pasireotide because of persistent hypercortisolemia.
Conclusions
The authors present long-term difficulties in establishing the diagnosis of Cushing's disease, mainly because of cyclic nature, long period of remission and diagnostic limitations in finding the source of ACTH excess. Delay in diagnosis of Cushing's disease leads to worse effects of treatment and the need to search for new therapeutic approaches.

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EP264

The endocrine trifecta: rarer presentation of a rare disease

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Introduction
Autoimmune polyendocrine syndrome type 2 is a rare disease characterized by the presence of autoimmune Addison's disease in combination with thyroid autoimmune disease and/or type 1 diabetes mellitus, and possible occurrence of other autoimmune non-endocrine disorders. The combination of the three glands diseases is even rarer and is referred to as Carpenter's syndrome.
A long time interval is often present between the manifestations of the first to second/third component of the disease which may reach years and decades and it is unusual to find simultaneous occurrence of two or more glands disorders.
Case report
We present here a case of 47 years old British woman who was admitted with hyponatremia and significant postural hypotension and was subsequently confirmed to have Addison's disease. Upon starting her on steroids replacement, she was re-admitted within 3 weeks with non-ketotic hyperglycaemia where an underlying autoimmune diabetes was confirmed. Subsequently she was found to have an autoimmune subclinical hypothyroidism, fulfilling the criteria of Carpenter's syndrome. We believe that the long standing cortisol deficiency in our patient had masked her underlying autoimmune diabetes and prevented her from having marked hyperglycaemia which was only spotted upon replacing her with glucocorticoids.
Conclusion
Autoimmune polyendocrine syndrome type 2 is a rare entity, but can lead to serious life-threatening problems if not identified and treated early, so a high index of suspicion is required.
Carpenter's syndrome is rare and only few cases have been reported in literature. Our case to the best of our knowledge is singular as the syndrome manifested with all the features presenting almost simultaneously within a short time span.

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EP265

Late complications in a man with poorly controlled congenital adrenal hyperplasia – case report

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Introduction
We report a case of CAH who developed several complications due to poor control. Proper diagnosis and treatment can enable men with the disease to have a normal life and fertility. Case report 39-year-old patient with a history of primary adrenal insufficiency was admitted to our department because of infertility. Semen analysis performed prior to hospitalization showed azoospermia. The patient did not have medical documentation regarding his disease and was not able to explain exactly why the glucocorticoid therapy was initiated. In referral letter to the hospital, Addison's disease was written in the diagnosis. We learned from parents, that hydrocortisone was introduced after life-threatening episode in the neonatal period and maintained untill now. The study examination revealed dark complexion and brown spots on mucous membranes, livid lips, and enlarged testes with palpable nodules. Laboratory studies have shown: increased level of RBC, *hyperlipidemia,* high values of ACTH (>1250 pg/ml) and testosterone (>15 ng/ml) and low concentrations of gonadotropins. After 2 days of hydrocortison withdrawal, cosyntropin test was performed revealing impaired cortisol response. Moreover, basal level of 27-OH progesterone and after cosyntropin stimulation was very high. The abdominal computed tomography scan revealed grossly enlarged and heterogeneous adrenal glands (right $39\times71\times70$ mm, left $38\times89\times110$ mm). They showed progression comparing to previous CT. Ultrasonography of the testes revealed variable echogenicity. The tumor markers (CEA, α-FP, β-HCG) were negative. Biopsy of testes was performed. Urinary steroid profiling was performed to confirm the salt wasting form of CAH. In the treatment 0.5 mg of dexametasone was introduced.
Conclusion
This case illustrates that congenital adrenal hyperplasia due to 21-hydroxylase deficiency can progress to chronic complications. Children with CAH require regular screening for complications and metabolic sequelae. It is desirable for all men with CAH to have a testicular ultrasound and routine semen analysis. Patients and their relatives should be well educated and informed about disease.

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EP266

Insulin-mediated pseudoacromegaly with nonfunctioning pituitary adenoma

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Pseudoacromegaly is a rare disorder characterized by cutaneous manifestations of growth hormone excess but with normal growth hormone levels or IGF-1. This condition described in patients with insulin resistance, hypothyroidism, pachydermoperiostitis and drug intake such as minoxidil. The hyperinsulinaemia impaired metabolic signalling may activate intact mitogenic signalling pathways and stimulate pathological tissue growth.
A 41-year-old man presented with acral enlargement and excessive sweating. On physical examination He was tall (190 cm) and weighed 110 kg. His hands and feet were sweaty and enlarged. Skin tags and acanthosis nigricans of axilla, prognathism, acne were seen on examination. Serum GH:0.05 ng/ml (*n*:0–8.6), IGF-1: 115 ng/ml (*n*:101–267), prolactin:10 ng/ml (*n*:2.1–17.7), TSH: 1,3 uIU/ml (*n*:0.55–4.78) and other pituitary hormon levels were normal. After overnight 1 mg dexamethasone suppression test cortisol level was 0.8 µg/dl ($n<1.8$). Insulin like growth factor binding protein-3 was also normal. The fasting glucose levels were 102 mg/dl (*n*:70–105), fasting insulin levels were 78.2 mU/l (*n*:3–25). HOMA-IR: 19.6. GH level was suppressed after 75 g oral glucose test. Pituitary magnetic resonance imaging revealed intrasellar mass lesion $3\times4\times4$ mm microadenoma, in the left part of pituitary gland, believed to be non-secretory with normal pituitary hormonal workup. The patient did not approve of any pituitary surgery, admited metformin 1000 mg twice daily and has been followed up.
This is a rare case of pseudoacromagely with nonfunctioning pituitary adenoma. Physicians should be aware while evaluating patients with similar clinical and laboratory features.

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EP267

«Clinically silent» somatotropinoma

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Introduction
Somatotropinomas are typically recognized when GH excessively secretion causes acromegaly**.** «Silent» somatotroph adenomas (immunohistochemical evidence of GH excess without biochemical or clinical evidence) and «clinically silent» somatotroph adenomas (immunohistochemical and biochemical evidence without clinical evidence) have occasionally been reported. The relative frequency of each presentation is unknown.
The aim is to describe the clinical course of a patient with clinically silent somatotroph adenoma.
Case presentation
In a female patient disease presented at the age of 22 years with oligomenorrhea and hyperprolactinemia – PRL 881.37 mU/l (127–637) for which she received cabergoline 0.25 mg per week with induction of normoprolactinemia and normalization of menstrual cycle. Within a year MRI revealed endo-suprasellar pituitary adenoma $16\times15\times13$ mm, without chiasm compression. The levels of TSH, cortisol, LH, FSH, prolactin were in normal ranges. These changes were regarded as nonfunctioning pituitary adenoma and annual follow-up was

recommended. Subsequent MRIs showed an enlargement (21×18×17 mm), mainly due to suprasellar component without chiasm involvement. ACTH, cortisol, PRL, LH, FSH were within reference ranges and a decrease of free T4 8.1 pmol/l (9–20) and IGF-1 elevation 816.9 ng/ml (128–315) were noted. The high fasting GH levels confirmed biochemical acromegaly as at physical examination there were no clinical signs of this disease. Transsphenoidal surgery was performed and immunohistochemical staining showed that tumor cells were strongly reactive to GH and relatively mildly reactive to PRL, with ki-67 2% confirming the presence of clinically «silent» somatotropinoma. After 3, 6, 12 months after the surgery the levels of IGF-1 remain in normal ranges. The brain MRI was repeated after 12 months thereafter with no signs of adenoma.
Conclusion
This case demonstrates the need to perform an extensive hormonal testing for all patients with presumably non-active pituitary adenoma.

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EP268

Delayed diagnosis of isolated postpartum TSH deficiency: Sheehan's syndrome or lymphocytic hypophysitis?

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Introduction
Sheehan's syndrome (SS) is a rare complication of postpartum hemorrhage resulting in varying degrees of pituitary insufficiency. The diagnosis of SS has often been overlooked and thus delayed for many years due to its nonspecific signs and symptoms. Lymphocytic hypophysitis (LL) is also an uncommon autoimmune disorder that has to be suspected in women with recent delivery presenting with changes of one or more pituitary hormone secretions, especially when associated with other autoimmune endocrine or non-endocrine disorders.
Case report
We report the case of a 33-year-old female who presented to our clinic in August 2012 with complaints of fatigue, depression, impaired memory, bradipsychia, upper and lower limbs paresthesias. In October 2010 the patient had severe postpartum hemorrhage with headache, lactation failure and oligomenorrhea. Physical examination at admission: BMI = 26 kg/m^2, dry skin, cold extremities, bradycardia (50/min), low blood pressure = 90/60 mmHg. Laboratory results: TSH = 1.28 μIU/ml, TT3 < 40.0 ng/dl, FT4 < 0.30 ng/dl, TPOAb = 67.6I U/ml (n < 35 IU/ml), 8:00 h plasma cortisol = 10.1 mg/dl with normal increment after Synachtene retard stimulation test, ACTH = 12.7 pg/ml, FSH = 4.53 mIU/ml, LH = 1.94 mIU/ml, estradiol = 38.26 pg/ml, Prolactin = 6.45 ng/ml, IGF1 = 167.3 ng/ml (80–277 ng/ml). Thyroid ultrasound revealed diffuse glandular enlargement with heterogeneous and hypoechoic parenchymal echo pattern that together with the TPOAb levels supported the diagnosis of Hashimoto's thyroiditis (HT). Pituitary MRI showed empty-sella. The pituitary stalk was slightly thickened and deviated. No pituitary tumors were detected. The patient was diagnosed with TSH insufficiency and HT and replacement treatment with levothyroxine was started. The follow up was favorable, without functionally progress to combined pituitary dysfunction. In 2014 the patient uneventfully gave birth to a second child.
Conclusions
We present the case of a young women diagnosed at 2 years postpartum with isolated TSH deficiency and chronic autoimmune thyroiditis. Long-term follow-up is mandatory because although the severe postpartum hemorrhage and the empty sella suggest SS the association with HT may rise the suspicion of a LL.

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EP269

Pregnancy in patient with GH secreting pituitary adenoma: a case report

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Introduction
GH producing pituitary adenomas are associated with infertility. Hereby the first case in Lithuania, when acromegaly patient got pregnant and delivered is reported.
Case presentation
33-year-old woman visited endocrinologist complaining of secondary amenorrhoea. Due to elevated prolactin – 3016 mU/l (NR < 418), bromcriptine treatment was started. The patient discontinued treatment after three months because of restoration of regular menstrual cycle and dropped out from follow-up. Four years later the patient visited our hospital having complaints of typical acromegaly symptoms. Her IGF-1 was 150.7 nmol/l (x3 ULN). Pituitary MRI disclosed a macroadenoma 1.6×1.2×0.6 cm. Total macroadenoma's removal was not possible, because of invasion into left cavernous sinus, there was no visual impairment, so the patient was enrolled into the III phase clinical trial and treated with subcutaneous injections of study drug (dopamine-somatostatine chimeric molecule). Due to insufficient effect, treatment was discontinued. One month later IGF-1 was 846.9 ng/ml (x3.4 ULN). Transsphenoidal resection of adenoma was performed, pathological examination confirmed GH/TSH secreting cells. Three months later, treatment with somatostatin analogues was started due to GH and IGF-1 hypersecretion and continued for 280 days, giving Lanreotide 120mg every 56 days for the last three injections. When patient came for fourth Lantreotide dose, she was pregnant for 6 weeks and treatment was discontinued. Normal fetal growth and development was observed, with no maternal complications. The patient delivered a full-term 4060 g weight, 52 cm height new-born and APGAR 9–10 points by caesarean section. Lanreotide therapy was restarted in three months. Seven months after delivery MRI scan disclosed reduced adenoma size, hormone levels decreased as well.
Conclusion
The case of successful pregnancy in patient with active GH secreting adenoma, treated with Lanreotide, is presented. Only a few such cases are reported worldwide. Although lanreotide is assigned to category C by FDA, no pregnancy complications were observed in our case.

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EP270

Differential diagnosis of adrenal insufficiency in a patient with APS syndrome and Rosai–Dorfman disease

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Primary adrenal insufficiency could be a rare manifestation of antiphospholipid syndrome (APS) and may be a consequence of bilateral adrenal hemorrhage. Rosai–Dorfman disease (RDD) is sinus histiocytosis with massive lymphadenopathy, a rare histiocytic proliferative disorder with a distinctive microscopic appearance. The retro-peritoneum is an infrequent site of involvement as well as extranodal sites.
We report a case of a 39-year-old female patient with diagnosed APS 3 years ago treated with anticoagulant therapy and glucocorticoids who presented with fatigue, loss of appetite and abdominal cramps. One-year prior admission an abdominal ultrasound showed acalculose cholecystitis along with lymphadenopathy and a right adrenal gland enlargement 3 cm in diameter, while left was described as normal. At the time of admission primary adrenal insufficiency was diagnosed while other hormone tests were normal and prednisone was replaced with hydrocortisone. In the mean time abdominal CT revealed again acalculose cholecystitis but now both adrenal glands were enlarged and hypodensly structured, left 2.6×3.9, right 3.8×1.8 cm with numerous enlarged lymph nodes in the area of hepatoduodenal ligament largest being 3.3 cm in diameter. Surgical removal of gallbladder was performed along with extirpation of lymph nodes and patohistological finding showed sinus histiocytosis. Postoperative synacthen test indicated low basal cortisol production with no response to stimulation and hydrocortisone therapy was continued.
Differential diagnosis included adrenal hemorrhage associated with APS or RDD which can be associated with APS (only two cases reported presently) but retroperitoneal location is extremely rare let alone extranodal sites. However, since CT imaging characteristics showed no signs of hemorrhage, thrombosis or embolism of adrenal glands, it is entirely possible that bilateral enlargement and adrenal insufficiency was a result of sinus histiocytosis infiltration as a sign of RDD.

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EP271

Chronic lymphocytic leukemia in an acromegalic patient

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Introduction
Acromegaly patients are known to have an increased risk of malignancies. This may be as a result of the effect of insulin-like growth factor I (IGF-I) on cellular proliferation and apoptosis inhibition. Although there are various reports related with hematological malignancies in children who treated with growth hormone (GH), few data are available about hematological malignancies in acromegaly patients. Here, we report a patient with acromegaly who has been developed chronic lypmhocytic leukemia (CLL) in the follow-up period.
Case
A 30-year-old woman who was at 25th weeks gestation were consulted for gestational diabetes mellitus 9 years ago. Physical examination, random GH, IGF-I levels and glucose suppression test results were consistent with acromegaly. She reached full term without treatment and had a caesarian section and delivered a 4200-gr-baby boy with Apgar score of 9. After 1 year delivery transsphenoidal surgery was performed and 3 months after the operation long-acting somatostatin analog treatment was begun. Since she had residual adenoma and biochemical remission was not achieved with medical treatment, she had underwent second operation after 1 year later the first surgery. Since the remission was not achieved despite the medical treatment, after 1 year later the second operation gamma-knife therapy has been performed. After 5 years later the radiotherapy, GH and IGF-I levels were decreased gradually, somatostatin therapy was lowered and finally discontinued. However, the patient had progressive leukocytosis with 90% lymphocytes. Flowcytometric analysis of the peripheral blood was consisted with CD5+, CD19+, CD20+, CD22+, CD79b+, CD43+, CD200+ lymphocytes with surface anti-kappa monoclonality. Fluorescent *in situ* hybridization analysis of bone marrow aspiration revealed 20% deletion 17p13.1(TP53). Her findings were consistent with CLL-stage II.
Conclusion
Occurrence of CLL in the course of acromegaly may have been caused by excessive endogenous GH or may be a coincidental situation.

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EP272

Diagnostic challenges in severe primary hyperaldosteronism

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Primary aldosteronism (PA) is generally caused by an adenoma or adrenal hyperplasia. To discern between these two, selective adrenal vein sampling (AVS) is necessary. Adequate interpretation requires that RAAS-interfering medication be withdrawn. We report a patient with severe PA, where it was not possible to safely withdraw RAAS-interfering medication.
Case
A 37-year-old male was referred for AVS. He had documented PA and bilateral adrenal adenomas on CT-abdomen. Previous attempts to withdraw medication had led to hypokalaemia (despite supplementation) and hypertensive crisis. Medication included spironolactone (up to 400 mg), barnidipine, doxazosine, metoprolol, and potassium. The patient complained of aggressiveness and sexual dysfunction. Blood pressure was 150/110 mmHg. Since AVS was required, RAAS-interfering medication was carefully withdrawn. Subsequently, potassium requirement increased to 400 mmol/day. Blood pressure medication consisted of doxazosine 16 mg, verapamil 240 mg and hydralazine 200 mg. Ten days before AVS, the patient presented with hypertension (185/110), headache and blurry vision. Enalapril was added and renin concentration monitored. Baseline renin was 3.81 mU/l, after titration to enalapril 40 mg/day it was 4.10 mU/l. Blood pressure decreased to 160/90 mmHg. AVS demonstrated a right-sided source. After surgery, the patient recovered uneventfully and was normotensive and normokalemic without medication. Two months later blood pressure was 135/88 mmHg with Lisinopril 10 mg/day; aldosterone concentration was low. The patient's symptoms had resolved.
Conclusion
Even in severe PA, it is worthwhile to withdraw RAAS-interfering medication and perform AVS, so that surgical curation remains possible. If RAAS-interfering medication cannot be withdrawn, then renin (activity) should be monitored; diagnostic procedures can be interpreted reliably if this remains suppressed.

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EP273

Addison's disease caused by adrenal gland tuberculosis

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Addison's disease (primary adrenal cortical failure) is the lack of glucocorticoids due to disease of the adrenal gland. At 1855, when Addison described it tuberculosis (TB) was the main etiology. May be we are coming to that time. TB is an infectious disease caused by *Mycobacterium tuberculosis*. The most commonly (third of the patients) affects the lungs, as well as the other organs. Symptoms of the disease are non specific and are deteriorating slowly, so the disease is often overlooked, or not recognized until comes to infection or another stressful situation of the body.
51-year old women with a functional right kidney, after cholecystectomy was first time admitted in the hospital due to the upper urinary tract infections and renal failure. She was treated with ciprofloxacin. Then she suffered from severe headache, nausea and vomiting. She passed lumbar puncture. Cerebrospinal fluid exam was typical for serous lymphocytic meningitis. At the same time mild hyperkalemia (6.0 mmol/L) and hyponatremia (132 mmol/L) were diagnosed and treated symptomatically. In the next two months she felt worse, lose about 30 kg. The laboratory exams confirmed the failure of the adrenals.
The clinical signs were masked because the women is the Roma ethnicity and with hyperpigmented skin. We found even primary hypothyroidism. The treatment with hydrocortisone and levotiroxine started. The abdominal CT-scan showed small adrenals with microcalcinations. We preformed US-guided fine needle aspiration (FNA) biopsy of the adrenals, because the other tests for TB were negative. The PCR diagnostics for TB in the FNA biopsy sample was positive and confirmed suspected adrenal TB. She started with treatment for TB. TB is becoming one of the infections of the developed world we have to think about, because of the migrations.

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EP274

Hereditary Pheocromocytoma-Paraganglioma Syndrome: a case report

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Introduction
Paraganglioma (PGL) develops from cells of the parasympathetic and sympathetic system. It usually manifests as a slow- growing and painless mass. PGL may be hereditary, benign, malignant, unilateral or bilateral tumors. In most cases PGL is located around the common carotid artery but may also be located within the middle ear or in the abdomen. Non functional retroperitoneal PGL are rare tumors, usually asymptomatic, and can attain big dimensions. Mutations in the succinate dehydrogenase gene complex have been identified as a cause of inherited Pheocromocytoma-Paraganglioma Syndrome (PGL/PCC). Malignant PGL is a uncommon presentation diagnosed by local recurrence after total resection of primary mass or findings of distant metastases.
Case report
A 47 years-old woman with a non functional retroperitoneal PGL. A large pararenal tumor was removed completely. No distant metastases were found in imaging studies. After a follow up period of 10 months the patient was in a good health, asymptomatic, but a second operation was performed because of evidence of tumor recurrence. After surgery the patient was treated with Radiotherapy. Genetic analysis revealed succinate dehydrogenase B mutation in our patient (and subsequently in two of her three children.)
Conclusions
The malignant potential of the PGL is determined by local invasion as well as distant metastases as there are no characteristic cellular changes. In

retroperitoneal PGL 50% are thought to be malignant. The SDHB mutation plays an important role in malignant PCC/PGL. The present case indicates that conducting genetic testing, including SDHB mutation analyses, is required to determine the prognosis in patients highly suspected of having malignant tumors in the context of a PGL/PCC Syndrome.

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EP275

A novel case of hypomagnesaemia secondary to fludrocortisone

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We present a case of fludrocortisone-induced hypomagnesaemia in a 27-year old female with Autoimmune Polyglandular Syndrome Type1, manifesting as adrenal insufficiency, hypothyroidism and hypoparathyroidism. Her medications were; Alfalcidol 4 mcg; Levothyroxine 100 mcg; Hydrocortisone 20 mg bid; Fludrocortisone 200 mcg mane and 100 mcg nocte. The nocturnal dose of fludrocortisone was started 4 months prior to her presentation. She presented with a history of abdominal pain and carpopedal spasm. Her admission blood tests revealed hypomagnesaemia, hypokalaemia and hypocalcaemia.

Blood result	Admission	Discharge (Day 3)
Magnesium	0.53	0.72
Potassium	3.1	3.2
Corrected Calcium	1.94	2.43
Ionised Calcium	0.88	N/A

She was treated with intravenous electrolyte replacement. There was a clear temporal relation between the change in the dose of fludrocortisone and onset of symptoms and there was no other dietary or pharmacological cause for her hypomagnesaemia. An Ovid Medline search revealed no cases of fludrocortisone-induced hypomagnesaemia though there are reported cases to FDA.

Magnesium, mainly an intracellular cation with serum concentration of 0.7–1 mmol/l; 1% of total body magnesium(1) SPC does not mention hypomagnesaemia as an adverse effect (2).

The likely mechanism of action is interference of renal handling of magnesium. Approximately 80% of plasma magnesium is filtered through the glomerulus, the majority reabsorbed via the paracellular route at the thick ascending limb of the loop of Henley, dependent on electrical gradient across the membrane and 5–10% is absorbed at the distal convoluted tubule via the transcellular route, dependant on potassium secretion into the distal tubule to create a voltage gradient. The distal reabsorption is physiologically important process in fine-tuning magnesium balance and has been shown to be reduced in hypokalaemia (3). Fludrocortisone is known to produce hypokalaemia through its effects in the distal convoluted tubule.

Recommendation

We propose that fludrocortisone causes hypomagnesaemia via reduction of magnesium reabsorption at the distal convoluted tubule. We recommend that serum magnesium and calcium be checked regularly in patients taking fludrocortisone, especially after a change in dosage.

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EP276

The importance of early detection of Adrenomyeloneuropathy (AMN): a case report

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Introduction

Adrenomyeloneuropathy (AMN) is a form of X-linked adrenoleukodystrophy (X-ALD) a rare inherited disorder (estimated prevalence 1:20 000 to 1:50 000) characterized by the accumulation of very long chain fatty acids (VLCFA) and affects mainly the nervous system white matter and the adrenal cortex and nearly 100% penetrance in males. Widely varying phenotypes and prognoses often co-occur in a single kindred.

Methods

We report a case diagnosed at age 14 with idiopathic Morbus Addison. He was treated with corticosteroid replacement therapy and was stabilized. At age 27 he was hospitalized in neurology department with right coxo-femoral articulation pain, walking difficulty, progressive weakness and stiffness of the legs and loss of the ability to coordinate muscle movement. In laboratory evaluation routine hemogram resulted normal. Brain and cervical spine MRI resulted normal. Nerve conduction tests revealed a bilaterally significant increase in the central conduction time, four limbs electromyography examination resulted normal. The neurologist diagnosis was a spastic paraparesis (sporadic form) in a subject with morbus Addison. The patient married at age 25 and had 2 children a girl and a boy. The case described above went undiagnosed for almost 10 years until he was sent to our Endocrinology Department at age 37 with worsening of the neurological symptoms. The diagnosis of AMN was established by elevated plasma concentration of VLCFA C26:0, C24:0 and elevated ratio of C24/22 and C26/22. After genetic counseling, blood samples of other family members (mother, sister, brother and children) have been sent for VLCFA analysis. Plasma concentration of VLCFA of his mother, sister and daughter resulted elevated (carriers of X-ALD) but his son and brother resulted normal.

Conclusion

Males with idiopathic primary adrenal insufficiency should be evaluated for underlying ALD or AMN. Early diagnosis of AMN helps for detecting the carriers, at-risk female relatives and to decide on prenatal testing for pregnancies at increased risk.

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EP277

Difficulties of management of a VHL family

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Introduction

Von Hippel-Lindau (VHL) disease is an inherited, autosomal dominant syndrome manifested by a variety of benign and malignant tumors, with an incidence of about 1 in 36 000 individuals and a mean age at presentation of 26 years.

We present a family (mother and daughter) case of possible type 2A VHL disease diagnosed with multiple VHL-associated tumors in the absence of an available genetic testing. They both presented in our clinic in 2013 with biochemical profiles suggestive of pheochromocytoma (PHC). No genetic counseling was giving to the mother.

Clinical cases

G.F, 54 y.o, F, first diagnosed with bilateral PHC at the age 13, with a second bilateral PHC followed by a right adrenal tumor recurrence – each time a partial adrenal resection. She presents retinal angiomas with blindness of the RE and multiple hemangioblastomas of the cerebellum and spinal cord requiring seven neurosurgical interventions for compressive tumors. On routine checking we diagnosed a fourth right adrenal recurrence of PHC in addition to pancreatic tumors. The patient chose to remain under chronic alpha and beta blockers treatment.

Her daughter, 15 y.o, prematurely born at 7 months, was diagnosed with retinal angiomas with blindness of the LE since 9 y.o., cataract and secondary glaucoma of the RE. She was admitted at the age of 12 with sweating, palpitations, headache and high BP- when a bilateral PHC was confirmed by CT scan- 2 right adrenal tumors and a left adrenal tumor- and increased plasma NMN (2842/2205 pg/ml). Surgical removal was performed (total left and subtotal right adrenalectomy). One year after she developed a right adrenal recurrence which was again removed. She is now under close surveillance at every 3 months.

Conclusions

The management of VHL disease needs a multidisciplinary strategy, the primary goal being an early diagnosis and avoiding potential tumor-related disability.

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EP278

Hypopituitarism in the course of secondary hemochromatosis in a patient with Diamond-Blackfan anemia

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Introduction
Diamond-Blackfan anemia (DBA) is a rare, inherited normocytic or macrocytic anemia due to aplasia of red cell lineage in the bone marrow. Patients with DBA are diagnosed with a hypocellular bone marrow with a significant absence of erythroid precursors typically in early childhood and require chronic treatment with corticosteroids and frequent blood transfusions. Chronic blood transfusions lead to iron-overload injury and DBA patients, therefore, require lifelong chelation therapy.
Case report
A 31-year old male patient with DBA diagnosed at the age of 8, maintained on chronic blood transfusions repeated every 4 weeks since the age of 18 years and iron chelation therapy (deferoxamine) with poor adherence, was admitted to the Department of Endocrinology with suspected primary adrenal insufficiency. Since several months the patient complained about weakness, fatigue, orthostatic hypotension and hyperpigmentation of the skin. The clinical observation and the morning plasma ACTH and cortisol levels excluded primary adrenal failure: 32 pg/ml (7.2–63), and 15.4 µg/dl (4.3–22.4), respectively. Further hormonal assessments suggested hypogonadotropic hypogonadism: LH: 1.8 mIU/ml (1.5–9.3); FSH: 2.8 mIU/ml (1.4–18.1); testosterone: 26 ng/dl (241–824) and the growth hormone deficiency: GH: 0.44 ng/ml (0.03–2.47); IGF-1: 38 ng/ml (113–202), probably in the course of secondary hemochromatosis: plasma Fe 211 ug/dl (65–175), ferritin 5442 ng/ml (22–322), following blood transfusions. MRI of the sella turcica revealed a small pituitary gland with poor enhancement after gadolinium injection, what might confirm iron deposits in this region.
Conclusion
Pituitary dysfunction following secondary hemochromatosis should be considered in patients maintained on chronic blood therapy. Accurate evaluation and long-term follow-up of all patients with iron over-load are necessary in order to detect the occurrence of hypopituitarism, regardless of clinical evidence for pituitary dysfunction. An adequate replacement therapy is necessary in order to improve quality of life and outcomes in this group of patients.

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EP279

Addison disease in antiphospholipid syndrome – case report

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Introduction
Primary adrenal insufficiency or Addison disease (AD) is a potentially fatal condition if not diagnosed in time. Rarely, it can arise as a manifestation of antiphospholipid syndrome (APS), caused by adrenal venous thrombosis and consequent hemorrhagic infarction.
Case report
We present the case of a 36-year-old caucasian woman with APS diagnosis since she was 24, with history of arterial hypertension and multiple thrombotic events (deep vein thrombosis, spontaneous abortions, splenic vein thrombosis). She had been hospitalized for acute renal failure after her third spontaneous abortion and was discharged under corticotherapy (prednisolone 1 mg/Kg/day) with progressive reduction of dose. One month after being hospitalized and one week after suspending corticotherapy, she was admitted in the emergency department after 4 days of nausea, persistent vomiting and progressive asthenia. Medicated then with warfarin and antihypertensive medication. Initial analytical study revealed hyponatremia (114 mmol/l), hyperkalemia (7.9 mmol/l) and significative worsening of renal function (creatinine 4.90 mg/dl). She was readmitted and restarted on therapy with prednisolone; the basal adrenal function tests under prednisolone revealed morning serum cortisol 1.3 µg/dl (reference range 5–25) and ACTH 15 pg/ml (9–52). Abdominal CT showed 'nodular heterogeneous lesion (72× 50 mm) suggestive of adrenal hemorrhage in the right adrenal gland; left gland poorly visualised'. The patient initiated glucocorticoid and mineralocorticoid replacement with very good clinical and analytical response. Further study after stabilization showed morning cortisol <1 µg/dl (5–25), ACTH 138 pg/ml (9–52); low levels of aldosterone and adrenal androgens; negative anti 21-hydroxylase antibodies; normal thyroid function and no anterior pituitary deficits. She continues to be followed in regular endocrinology consultation.
Conclusion
High index of clinical suspicion for AD in APS is needed – in suspected cases, the diagnosis should be investigated and treatment promptly initiated. Conversely, the possibility of APS should be considered in patients with AD of unknown etiology, after exclusion of more common causes.

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EP280

Pheochromocytoma – the rare reason of Cushing's syndrome due to ectopic corticotropin secretion

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Cushing syndrome due to ectopic (adrenocorticotropic hormone) ACTH secretion (EAS) constitutes approximately 10% of Cushing's syndrome (CS). In this group only in about 5% cases pheochromocytoma is the source of ACTH.
We present two patients with EAS by pheochromocytoma.
1. A 70 year-old woman with 3-months history of malaise, weakness, abdominal pain, loss of weight and appetite, hypertension and diabetes mellitus. One month earlier she had an episode of acute renal insufficiency after coronarography. Patient revealed mental confusion, cachexia, swelling of legs, skin with increased pigmentation, echymoses and petechiae. The laboratory data showed elevated leukocytosis, hyperglycemia, severe hypokalemia, and metabolic alkalosis, markedly elevated serum cortisol concentration and ACTH without cortisol suppression after dexamethasone. Measurements of Metanephrine and Normetanephrine in urine were increased. MRI and somatostatin receptor scintigraphy (SRS) disclosed 40 mm mass in right adrenal gland. After pharmacological treatment patient was laparoscopic operated. Histological examinations confirmed EAS and pheochromocytoma. Unfortunately in the 9-th day after surgery patient died because of ARDS syndrome.
2. A 61 year-old woman with 2-months history of weight gain, proximal myopathy, depressive disorders, abdominal pain, diabetes mellitus of recent onset and worseness of hypertension control. Patient had facial and leg edema, plethoric face, dermal and muscle atrophy and moderate central obesity. The laboratory data showed hyperglycemia, moderate hypokalemia, moderate leukocytosis, disturbed circadian cortisol rhythm and increased ACTH level. Measurements of Metanephrine and Normetanephrine in urine were increased. Abdominal CT scan and SRS revealed 30 mm mass in right adrenal gland and radiological signs suggested pheochromocytoma. After pharmacological treatment patient was successful laparoscopic operated, and all signs of CS regressed. Histological examinations confirmed EAS and pheochromocytoma.
EAS is difficult to diagnose. Other organs lesions make the prognosis worse.

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EP281

Managing a complex case of acromegaly – lessons to learn

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Our 42-year-old patient presented with breathlessness and signs of congestive cardiac failure. Her 'spade-like hands and acromegalic appearance' were noted on the post-take round. She had headaches, orthopnoea and secondary amenorrhoea. She was a poorly controlled diabetic (so OGTT was not performed), anaemic, and previously had a thyroidectomy.
Pituitary profile showed secondary hypogonadism, normoprolactinaemia and normal free T4 indicating adequate Thyroxine replacement. A growth hormone day curve established levels consistently above 70 μg/l with elevated IGF-1 level of 65.4 nmol/l. Pituitary MRI confirmed a large 2.5 cm pituitary macroadenoma with carotid sinus invasion and compression of the right optic nerve and chiasm. Visual fields revealed primary inferior right hemifield and left nasal field loss. There was significant non-ischaemic dilated cardiomyopathy, with global left ventricular hypokinesis and ejection fraction of 15% on echocardiogram and cardiac MRI. Monthly injections of 120 mg Lanreotide were started, then uptitrated to once weekly with addition of 250 mcg Cabergoline weekly. There was minimal biochemical and radiological response after 5 months, with growth hormone levels staying above 30 μg/l and IGF-1 persistently raised at 51.3 nmol/l.
At the pituitary MDT, a 6-month-prognosis was quoted on lone medical therapy. However, surgical debulking under general anaesthetic was high risk with estimated mortality of $>50\%$ in patients with ejection fraction of $<30\%$, and unlikely to be curative. Cardiologists felt there was no role for cardiac resynchronisation therapy pre-operatively, as this would not improve her ejection fraction. Cardiac failure optimisation and rapid uptitration of Lanreotide improved symptoms and allowed her to tolerate radiotherapy, which was the safest definitive treatment option. If her cardiomyopathy improves, fitness for surgery will be re-evaluated. Our case highlights challenges in diagnosing and managing acromegaly in a patient with pre-existing Type 2 diabetes, and cardiomyopathy induced by a large growth hormone secreting pituitary adenoma.

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EP282

Cyclic Cushing's syndrome – a diagnostic challenge

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Introduction
The diagnosis of Cushing's syndrome is often challenging considering that none of the used laboratory tests has an ideal diagnostic accuracy. The complexity of the diagnosis increases in cyclic disorder, which is characterized by repeated episodes of cortisol excess followed by periods of normal cortisol secretion.
Case report
A 32-year-old woman with history of arterial hypertension and obesity presented with weight gain, hirsutism, abdominal striae, uncontrolled hypertension, proximal muscle weakness and peripheral edema. Her plasma cortisol and ACTH levels were 33.8 mcg/dl (6.2–19.4) and 52.5 ng/l (<63.3), respectively. 24-hour urinary-free cortisol levels were 930 mcg/day (36–137). The 1-mg overnight dexamethasone suppression test revealed a morning serum cortisol concentration of 24.3 mcg/dl (<1.8). Pituitary MRI identified a lesion in the lateral aspect of the left lobe of adenohypophysis with ≈ 4 mm. She performed a 48-hours 2 mg/day low-dose dexametasone test 3 months later that showed a final cortisol level of 1.3 mcg/dl (<1.8). The patient was revaluated 4 months later and she was clinically better. Six months later she presented with relapsed symptoms. Several samples of late-night salivary revealed mixed results: 0.680/0.223/0.395/1.680 mcg/dl (<0.32). A new pituitary MRI showed a slight increase in the aforementioned area, now measuring ≈ 5.3 mm. The patient performed another 48-hours low-dose dexametasone supression test with a final plasma cortisol level of 31.3 mcg/dl, and then a high-dose dexametasone supression test with initial and final cortisol levels of 29.5 and 16.3 mcg/dl, respectively, confirming ACTH-dependency (74.7 pg/ml). The patient underwent transsphenoidal surgery to remove the pituitary lesion. Anatomopathological analysis revealed pituitary tissue with no significant changes.
Conclusions
This case report documents a cyclical Cushing's disease. The duration of the periods of normal and abnormal cortisol secretion can vary significantly, so the correct diagnosis can be a challenge in clinical practice.

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EP283

Long-term remission (cure?) of acromegaly after discontinuation of somatostatin analogs

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In acromegaly, treatment with somatostatin analogs (SSA) normalizes growth hormone (GH) and insulin-like growth factor 1 (IGF1) secretion in about half of the patients. Usually, the disease relapses biochemically within few months after treatment withdrawal.
We present two acromegalic patients, women of 49 and 53 years at diagnosis, respectively, who achieved stable remission of the disease after medical treatment withdrawal. One had a microadenoma, the other a macroadenoma; no visual field defect. Both underwent transsphenoidal surgery as first line treatment, and had hypersecreting remnant tumors, treated with SSA.
In the first case, the first evaluation at 2 months after surgery revealed elevated GH nadir in OGTT (GHn) of 8.3 ng/ml, with IGF1 of 2.66× upper limit of normal (ULN). The pituitary remnant was 9/8/12 mm and remained stable until present. She received medical treatment for 3years, achieving disease control only on Octreotide LAR 30 mg/28 days associated with CAB 2 mg/week (random GH 0.85 ng/ml, normal IGF1). Currently, 6 months and two evaluations after medication withdrawal, she has normal GHn in OGTT (0.5–0.94 ng/ml) and stable IGF1 of 1.2×ULN.
Two months after pituitary surgery, the second patient had a mildly elevated GHn in OGTT (1.2 ng/ml), with IGF1 of 1.36×ULN and a pituitary mass of 11.5/7/13.5 mm. For 3 years, she received Octreotide LAR 20 mg/28 days, during which random GH was 0.28–0.33 ng/ml, with normal IGF1. Now, 1.5 years and three evaluations after SSA withdrawal, she has normal GH nadir in OGTT (0.7–0.3 ng/ml), IGF1 of 1.1×ULN and a stable pituitary nodule (4/6 mm). She received CAB 1 mg/week for 4 months, which did not reduce this IGF1 level.
Conclusion
In a few patients with acromegaly, treatment with somatostatin analogs may induce a prolonged remission of GH hypersecretion that may persist years after treatment discontinuation. Long-term monitoring will decide if this is a real cure of the disease or just a prolonged inhibition of the tumor secretion. Thus, intermitent discontinuation of the long-term SSA treatment seems justified in controlled patients with acromegaly.

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EP284

Isolated hypoprolactinaemia: two cases

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Case 1: 38 year old was referred for sub-fertility. She had one normal childbirth 5 years ago. There was failure to lactate following the childbirth. There was some puerperal blood loss, but she resumed normal menstrual periods and had no other manifestations of hypopituitarism. Pituitary profile showed normal results FSH 2.7 IU/l; LH 1.5 IU/l; 0900 h cortisol 305 nmol/l/l/ TSH 2.85 μ/l. Prolactin was 85 μ/l. IGF1 18.6 nmol/l. Short synacthen was normal. Previous MRI showed normal pituitary. She had difficulty conceiving second child. Day 21 progesterone was >30 suggesting ovulation. Few months after being seen in clinic she conceived naturally and is currently expecting her second child. There was no history of recurrent infections.
Case 2: 25 year old was referred for labile mood and irregular periods. Investigations by her general practitioner had shown low prolactin level on two occasions. She has two children and had failure of lactation following childbirth. Her main symptoms were consistent with mild depression. Her periods were mildly irregular but she had conceived twice naturally. 0900 h pituitary profile

was normal with 0900 h cortisol of 550 nmol/l. Prior to being seen in clinic she had an MRI of pituitary, requested by her GP, which showed no abnormalities. There was no history of recurrent infections.

Discussion

We present two cases of isolated hypoprolactinaemia with failure of lactation following childbirth. Both detected incidentally and referred to endocrinology for evaluation. Most cases of hypoprolactinaemia are secondary to pituitary tumours/surgery or other pituitary disorders. There are only occasional case reports of isolated hypoprolactinaemia.

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EP285

Polyglandular autoimmune Syndrome type 2/Schmidt's syndrome

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25-years-old lady presented to gastroenterologist with recurrent bouts of vomiting associated with abdominal pains, fatigue, muscle aches and dark tan. Initial biochemical profile and upper GI endoscopy were normal. On examination she had dark pigmentation of the palms well hydrated and haemodynamically stable. No family history of autoimmune conditions. She had traumatic laceration of the liver as a child, otherwise no significant past medical history.

A few days later admitted to A&E with a history of continued vomiting. She was found to be hypotensive with postural drop and hyponatremic. Random cortisol was <20, Addison's disease has been diagnosed. She has been rehydrated and commenced on IV steroids. Adrenal antibodies were positive. She was started on oral steroid replacement once haemodynamically stable. She had subclinical hypothyroidism with positive thyroid antibodies now has progressed to hypothyroidism on levothyroxine replacement. Recently, she has developed alopecia areata been treated with topical steroid cream by dermatologists.

Discussion

PGA type 2 is common of the immunue-endocrinopathy syndromes affecting two or more endocrine organs and other non-endocrine organ. It is characterised by the occurrence of autoimmune Addison's disease, thyroid autoimmune diseases and/or type 1 diabetes mellitus. Primary hypogonadism, myasthenia gravis, coeliac disease also are commonly observed in this syndrome. Rarely is associated with Alopecia, pernicious anaemia, myasthenia gravis, immune thrombocytopenia purpura, Sjogren's syndrome, rheumatoid arthritis. The prevalence of Schmidt's syndrome is 1.4–2.0 per 100 000 populations, most commonly affects middle aged female.

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EP286

Successful management of a case of cerebral salt wanting syndrome (CSWS) related hyponatremia

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43-year-old lady with a history of rheumatoid arthritis (On Sulfasalazine and Infliximab IV every 8/52), was brought in to our hospital following a collapse. She had had acute onset of headache 6 weeks prior to admission with nausea, vomiting and blurred vision but her symptoms had gradually resolved. Her GCS on arrival was 5. Subsequent CT scan brain showed acute right-sided subdural haematoma and subarachnoid haemorrhage and was indicative of coning. She was taken to theatre immediately for decompressive craniotomy and evacuation of her acute subdural haematoma. She was transferred to the ITU.

On day 4 post operatively, she was hyponatremic with sodium 127 mmol/l (base line Sodium was 144 mmol/l pre-operatively). Her sodium continued to fall progressively, reaching 118 mmol/l at day 6. Investigations showed TSH 1.1 mu/l, urine osmolality 512 mosmol/kg, plasma Osmolality 241 mosmol/kg, urine sodium 167 mmol/l, urea 2.2 mmol/l, creatinine 39 μmol/l, K 3.5 mmol/l.

She was not dry clinically and her CVP was 5–6 cm H_2O. It was difficult to differentiate between cerebral salt wasting syndrome (CSWS) and SIADH. She was cautiously treated with hypertonic saline and her hyponatremia corrected over a couple of days to134 mmol/l.

Discussion

We report a case of hyponatremia secondary to assumed Cerebral salt wanting syndrome which was successfully and wisely treated with hypertonic saline in the ITU. The cause of hyponatremia post brain injury is often difficult to ascertain. We recommend patients should be carefully clinically and biochemically assessed. If this is supportive of cerebral salt wasting syndrome then fluid replacement should be commenced and cautious use of hypertonic saline considered. Hypertonic saline at a rate between 50 and 150 ml/h as a bolus initially, and then review as per current standard of care, so as not to increase the sodium concentration by more than an average of 0.5 mmol/l per h or an increase no >10 mmol/l in the first 24 h. This is to prevent the development of osmotic demyelination.

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EP287

An adrenal vascular cyst masquerading as malignancy

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Introduction

Adrenal vascular cysts are rare, in most cases incidentally discovered during abdominal imaging for other reasons. We present a case of adrenal endovascular cyst with initial suspicious features of adrenal malignancy and subsequent management and complications.

Case report

This 72-year-old male was initially admitted with a weight loss over 2 months and new onset fever and rigors and right leg pain. He was noted to have an abdominal mass. He was treated along the lines of urosepsis and an ultrasound Doppler of his leg showed femoral and popliteal aneurysms and ultrasound of his abdomen revealed a large heterogeneous right-sided adrenal mass of 25 cm.

He had a past history of well-controlled hypertension. Hormonal workup revealed normal adrenal reserve and normal levels of serum aldosterone, renin and metanephrines. A CT scan confirmed the adrenal mass with displacement of the liver and some IVC compression and this had increased in size significantly from 6 cm, 5 years ago. The patient was referred to a tertiary centre for further management. He presented 2 weeks later with severe abdominal pain and hypotension. A repeat CT scan showed evidence of rupture of the mass with bleeding into the peritoneum and also haemorrhage into the mass. He was empirically treated with steroids and transferred to the tertiary centre for emergency surgery and mass removal. Histology subsequently revealed haemorrhage and necrosis from rupture of a large adrenal pseudo cyst with negative immunohistochemistry for necrotic tumour cell population but with a presence of a focal vascular lining suggesting an adrenal endothelial cyst.

Conclusion

Rare adrenal vascular cysts should be considered in the differential of adrenal masses. Prompt surgical removal after appropriate imaging and hormonal assessments can avoid complications such as rupture and bleeding.

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EP288

Another case report of ipilimumab induced hypophysitis

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Introduction

We are presenting a case of presumed ipilimumab induced hypophysitis, after completion of 4th cycle of Ipilimumab for stage 4 melanoma.

Case Report

A 72-year-old gentleman diagnosed with stage 4 melanoma, Presented with generalised joint pain and fatigue after 4th cycle of ipilimumab, he had short synacthen test, baseline serum cortisol was <30 nmol/l, 30 min cortisol 379 nmol/l, he was started hydrocortisone therapy 10 mg in the morning, 5 mg at lunch, 5 mg in the evening.

His thyroid function at that time showed TSH <0.1 mU/l, with free T_4 of 10.7 pmol/l, and a free T_3 of 4.2 pmol/l. He had a normal prolactin, and low testosterone at 0.6 nmol/l. He underwent MRI of pituitary which showed normal appearance of pituitary gland, stalks and optic chiasm.

Discussion

Ipilimumab is a human monoclonal antibody that has been shown to overcome the suppressive effects of cytotoxic T lymphocyte Antigen 4 expression, thereby enhancing the immune response against tumours. It is used in the treatment of metastatic melanoma. Side effects include hypophysitis, colitis, uveitis, dermatitis and arthritis among others.

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EP289

Management of the patient with true forms of the precocious pubertal development: clinical case

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Background
Appearance of the secondary pubertal signs before the age of 7 years.
Case report
In the Children's Department of the Republican Specialized Scientific Practical Medical Center of Endocrinology the patient N., date of birth 2012, under the examination during the period from 22 January 2014 to 01 February 2014.
Complains at admission were included that increasing size of mammary glands, menstruation is appearanced, frequent to catch a cold.
From medical history
The girl who is first daughter is family was not born consanguinity. The head delivery was at term. Examination showed increasing size of the mammary glands (stage 2 by Tanner), sparse pubic hair.
The patient was being followed up by a neuropathologist because of her convulsive syndrome. The recently treatment was: drug Oxapin 300 mg/1/2 tab 2 times a day and drug Letiram 500 mg/1/2 tab 2 times a day.
The patient's state at admission was relatively satisfaction. The skins are pale and moderately moist. Auscultation: in the lung there was vesicular breathing, without wheezing. The respiration rate was 24 in min. The heart sounds are clear, heart rate was 130 b/min., AP 90/60 mmHg. Diffusive goiter was on the 1st stage. The pubertal development; Ma2Ax1P1 Me 1 year, Height – 88 cm (norm 81), weight – 18 kg 3 S.D.
By Roentgenography of the hand (2014), Bone age was 12-15 years. Growth plate was open.
Ultrasonography of the small pelvis (2014.08.07), Sizes of the uterine length together with cervix was 30 mm, thickness was 8 mm, width – 15 mm (norm 36×14×30 mm). Ovaries: the right ovary located at the ½ of fallopian tube. Sizes: 17–16 mm/follicles: 8.7, 15, 12, 5.3 mm. Conclusion: Show PPD.
MRI of the brain and pituitary gland (15.06.2013) – MRI findings of the mass (hamartoma). There were indirect signs of the intracranial hypertension.
Hormonal analysis: TTG – 1.8 (0.17–4.05 mME/l, T_4 – 105 (60–160 ng/dl), GH – 24 (2–20 mME/l), LH-16.1 (0.3–1.0) mIU/ml, FSH – 18.3 (1.0–4.2) IU ml, Estradiol – 53.1 (<14.9) pg/ml. An analysis of investigations showed that significant increase in LH by 16 times, FSH – by 4.4 times, estradiol – by 3.6 times and insignificant level of GH by 1.2 times in comparison with normal values. The treatment was recommended with Difirilini 3.75.
Conclusions
On the basis of clinical-laboratory data and MRI findings, the diagnosis was established: the true precocious pubertal development, hamartoma in the pituitary body.

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EP290

Virilizing adrenocortical tumor: a case report

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Introduction
Adrenal masses are among the most frequent tumours in humans (ACT). A vast majority of these tumours are benign (ACAs). Only a small subset of adrenal masses are malignant adrenocortical carcinomas (ACCs). Tumour size, tumour weight, hormonal function and pathologic criteria are useful clinicopathological criteria that can result in accurate diagnosis of most ACCs and ACAs.
Case report
31-years-old woman, without relevant previous history. She had long evolution hirsutism, acné and androgenetic alopecia, with gradual worsening (SAHA syndrome). Menarche: 9 years old. She had always had irregular menstruations, and amenorrhea periods, alternating with polymenorrhea. She was treated with oral contraceptives previously. Physical examination: 50 kg, 148 cm, BMI 22.8 kg/m^2, blood pressure 115/85 mmHg, Ferriman scores 25 points. Hormonal study: TSH 0.57 μUI/ml, free-T_4 0.76 ng/dl, FSH 3.85 mUI/ml, LH 4.28 mUI/ml, prolactin 18.6 ng/ml, testosterone 2.93 ng/ml (<1.2), DHEA-S 1.825 μg/dl (<560), 17-OH progesterone 5.14 ng/ml, basal cortisol 21.2 μg/dl (<25), ACTH 1 pg/ml, androstendione 12.4 ng/ml (<3.5), overnight dexamethasone suppression test 9.8 μg/dl, UCL 381 μg/24 h (diuresis 1.700 ml/24 h, Cr.43 mg/dl). MRI: right adrenal mass (6.1×5.6 cm), with inferior vena cava mark, heterogeneous intensity, isointense in T1 and lightly hyperintense in T2. We decided right adrenalectomy. Histopathology: 6.8 cm and 120 g homogeneous lesion, smooth surface, compatible with corticoadrenal adenoma. Post-surgery she began hydrocortisone replacement therapy and remained stable. She spontaneously menstruated and losted 4 kg. Biochemistry: testosterone <0.01 ng/ml, DHEA-S<15 μg/dl, 17-OH progesterone 0 ng/ml, basal cortisol 4.9 μg/dl, ACTH 1 pg/ml, androstendione 0.1 ng/ml y UCL 91 μg/24 h. Now treatment is being reduced gradually, according to clinical evolution.
Conclusion
It is difficult to distinguish between a benign and malign ACT, even with anatomo-pathology diagnosis. There are no good histologic criteria to distinguish adenoma from carcinoma. The best way to determine malignancy is the clinical evolution. In our patient, the fast androgens reduction post-surgery is an indicator of surgical success. Clinical evolution and biochemistry determine initial pathology report.

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EP291

Radiotherapy for nasopharyngeal carcinoma: a rare cause of hypopituitarism

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Introduction
Radiotherapy to the head and neck area is the standard therapy used for the treatment of nasopharyngeal carcinoma. Hypopituitarism is a well-known late complication of cranial radiotherapy. Although very rarely, it may be observed following radiotherapy to the head and neck area, as well.
Case report
A 53-year-old man was referred to our endocrinology department for hyponatremia and low free thyroxine (T_4) with normal thyroid- stimulating hormone levels. His medical history was remarkable only for the nasopharyngeal carcinoma that had been treated with radiation and chemotherapy seven years before admission. He had been hospitalized many times due to hyponatremia in other hospitals within the last six months. He had been discharged every time after the correction of his serum sodium levels.
On physical examination, he was pale and lethargic. Blood pressure was 85/50 mmHg, heart rate was 74 bpm. His random cortisol level was 3 μg/dl. Besides cortisol, his testosterone, luteinizing hormone and insulin-like growth factor-1 levels were also below normal limits. Magnetic resonance imaging (MRI) exhibited normal findings in his pituitary. Based on these results, the patient was diagnosed to have panhypopituitarism due to the radiotherapy that he once had for his nasopharyngeal carcinoma. Hormonal substitution therapy with IV glucocorticoids and levoT_4 was started sequentially. His serum sodium level gradually rose up to normal limits. He no longer required intravenous sodium replacement.
Conclusion
Hyponatremia is often seen in patients with adrenal insufficiency but the diagnosis of hypopituitarism in hyponatremic patients is often overlooked and these patients had been admitted to the hospitals many times before the underlying hypopituitarism was diagnosed. Radiotherapy to the head and neck area may cause hypopituitarism and thus hyponatremia in long term follow-up. Taking careful medical history plays the pivotal role in making the correct diagnostic approaches.

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EP292

Congenital adrenal hyperplasia and multiple sclerosis: coincidence or not?

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Introduction
Congenital adrenal hyperplasia (CAH) is an inherited recessive disorder of adrenal steroidogenesis, generally caused by total or partial deficiency in

21-hydroxylase, due to deletions or mutations of *CYP21* gene. Some studies suggest that the association between CAH and multiple sclerosis (MS) could be nonincidental: a possible MS susceptibility locus is on chromosome 6p21, on which the *CYP21* gene is located.
We report the case of a 16-year-old female who presented to our clinic in November 2015 with complaints of severe hirsutism exacerbated during puberty, diplopia, vertigo. In April 2014 the patient was treated for hirsutism with Spironolactone 75 mg/day but she developed nausea, vomit, ataxia and the treatment was stopped after 1 month. The patient recovered spontaneously after a few weeks but diplopia and vertigo appeared one year later. Physical examination revealed overweight (BMI = 29.4 kg/m^2), severe hirsutism (Ferriman Gallwey score = 24), normal pubertal development, regular menses, no genital anomalies. Laboratory tests: Estradiole = 43.66 pg/ml, FSH = 5.84 mIU/ml, LH = 3.08 mIU/ml, cortisol-0800 h = 27.8 μg/dl, ACTH = 56.5 pg/ml, Cortisol-0800 h after 1 mgDXMovernight = 1.41 μg/dl, DHEAS = 438.6 μg/dl (65–368), testosterone = 46.72 ng/dl, 17OH-progesterone = 2.28 ng/ml, 17OH-progesterone after ACTH stimulation test = 21 ng/ml, normal TSH, ATPO, FT_4, prolactine. Abdominal ultrasound was normal. Ophthalmologic evaluation: horizontal nystagmus, papilledema, sixth nerve paresis. Brain IRM revealed several T2-hyperintense white matter lesions, located supra-and infratentorial maximum size 2.4 cm. Non-classic CAH and MS were diagnosed and the patient was referred to the pediatric neurology department. The association between oral contraceptive (OC) and Spironolactone is probably the best treatment for hirsutism although there are contradictory data regarding the use of OC in MS patients.
Conclusions
To the best of our knowledge this is the second case of CAH associated with MS to be reported in the literature. Further extensive epidemiological and genetic studies could explain the relationships between MS and CAH. Endocrinologists should search for neurological signs and symptoms in CAH patients and neurologists should recognize the presence of CAH in MS patients.

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EP293

Ectopic prolactin-secreting adenoma at the pituitary stalk

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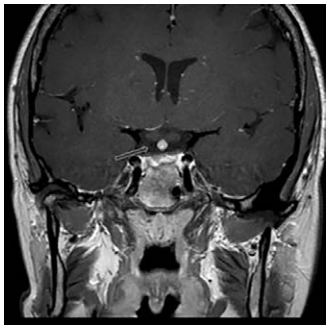
Almost all cases of prolactinomas are benign intrasellar micro- or macro-adenomas. Very rarely benign prolactinomas are located outside the sella and in most of these cases the tumors are located in the sphenoidal sinus.
We here report a 35 year old woman who presented to the clinic with secondary amenorrhoea and galactorrhoea. Initial laboratory testing revealed mild hyperprolactinemia between 1100 and 1600 μU/ml and hypogonadotropic hypogonadism without further pituitary insufficiency. MRI showed normal intrasellar structures but a mass (5 × 6 × 5 mm) at the pituitary stalk just below the optic chiasm. Further investigations did not show any evidence of underlying systemic disorder or malignancy.
Stereotactic biopsy was discussed but not performed due to the risk of severe side effects. Considering the most likely differential diagnosis of an inflammatory process such as hypophysitis or sarcoidosis the patient was treated with glucocorticoids for 5 month which did not have any effect on the stalk mass or the laboratory findings. Treatment was then switched to Cabergolin and only 8 weeks after initiation of the dopamine-agonistic therapy prolactin-levels were normalized, the tumor was hardly noticeable and the patient had a regular menstrual cycle again.



Due to the course of the disease under the different pharmacological approaches we diagnosed an ectopic microprolactinoma of the pituitary stalk, a rare entity which has been described twice so far.

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EP294

A case of hypothalamic-pituitary sarcoidosis with hypothermia

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Introduction
Sarcoidosis is a multisystem noncaseating granulomatous disease with prevalence of 40/100 000. One percent of patients with sarcoidosis have isolated neurosarcoidosis, few cases involve the hypothalamus/pituitary (65 reported cases from 2002 to 2014). We present a case of hypothalamic-pituitary sarcoidosis with hypothermia (one case reported between 2002 and 2014), leptomeningitis, diabetes insipidus and pan-hypopituitarism.
Case report
Family brought a previously healthy 23-year-old African American male to the hospital due to fatigue, hypersomnolence for 2 weeks, intermittent headache for one month. Physical exam revealed non-focal neurological exam, photophobia. MRI of the brain showed diffuse leptomeningeal enhancement with increased signal in suprasellar, optic chiasm, optic tracts. Differential diagnosis was TB/pyogenic meningitis, sarcoidosis and diffuse carcinomatosis. Cerebrospinal fluid showed protein 418 mg/dl (normal 15–45), WBC 230 cumm (normal 0–5) (84% lymphocytic), ACE 4 U/l (normal 0–2.5), negative gram stain and culture. CT chest showed sub centimetre pre-tracheal lymph nodes. Pituitary functions showed free T4 0.6 ng/ml (normal 0.93–1.7), TSH 1.37 μIU/ml (normal 0.27–4.2), FSH 0.4 milliUnit/ml (normal 1–11), LH < 0.1 milliUnit/ml (normal 1–8), ACTH 39.5 pg/ml (normal 7.2–63), Prolactin 14.3 ng/ml (normal 0.5–17), total testosterone < 20 ng/ml (normal 37–198). He tested negative for ANA, HIV, Hepatitis C, Mycobacterium TB Interferon-Gamma. He later developed diabetes insipidus and hypothermia (temperature of 33°C). He underwent transphenoidal biopsy of the Dura (frozen section showed no granuloma), biopsy of inferior portion of pituitary gland (frozen section showed granuloma). He was started on desmopressin, methylprednisolone, levothyroxine and external warming. Patient had significant improvement following treatment. Repeat brain MRI showed near complete resolution of previous findings. He was discharged home on hydrocortisone, desmopressin and levothyroxine.
Conclusion
Neurosarcoidosis can present with diverse clinical features depending on the anatomical location of the disease. Common presentations include facial palsy, leptomeningitis, hypopituitarism. Rarely, it can affect thermo regulation centre of hypothalamus. It is important to recognize and treat early as it can be life threatening.

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EP295

A patient with radiological dilemma: hemorrhagic pituitary adenoma or rathke's cleft cyst?

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Introduction
Rathke's cleft cyst is one of the pituitary non-adenomatous tumors that found in about 20% of pituitary glands at autopsy. Symptomatic Rathke's cleft cysts are rarely, but these cysts can cause serious medical problems associated with compression of the pituitary gland, pituitary stalk, optic nerve or hypothalamus. Here, we report a rare case of 73 years old man with sudden onset headache due to Rathke's cleft cyst present with symptoms and radiological features like apoplexy of pituitary adenoma.
C**ase**
A 73-year-old man admitted to our hospital with weight loss and sudden onset headache. His body mass index were 31.8 kg/m^2, blood pressure: 120/84 mmHg and 68 per min with a regular rhythm. Neurologic examination was normal. Laboratory findings were as follows: CBC was normal, Serum sodium: 138 mmol/l, potassium: 4.8 mmol/l, urea nitrogen: 35 mg/dl, creatinine: 1.1 mg/dl, fasting plasma glucose: 102 mg/dl, hemoglobin A1c: 7.3%. Anterior

pituitary function tests were as follows: morning serum cortisol 0.99 μg/dl, Adrenocorticotrophic hormone (ACTH) 14.2 pg/ml, free T3 1.82 μg/dl, free T4 1.32 μg/dl, thyroid stimulating hormone (TSH) 2.36 mIU/ml, luteinizing hormone (LH) 1.18 mIU/ml, follicle stimulating hormone (FSH) 2.47 mIU/ml, serum testosterone <0.0025 ng/dl and serum prolactin of 12 ng/ml. His laboratory tests revealed panhypopituitarism. Brain magnetic resonance imaging (MRI) showed a 20×15 cm sized sellar cystic lesion, which consisted of a Rathke's cleft cyst. On the basis of these results, supplementation with thyroid hormone and glucocorticoid was started. After 1 month of supplementation treatment control MRI showed a 8.7×4.3 cm Rathke's cleft cyst which was regressed compared to initial imaging.

Conclusion

The neurologic symptoms of endocrinopathies can be associated with Rathke's cleft cyst and hemorrhagic pituitary adenoma. The radiological evaluation can be spurious in these patients. Longer follow-up must be needed in order to confirm the exact diagnosis.

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EP296

Functional gonadotrophin axis evident as spontaneous puberty in a pediatric patient with hypopituitarism after caniopharyngioma resection: a case report

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Objective

To report a case of hypogonadism reversal and spontaneous puberty in a craniopharyngioma patient who suffered from hypopituitarism as a result of complete surgical resection.

Methods

A 13-year-old boy with hypopituitarism was evaluated for right testicular sensitivity.

At the age of 6 the child presented with growth arrest and a craniopharyngioma causing pituitary insufficiency was diagnosed. Treatment with hydrocortisnone and thyroxine supplementation was initiated and he was subjected to a transphenoidal surgery that resulted in complete tumor resection (adamantinoma). Postsurgical biochemical testing confirmed panhypopituitarism and he was prescribed levothyroxine, hydrocortisone and desmopressin supplementation. Recombinant growth hormone was initiated 2 years later since growth had not resumed. Gonadotropins had been undetectable since diagnosis and the last evaluation had confirmed prepubertal status.

On clinical examination increased testicular volume was found (10–12 ml) with absence of pubic hair and mild sensitivity was confirmed. The Scrotum ultrasound revealed normal appearing testes with a maximal diameter of 4.5 cm left and 4.1 cm right. Testosterone and adrenal androgen levels were below normal limits but a GnRH stimulation test (2.5 μ/kg) provoked a four fold increase of LH. Onset of puberty was suspected.

Results

Six months later, measurement of basal gonadotropins (FSH = 1.4 U/L, LH = 1.8 U/L), testosterone (98 ng/dl NL 10–572) and inhibin B (216 pg/ml NL 68–300) indicated the onset of puberty that was confirmed by a tenfold increase of LH in the GnRH stimulation test.

Conclusions

Recovery of pituitary function in craniopharyngioma patients who had panhypopituitarism both prior and after complete surgical resection of the tumor has only rarely been reported. Nevertheless, this case depicts that one should consider the possibility of a functional gonadal axis prior to steroid supplementation for puberty induction to children suffering from hypopituitarism due to craniopharyngioma diagnosed and treated before the onset of puberty.

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EP297

Endocrine manifestations in a case of adult-onset Langerhans cell histiocytosis with multisystem involvement

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Introduction

Langerhans cell histiocytosis (LCH) is a rare disorder with variable clinical presentations. Among the endocrine compromise, the LCH has a predilection for the hypothalamic-pituitary axis. However, primary thyroid involvement is rare and usually related to multisystemic disease.

Case Report

We present a 30-year-old woman who requested a medical consultation because of polyuria and was found to have central diabetes insipidus (CDI). The patient was diagnosed 6 months later with hypopituitarism. Pituitary stalk thickening was detected on magnetic resonance imaging (MRI). Hepatomegaly was also found. Liver biopsy revealed nonalcoholic steatohepatitis with cirrhotic evolution. Three years later she was diagnosed with type 2 diabetes and morbid obesity. Shortly after she was referred to the hospital because of lost of recent memory and dyspnea. Laboratory tests were within the normal range. Magnetic resonance imaging revealed a $15\times13\times22$ mm mass involving pituitary stalk and hypothalamic region. On computed tomography scan a diffuse goiter, a thymic tumor and diffuse interstitial lung disease were observed. Transbronchial biopsy was diagnosed of LCH. Positron emission tomography imaging revealed a hypermetabolic pituitary lesion and moderate tracer uptake in the thymo, thyroid and lungs. The patient was given chemotherapy with cladribine and prednisone with excelent tolerance.

Conclusions

In patients with CDI and pituitary stalk thickening, LCH should be considered in the differential diagnosis. Close surveillance for this patient population may be warranted to detect other pituitary hormone deficiencies and even a multisystem disease involving other endocrine glands, such as the thyroid.

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EP298

Cases of Cushing syndrome manifesting after delivery

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Background

Pregnancy with Cushing syndrome (CS) is rare because infertility is associated with hypogonadotrophic hypogonadism by cortisol and androgens excess. Here we reported the cases of CS that presented signs and symptoms of CS after delivery.

Case reports

The first case is a 30-year-old woman who presented 8 months after second baby delivery amenorrhea even though she stopped breastfeeding. For 3 months before her visit, she gained weight and had easy bruisability. She had a history of gestational diabetes. On physical examination, she had moon face, buffalo hump and abdominal striae with purple colored pigmentation. Urine hCG was negative. Plasma adrenocorticotropic hormone (ACTH) was high and low dose dexamethasone test was not suppressed. The brain magnetic resonance image showed a 6 mm sized adenoma in the left side of pituitary gland. A transsphenoidal adenomectomy was performed. Shortly after operation, she had adrenal insufficiency. However, 5 months later, clinical symptoms improved and her pituitary-adrenal function was normalized. The second case is a 33-year-old woman who presented 5 months after delivery 14 kg weight gain. She was diagnosed with hypertension 3 years ago. On physical examination, she had moon face, acne, hirsutism, central obesity and abdominal striae; 75 g oral glucose tolerance test showed diabetes. Plasma ACTH was normal and low dose dexamethasone test. Other hormone related adrenal gland was normal. The abdominal computed tomography showed 35 mm sized enhancing mass in the right adrenal gland. Laparascopic adrenalectomy was performed and she took hydrocortisone for adrenal insufficiency, anti-hypertensive drug for hypertension and metformin for diabetes. One year after operation, clinical symptoms and metabolic parameters were normalized and she stopped all medications.

Conclusion

CS with pregnancy is rare. We reported cases that manifested CS after delivery and resolved after operation.

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EP299

Initial presentation with diabetes insipidus in langerhans cell histiocytosis, can be marker of multisystemic and progressive involvement

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Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder most commonly characterized by osteolytic bone lesions. Central nervous system (CNS) involvement observed at 6% and Diabetes insipidus (DI) one of the important signs of CNS involvement.

A 40-years-old woman presented with polyuria, polydipsia and headache. Water deprivation test was compatible with DI. Magnetic resonance imaging (MRI) shows 4×4 mm focal thickening at the distal infundibular stalk. She was followed-up under desmopressin. At the sixth months of therapy, clinical situation negatively progressed with complaints of lethargy, diplopia, menstrual irregularity, headache and forgetfulness. MRI revealed progression of nodular thickness (18×15 mm) through hypothalamus. Secondary hypogonadism was detected while other pituitary functions were normal. Multiple, irregularly shaped cystic lesions at he posterior and upper lobes of lungs and multiple lymph nodes with max 20 mm diameter was observed in computed tomography. There were no bone lesion in direct radiographies and there was no skin involvement. Open thoracoscopic biopsy performed by surgeon and revealed LCH on histopathological examination with positive CD68, S100 and CD1a staining. After diagnosis, PET-scan performed and reveals increased osteoblastic activity at the 6th, 8th and 9th right ribs and in the central part of the left femoral shaft. Bone marrow biopsy was reported as normocellular. External radiotherapy and six cycle of chemotherapy (vinblastine + prednisolon) was planned. Also she was on desmopressin, prednisolone and levothyroxine treatment.

We reported this case to refer to diabetes insipidus as a rare presentation of Langerhans cell histiocytosis which a rare and some times multysystemic progressive disease. Diabetes insipidus, is an important indicator for stalk lesions and may be marker of very rare conditions such as atypical tumor of the sellar region, sarcoidosis, lymphocytic hypophysitis or histiocytosis like in this case. It should be monitored dynamically because of the possibility of progressive nature of the disease.

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EP300

Temozolomide treatment in pituitary tumor causing Cushing's Disease resistant to conventional therapy – case report

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Objective

The management of pituitary tumors causing Cushing's Disease are a multidisciplinary challenge to clinicians with neurosurgery as a first line treatment followed by the radiotherapy and pharmacotherapy including chemiotherapy. Such tumors are difficult to treat with high rate of recurrence. To date only 25 patients with Cushing Disease treated with the new alkylating agent temozolamide (TMZ) have been reported.

Materials and methods

Sixty-one year old male patient was diagnosed as Cushing's Disease in the course of pituitary macradenoma in 2011. Patient underwent four transphenoidal non radical neurosurgeries (2012, 2013) with rapid tumor progression, with postsurgical insufficiency of gonadal and thyroid axis, repeated non radical bilateral adrenalectomy (2012, 2013) and stereotactic radiotherapy and gamma knife surgery (2013, 2015). Histopatological examination revealed macroadenoma with high cell polimorfism and presence of the Crooke's cells. Patient has been treated with 600 mg of ketokonazol. From 2015 treated with six cycles of temozolamide with important clinical improvement with the 23–25% decrease of morning and midnight cortisol and the decrease of ACTH from 1317 to 689 pg/ml. In the control MRI the size of the tumor was the same as in the previous examination MRI-(30×35×35 mm). There were not side effects of TMZ. After oncological consultation the decision to continue TMZ treatment was undertaken. After the 9th cycle of TMZ in XII 2015 in the PET examination there was an increase in the size of the tumor to 35×53×54 mm. ACTH increased to 779 pg/ml, with morning and midnight cortisol increase. The clinical status and sight deterioration and hearing loss were observed.

Conclusions

The treatment with TMZ was effective and safe during first six cycles with progression observed during the continuation of the treatment. Further studies on the effectiveness of TMZ and other agents should be continued in patients with corticotrophin tumors resistant to conventional therapy.

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EP301

Acromegaly in a male patient with Kleinfelter syndrome

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Introduction

Klinefelter syndrome is known as the set of symptoms that result from two or more *X chromosomes* in males. There is no known association of this syndrome with GH hypersecretion. The most remarkable symptom is gigantism and it can also be observed in androgen deficient states as such as the Klinefelter syndrome and some more genetic syndromes such as the Sotos syndrome, the Marfan syndrome, the homocystinuria, and the fragile X-syndrome. Herein we presented a case with both Kleinfelter and acromegaly.

Case

A 40-year-old male with previously known hypergonadotropic hypogonadism due to Kleinfelter syndrome (47, XXY) was referred to our clinics with the symptoms of increased ring size, arthralgia, excessive sweating and headache. Physical examination revealed multiple skin tags, mild coarsening of the facial features, soft fleshy hands and interdental separation. He was 186 cm in height and 82 kg in weight. In the hormone panel, basal gonadotropins were elevated with low plasma testosterone, spot growth hormone (GH) was 4.22 μg/l serum and insulin like growth factor-1 (IGF1) level was 611 μg/l which was above the age matched reference range (105–280 μg/l). We performed OGTT with 75 mg oral glucose and the nadir GH was 1.0 μg/l. MRI scan of the pituitary revealed an adenoma 12 mm in size. Adenoma was resected with endoscopy guided transsphenoidal approach and the histopathology was consistent with adenoma stained positive with GH. His IGF-1 was normalized and spot GH was <1 μg/l 3 months after the operation.

Conclusion

Acromegaloidism was reported in Kleinfelter syndrome which was recognized as a condition which resembles acromegaly by its clinical manifestations without excess secretion of GH and somatomedins. Ours was the first Kleinfelter case in the literature diagnosed with acromegaly that means clinical tests are indicated in the presence of suspicious findings.

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EP302

Hypophysitis as a complication of ipilimumab treatment

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Introduction

In the last few years new imunomodulatory drugs are used for the treatment of metastatic melanoma. One of these drugs is ipilimumab, a monoclonal antibody that activates the immune system by targeting CTLA-4 protein receptor. This monoclonal antibody is very effective but there is a higher risk of endocrinopathies like an adverse effect of treatment, mostly hypophysitis and hypothyroidism.

Case

We present a 68-year-old patient with metastatic melanoma after four cycles of ipilimumab treatment. She was admitted for malaise, headache, nausea and vomiting. In the laboratory results hypocorticalism was diagnosed (cortisol lower than 28 nmol/l) with normal ACTH (12.7 ng/l). Administration of corticosteroids was started with an immediate effect and after 3 days MR of hypophysis was performed with a normal result. Nine months after hypophysitis the patient is still on corticosteroids.

Conclusion

Ipilimumab is a very effective CTLA-4 inhibitor that prolongs survival in patients with metatstatic melanoma. In the literature cases of hypophysitis were described as an adverse effect of treatment. That is why during therapy they are necessary regular controls of pituitary hormones. In case of hypophysitis high-dose corticosteroids should be given.

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EP303

Diabetes insipidus due to hypophysitis

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Introduction
Hypophysitis is a rare entity, more common in women in pregnancy and the postpartum period and can cause various symptoms such as headache, hypopituitarism and visual disturbances. Stalk thickening and homogeneous enhancement of the gland are the characteristic magnetic resonance imaging (MRI) findings. The diagnosis is based on the clinical picture and on follow up MRIs. Usually involves the anterior pituitary alone, whereas isolated-posterior-pituitary-involvement is quite rare.
We present here two cases of diabetes insipidus (DI) due to hypophysitis.
Case reports
A 35-year-old woman presented with a 2-month history of headache and the last fortnight she developed polydipsia, polyuria and nocturia. Her past medical history, except autoimmune thyroiditis, was unremarkable. Clinical and biochemical findings were in accordance with DI. The anterior pituitary function was intact. Pituitary MRI showed enlargement of posterior lobe, stalk thickening and homogeneous enhancement of pituitary's signal after gadolinium administration. She was treated with prednisolone 40 mg tapered over 3 months. The symptoms gradually subsided, with a significant improvement of her imaging findings at 3 months.
A 46-year-old woman, with history of hyperlipidemia, developed suddenly symptoms of extreme polyuria and polydipsia and presented with hypernatremia. On the basis of the clinical and biochemical findings the diagnosis of DI was made. Further evaluation revealed no anterior pituitary dysfunction. MRI of the sella showed pituitary stalk thickening and the diagnosis of possible hypophysitis was made. Due to the severity and the persistence of her symptoms, she was also treated with 40 mg of prednisolone tapered gradually. Her symptoms gradually improved and diabetes insipidus completely disappeared at 3 months. MRI of the pituitary at 3 months showed a normal pituitary stalk.
Conclusion
Hypophysitis can have a variable clinical and imaging presentation. As in our cases, DI, although rare, can be one of the clinical presentations. Corticosteroid treatment can improve the clinical course and the imaging findings.

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EP304

Association of two aggressive tumors (prolactinoma and multiple meningioma) – difficult issue, difficult management

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Introduction
The coexistence of pituitary adenoma and meningiomas is very rare. It is debatable if meningiomas result as a consequence of hormone dependent growth or secondary to radiation.
We report a rare case of coexisting brain tumors: a prolactin secreting pituitary adenoma and two meningiomas in a 54-year-old female patient.
Case report
Onset at 46 years with bitemporal hemianopsia, without other clinical complaints. MRI confirmed a pituitary macroadenoma (22/19/35 mm) with suprasellar evolution.
Hormonal balance revealed secondary thyroid and gonadal insufficiency with hyperprolactinemia for which Cabergoline was started with initial good evolution. Three years later, acute intracranial hypertension was solved by partial transcranial adenomectomy. Gamma knife radiation completed the treatment, with subsequent secondary adrenal and thyroid insufficiency. Same year, the patient underwent a subtotal thyroidectomy for nodular goiter. After 4 years of treatment with variable doses of cabergoline, the progressive tumor growth imposed a new intervention – transsphenoidal adenomectomy, with initially good evolution. One year later (01.2016), intensive vertiginous syndrome imposed reinvestigations and cerebral MRI identified two cerebral meningiomas, one of them located at the cranio-spinal junction, which needed urgent excision. Postoperatory, the patient complains of gait dysfunction, nausea, and headache. Clinically, left cranial nerves paresis X, XI, and Xll was objectified. Remnant pituitary adenoma of 19/21/18 mm located in left cavernous sinus was seen on MRI. Hormonal investigations confirmed pituitary insufficiency (thyroid, adrenal and gonadotrope axes), with normal prolactin levels. Currently, she is on thyroid and corticoid substitution, without dopamine agonists, with specific neurologic symptomatic treatment.
Conclusions
Recent studies have revealed the existence of prolactin receptors in meningioma, thus explaining the proliferative effect. In our case we may explain the growth of meningiomas not only secondary to the invasive prolactinoma, but as well as radiation induced.

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EP305

Malignant pheocromocytoma – a challenging diagnosis

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Malignant pheocromocytoma is a rare and problematic disease because it is diagnosed only in the presence of metastases, with no definitive histological or cytological criteria of malignancy. It typically metastasizes to bone, liver, lung and lymph nodes.
A 38-year-old woman presented for hypertension (max sBP = 160 mmHg), palpitation and dyspnea, with family antecedents of mammary cancer. Clinical examination was normal with the exception of palpable adenophaties at the submandibular level, bilateral laterocervical and in the left axilla, with maximum diameter of 1 cm, mobile on all plans; blood pressure equal at both arms = 110/60 mmHg without orthostasis. Biological tests were normal; at hormonal profile the only modifications were metanephrine raised 5.4-fold (486.8 pg/ml) and normetanephrine raised 1.35-fold (244.6 pg/ml), the other hormonal measurements being in normal limits: TSH, iPTH, ACTH and cortisol with normal nycthemeral rhythm, prolactin, gonadotropins, estradiol, testosterone. Imaging exams revealed: ultrasonography - normal thyroid gland, laterocervical and submandibular adenophaties and a node in left breast; abdominal contrast CT: an iodophil formation of 29/26 mm, with central necrosis in the left adrenal and multiple formations in the liver space; chest radiography: pulmonary micronodes in the apical area. It was preceded unilateral adrenalectomy and the histopathological results are expected.
This is a case of young woman with catecholamine hypersecretion and a mass in the left adrenal- most probably pheocromocytoma, which associated lymphadenopathies, liver formations and pulmonary micronodules- places where pheocromocytoma usually metastasize, so most probably a malignant pheocromocytoma with the doubt of coexistence of another tumor. Although the clinical presentation and the laboratory findings were not that impressive; the malignancy in case of pheocromocytoma cannot be excluded regarding its definition, so other noninvasive and sensitive criteria of diagnosis would be necessary.

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EP306

Visual impairment revealing a growth hormone-producing pituitary adenoma in an 14-year-old boy: a case report

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Background
Gigantism indicates excessive secretion of growth hormone (GH) during childhood Pituitary gigantism is very rare and the description of the disease is limited to small series and case reports. Here, we report a case of pituitary gigantism in a child revealed with visual defect.
Case report
A 14-year-old boy presented with headache and left visual loss. On examination, he had visual acuity in his right eye of 2/10. His height was 178.0 cm (3 cm above standard deviation) and body weight was 65 kg (+2.5 S.D.). He showed enlarged hands and feet, and prognathic mandibles. His bone age was normal for chronological age. Laboratory investigation showed the following results: random serum GH of 46.9 ng/ml (0–10 ng/ml); insulin-like growth factor 1 (IGF-1) = 1370 ng/ml (220–616 ng/ml); IGF-BP-3 = 6000 ng/ml (2.200–5.900 ng/ml); and prolactin = 12 ng/ml (3–25 ng/ml), free T4 = 5.5 (7–19 pmol/l) and cortisol = 110 ng/ml (70–200 ng/ml).

Magnetic resonance imaging (MRI) of the brain revealed a 50-mm-sized pituitary adenoma. The patient was put on hormonal replacement and transsphenoidal surgery was performed. Pituitary MRI scan was performed 6months after surgery and showed residual tumor. Medical treatment with a somatostatin analogue for six months was successful. GH level was 0.6 ng/ml and IGF1 was 205 ng/ml.
Discussion
We report a case of childhood gigantism caused by GH secreting pituitary adenomas which seems to be more invasive and aggressive in children than in adults. Treatment of pituitary gigantism in childhood is difficult and often unsatisfactory. Our patient should be closely followed up for the potential risk of developping of other hormonal deficiency.

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EP307

A rare complication of macroprolactinoma treatment with cabergoline: herniation of optic chiasma

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Introduction
Prolactinoma is the most common form of all pituitary tumors, and currently, treatment with cabergoline constitutes first choice therapy for prolactinoma. Surgical approach is recommended when medical therapy fails or visual disturbance due to pituitary mass develops. Here we present a case of macroprolactinoma who developed empty sella and optic chiasm protrusion secondary to cabergoline treatment.
Case
A 20-year-old male patient referred to our clinic, complaining of impotence and infertility. On laboratory investigation, he had an increased level of serum prolactin (1600) and low testosterone (100). His testicular ultrasonography was normal. MRI examination showed a pituitary mass, measuring $25 \times 18 \times 22$ mm. The mass replaced the sella and caused optic chiasm depression but caused no visual impairment clinically. The patient was diagnosed with macroprolactinoma and started cabergoline in a dose of 1 mg/weekly. During the 3rd month of therapy, prolactin level was decreased (48 IU/ml), there was no sign or symptom attributable to pituitary apoplexy. After 4 months of therapy with cabergolin, there was no visible mass in the pituitary and serum prolactin level was in normal range. Thereafter, cabergoline dose was decreased (0.5 mg/weekly) and he was advised to come for control after 3 months. However, the patient came later than said. His control MRI showed he had still no pituitary mass, but had empty sella and protrusion of optic chiasm into the sellar area. Luckily, he had no clinical sign of visual disturbance. We thought that the protrusion of optic chiasm may be secondary to cabergoline treatment since we had no other explanatory mechanism. During the following controls, there was no change in terms of clinical and laboratory findings, but pituitary gland height was highly decreased (1 mm).
Discussion
Cabergoline, used as a first-line agent for prolactinoma treatment, not only reduces the synthesis and release but also has cytolytic effects, thereby reducing tumoral mass. Consequently, macroprolactinoma patients treated with cabergoline should be followed-up more attentively and physicians should be alert in terms of therapy-related effects or complications.

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EP308

A rare case of panhypopituitarism: pituitary stalk interruption syndrome

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Introduction
Hypopituitarism is characterized by decreasing of pituitary hormones, which can result from diseases of the pituitary gland or the hypothalamus. The prevalence of hypopituitarism is 30–45 out of 100 000 in the world wide. Causes of panhypopituitarism are non-tumoral hypotalomopituitary reasons (50%), pituitary tumors (43%) and extra-pituitary tumors (7%). Here we want to present a very rare case of pan hypopituitarism; pituitary stalk interruption syndrome (PSIS).
Case report
A 22-year-old male patient applied to our policlinic for routine control while continuing His medical treatments for panhypopituitarism. His ongoing replacement therapy included hydrocortisone, levothyroxine and testosterone hormones for 10 years. His height was 1.85 cm, weight 75 kg, and had a pale appearance on the face. Laboratory examination results at our outpatient clinic were compatible with panhypopituitarism. MR imaging was done for panhypopituitarism etiology. Adenohypophysis and infundibulum were absenton MR screening. Neurohypophysis was located at infundibular recess neighborhood in front of third ventricle. As confirmed at MRI, the reason of panhypopituitarism was PSIS. We were not able to do molecular research due to our laboratory insufficiency. His drug regime was reviewed and advised to come regular follows.
Conclusion
Congenital panhypopituitarism is often related with a small pituitary, thinned or interrupted stalk, and ectopic neurohypophysis, all together referred the PSIS. Especially due to improvements in screening, the number of PSIS diagnosis has increased. Perinatal events and genetic mutations are accused by at PSIS etiology but exact reason has not illuminated yet. Usually posterior hypophysis functions are protected at PSIS, but, different degree impairment are seen in anterior hypophysis functions. In this case, especially all anterior hypophysis hormones were deteriorated thought neuroyhypophysis hormones were normal. Patient was clinically benefited from hormone replacement treatments.

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EP309

Psychiatric troubles revealing isolated primary hypoaldostronism

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Introduction
Hyponatremia's etiological diagnosis remains a challenge in the real life. Our aim was to report a patient who was sent for severe behavioral disorders revealing hyponatremia due to an isolated deficit in aldosterone. This observation emphasizes the extreme rarity of the disease which deserves to be reported.
Case report
A young patient aged 34 with a history of autoimmune thyroiditis consulted for an acute and severe psychiatric syndrome with normal cerebral MRI. His clinical examination was normal except for some signs of dehydratation. Biological assessment revealed a profound hyponatremia (<120 mmol/l, $n=135–145$) which did not respond to conventional treatment.
Blood glucose and kidney function were normal. Glucocorticoids deficiency was excluded as several plasma cortisol were normal (>500 nmol/l). Faced to this enigma, isolated aldosterone deficiency was suspected and confirmed. Actually, aldosterone in standing position was low (39–56 pmol/l, $n=208–1000$) and plasma renin was increased: 2139 mIU/l (n: 4.4–46.1). He was treated with fludrocortisone and the follow up showed sodium normalization, spectacular improvement of the general condition, and disappearance of psychiatric troubles.
Discussion
Typically hypo aldosteronism is suspected if there is a persistent hyperkalemia, but sometimes it can be revealed by psychiatric troubles due to severe hyponatremia causing infra-radiological cerebral edema as in the illustrated case in who all symptoms resolved after Fludrocortisone. On the etiological side, we have ruled out the obvious causes such as heparin intake, severe diseases, and adrenal metastases. Were also discussed late onset genetic enzyme deficits, but autoimmune etiology was the most probable because of the patient background and positivity to anti 21OHase anti bodies: 2.2 U/ml ($n<1$).
Conclusion
The isolated primary aldosteronism remains an underestimated cause of hyponatremia; it should be included in the etiological diagnosis of resistant cases to conventional therapy.

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EP310

Testicular adrenal rest tumors – a case report

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The patient had been diagnosed with congenital adrenal hyperplasia (CAH) at age 5 because of precocious of puberty. He had been receiving dexamethazone and fludrocortisone therapy over the course of his life. When he was 16 years old, a scrotal ultrasound had been performed for the evaluation of bilateral testicular pain which revealed multiple sharply marginated, hypoechoic masses throughout both testes. A biopsy of left testis had been reported as 'Leidig cell tumour'. He refused orchiectomy and exited the follow-up of the prior clinic. After 4 years, he was admitted to our endocrinology clinic at the age of 20. A review of his story and laboratory findings showed that he had 21 hydroxilase deficiency, bilateral tumor of the testes. His compliance to glucocorticoid treatment was poor. The first biopsy of testis and a new biopsy of left testis was evaluated by the same pathologist and reported as a proliferation of polygonal cells with abundant granular, eosinophilic cytoplasm. Reinke crystals were absent, Kİ67%1-2, CD56 (+). Immunohistochemically, synaptophysin was positive, inhibin-alpha was focally positive.

Testicular lesions in the setting of CAH are commonly referred to as testicular adrenal rest tumors. They may arise from aberrant adrenal cells that descend with the testes during embryogenesis. They are frequently benign, multiple and bilateral. The tumors are most prevalent in younger adult males with a peak incidence between 20 and 40 years of age. First line imaging modality in the detection and surveillance of these tumors is ultrasonography. Histologically, testicular tumors of the adrenogenital syndrome are commonly mistaken for Leydig cell tumors as in our case. Clinical follow-up without orchiectomies is recommended unless untreated nodules of adrenal rests expand and destroy the testicular parenchyma, resulting in low testosterone production and infertility. Patient compliance to treatment is important since their presence is suggestive of suboptimal hormone replacement therapy.

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Gynaecomastia secondary to human chorionic gonadotrophin secreting lung tumour

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Objective

To describe a 32-year-old patient presenting to endocrine clinic as painful gynecomastia.

Method

We present clinical and radiological course of a rare case of gynecomastia secondary to HCG producing lung tumour.

Result

A 32-year-old patient presented to endocrine clinic with symptoms of painful lumpiness of nipples for the last 6 months. There is no history of any milk or blood discharge from the nipples and he has not noticed any other lumps in his body. He is not taking any regular medications. He does regular exercise and denied any steroid intake. There is no history of any weight loss. There are no testicular lumps. There is a history of increase hair growth and acne of his chest and back. On examination, no palpable mass felt in his testes and he was having bilateral gynecomastia.

His hormonal profile showed markedly raised testosterone, oestradiol, high 17-hydroxyprogesterone and beta HCG. His LH and FSH was suppressed.

CXR showed right ung mass and CT thorax showed right lung tumor possible carcinoid awaiting biopsy under respiratory physicians.

Conclusion

Although gynecomastia is a common disorder, hormonal work-up including hCG beta subunit should be done in an adult male patient presenting with rapidly progressing or recent onset of painful gynecomastia. Lung cancer should be considered in the differential diagnosis of gynecomastia attributable to ectopic production of hCG beta subunit.

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EP312

Insipid diabetes and acute myeloid leukemia: genotypic/phenotypic correlation?

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Introduction

Central diabetes insipidus (CDI) is a rare complication of acute myeloid leukemia (AML) occurring in less than 0.6% of patients. It is associated with genetic changes in chromosomes 3 and 7. CDI may precede; occur simultaneously or after the diagnosis of AML.

Case report

51-year-old man, with no relevant past medical history, began complaining with polyuria, polydipsia, weakness and weight loss in March 2015.The patient was evaluated in the emergency department in June and was discharged with the diagnosis of urinary infection. As the complaints persisted he was again evaluated presenting also dehydration and easy bruising. Analytical findings suggested AML (Hb 8.8 g/dl, leukocytes 13.03×10×9/l, neutrophils 0.87, blasts 46%) with karyotype 45,XY,inv (3) (q21q26), – 7 (20). He was admitted to Hematology Department and began chemotherapy. He also had hypernatremia, 159 mEq/l(135–145), with serum osmolality of 332 mosm/kg (282–300), urine osmolality in the lower limit of normal 187 mosm/kg (50–1200) and negative water balance, in this context endocrinology evaluation was requested. CDI was suspected and the patient started desmopressin with resolution of hyponatremia, polydipsia and polyuria. Pituitary CT revealed pituitary with normal morphology and dimensions, although a low uptake area in the median/ right paramedian region was assumed. He was discharged with oral desmopressin 0.06 mg bid. Asas the patient did not show response to induction chemotherapy,he begun salvage chemotherapy.Given the patient's clinical context we decided not to conduct water restriction test and pituitary MRI was also delayed.

Conclusion

In this case the symptoms of diabetes insipidus led to the diagnosis of AML. There are descriptions in the literature that these cytogenetic changes are associated with the development of DCI in AML,although the causes of this association are not fully understood.

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EP313

Giant incidentally-detected non-functional adrenal myelolipoma – a case report

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Introduction

Adrenal myelolipoma is a rare benign tumour composed of mature adipose tissue and haematopoietic elements developed within the adrenal gland, usually unilateral, asymptomatic, and non-functional. Their real incidence is unknown.

Case report

A 56 year-old female was admitted to our surgery department for abdominal distension and the presence of a large palpable tumour in the right abdomen discovered during an abdominal ultrasonographic check-up for an incisional hernia, and with no noticeable symptoms. Patient's medical history: a 3rd stage systemic arterial hypertension, insulin requiring type 2 diabetes mellitus, hysterectomy with adnexectomy for a cervical cancer. The abdominal ultrasound examination showed a large hyperechogenic tumour, heterogenic, located in the right flank and hypochondriac region.

The contrast enhanced computed tomography scan revealed a large retro-peritoneal tumour (25×17×21 cm) well delimitated with a heterogenic structure (liquid and non-iodophile lipid densities, and central calcifications). The mass was in contact with the right hepatic lobe, inferior vena cava, ascendant and transverse colon, and, posteriorly, with the diaphragm. The CT showed also a 74 mm incisional hernia with incarcerated small bowel.

Biochemical evaluation: serum potassium = 4.2 mmol/l, serum cortisol = 204.8 nmol/l; after a 1-mg overnight dexamethasone suppression test serum cortisol = 22.1 nmol/l.

Taking into account the tumoral mass dimensions, surgical resection was decided. Because of the medial incisional hernia, a medial subxifoid-pubic incision was performed.

Histopathological evaluation: macroscopic examination revealed a large thin encapsulated tumour, firm in consistence, with a heteromorphic aspect with

calcifications in section; the microscopic examination: adrenal cortex, adipose tissue, and multiple (extramedullary) haematopoiesis sites – adrenal myelolipoma. The patient had a good postoperative evolution.
Conclusion
The incidentally detected tumoral mass in the clinical condition of the patient challenged to differentiate an adrenal adenoma (functional or not) from a retroperitoneal lipoma/liposarcoma, or metastasis. A particularity of this myelolipoma was the tumour size (approx. 8.925 cm^3).

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Early carbohydrate metabolism disorders in a patient with acromegaly and family history of pituitary adenomas

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Introduction
Acromegaly is a chronic, debilitating disorder caused by excessive growth hormone (GH) production predominantly due to a benign pituitary adenoma. The overall annual incidence of acromegaly is approximately 3.3 cases/million, with a prevalence of 58–130 cases/million people. Early carbohydrate metabolism disorders (ECMDs) are frequently associated with acromegaly. ECMDs – defined as IFG, IGT or their combination – its prevalence in patients with acromegaly has been shown to vary between 16 and 46%.
Case report
A 47-year old man with a family history of pituitary adenoma (father had a somatotropinoma) was consulted at the Endocrinology Research Centre in October 2015. He complained weight gain, reduction of libido, headaches, joint pain and snore. Physical examination: height 186 cm, weight 113 kg, BMI 32.66 kg/m^2. Laboratory and clinical investigations: GH (during OGTT) 0' – 2.08 ng/ml, 30' – 2.11 ng/ml, 60' – 2.46 ng/ml, 90' – 1.84 ng/ml, 120' – 1.41 ng/ml (<1 ng/ml); IGF-1 – 1199 ng/ml (75–212). Brain MRI: pituitary macroadenoma ($2.8\times3.0\times3.0$ cm). So, acromegaly was confirmed. Parallel sequencing was performed with MEN1, CDKN1B, PRKAR1A, GNAS, AIP, SDHA, SDHB, SDHC, SDHD genes determination. No significant mutations were found; considering family history of pituitary adenomas genotyping might be informative. Regarding possible metabolic complications, glucose during OGTT was measured; Glu 0' – 5.8 mmol/l, 120' – 8.9 mmol/l – IGT was found. Insulin – 40 mIU/l (2.3–26.4 mIU/l); C-peptide – 1.5 ng/ml (1.1–4.4).
Conclusions
Acromegalic patients are at high risk of developing ECMDs and secondary diabetes, so they all should be examined using multidisciplinary approach to prevent severe complications. As pituitary adenomas may be presented as FIPAs – genetic analysis (if there is a suspicion) should be performed.

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Posture-responsive primary aldosteronism – the utility of seated saline suppression test

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Introduction
The diagnostic procedure of primary aldosteronism (PA) includes one of four confirmatory tests, of which the saline suppression test (SST) seems to be the most convenient one. Current guidelines recommend SST to be performed in a recumbent position. However, a recent preliminary study demonstrated a higher sensitivity of SST when performed in the upright (i.e. seated) position. Here, we report a case of posture-responsive PA with a negative recumbent SST but clearly positive seated SST.
Case report
A 60-year-old woman was referred to our hospital with the suspicion of PA, based on her 10 years' history of rather resistant arterial hypertension with hypokalemia, together with a recent positive aldosterone/renin ratio (ARR) screening test and an adrenal CT scan revealing a unilateral mass of 22×15 mm in her left adrenal gland. On admission, the screening test was repeated; serum aldosterone level was 710 pmol/l and renin concentration was below detection limit. After an overnight rest and potassium level correction, the recumbent SST (2000 ml of saline infusion over 4 hours) was performed. Her aldosterone levels before and after the infusion were 60 and 100 pmol/l, respectively, i.e. the confirmatory test was negative. As our clinical suspicion was still high, we repeated the SST in the upright (sitting) position. In this case the aldosterone levels before and after the infusion were 894 and 657 pmol/l, respectively, while renin concentration stayed suppressed below detection limit, i.e. clearly positive test. The unilateral form of PA was then established by adrenal venous sampling (including cosyntropin stimulation) and the operation is scheduled on the first week in February 2016.
Conclusion
As many patients may have a posture-responsive PA, the seated SST may be preferable over recumbent SST, thus providing better sensitivity.

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EP316

Adrenal medullary hyperplasia recognized initially as incydentaloma

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Introduction
Adrenal medullary hyperplasia (AMH) is a rare syndrome of catecholamine excess. Adrenal overgrowth is usually bilateral. Due to similar clinical signs, laboratory results and radiological adrenal picture, AMH can be misdiagnosed as pheochromocytoma. The only method that allows determining a proper diagnosis of AMH is pathologic examination. It is regarded as a precursor of pheochromocytoma and has been reported as a component of MEN2.
Aim
The aim of the study was to present a patient with AMH primary diagnosed as adrenal incydentaloma.
Case report
54-year-old female, without hypertension or other symptoms of catecholamine excess, was admitted to our ward because of incidentally discovered nodular masses [18×8 mm] in right adrenal gland. Initial tumor CT density was 36 HU and after contrast administration it was in subsequent phases: 56, 78 and 55 HU respectively. Left adrenal gland was normal. Oncologic vigilance was suggested. Laboratory assessment excluded hormonal activity of the tumor and daily urinary excretion of metoxycatecholamines was 675 μg ($n<1000$). After the patient was prepared for surgery using doxazosine, laparoscopic left adrenalectomy has been conducted. A postoperative pathologic exploration revealed solid orange-yellowish 8 mm tumor. Microscopic evaluation confirmed nodular adrenal medullary hyperplasia, chromogranine (+), synaptofizyne (+). Because of the risk of developing a tumor in the opposite adrenal gland further observation was recommended.
Conclusion
AMH can develop without clinical symptoms of catecholamine excess and be recognized as adrenal incydentaloma.

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Bilateral large adrenal lesions in a patient with undertreated congenital adrenal hyperplasia

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Introduction
Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive diseases characterized by enzyme deficiencies in cortisol secretion. The most common form is 21-alpha hydroxylase deficiency. Here, we report a patient with undertreated CAH and bilateral large adrenal masses.
Case report
34 years old male patient diagnosed with CAH and testicular anorchia at the age of 7 admitted to our clinic for general weakness. Hydrocortisone treatment was started at the diagnosis but he never used it regularly and was not taking

glucocorticoid replacement for 10 years. In physical examination, blood pressure was 100/70 mmHg, there was diffuse hyperpigmentation, and no testicular tissue could be palpated. In laboratory examination, fasting blood glucose was 97 mg/dl, sodium 143 mmol/l, K 4.5 mmol/l and renal, liver and thyroid functions were normal. His serum cortisol, adrenocorticotrophin hormone (ACTH) and 17-OH progesteron levels were 4.8 mcg/dl, 366 pg/ml and 217 ng/ml, respectively. Serum aldosteron was low and and renin was high. In abdominal MRI, there were hypertrophied adrenal glands with solid nodular lesions of 47×44 mm in right and 22×24 mm in left glands. Pheochromocytoma was excluded by normal 24 hour urinary catecholamines. 17-OH progesteron decreased to 40.8 ng/ml after 2 months of 0.5 mg/day dexamethasone treatment.

Conclusion

Although, adrenal enlargement is an expected finding in untreated CAH due to excessive ACTH secretion, adrenal lesions are rarely observed. CAH should be included in the differential diagnosis of large bilateral adrenal lesions to avoid unnecessary adrenalectomies.

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Usefulness of the 4-mg intravenous dexamethasone suppression test in differentiating Cushing disease from pseudo-Cushing syndrome – a case report

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Distinguishing Cushing disease from pseudo-Cushing syndrome still remains a challenge, especially in some specific cases when absorption or compliance of dexamethasone used in diagnostical tests are questionable. Several versions of an intravenous (IV) test have been utilized and serve both in the initial and differential diagnosis of Cushing's syndrome.

We report a 59-year-old patient with macroadenoma of pituitary gland (revealed accidentally on MRI due to dizziness and headaches) 26×18 mm in size, compressing infundibulum and sella, probably adenoma according to radiological characteristics. Her medical history revealed surgical resection of stomach due to a gastrointestinal stromal tumor (GIST) in 1998, arterial hypertension since 1998, and diabetes type 2 (DMT2) diagnosed a year ago adequately regulated with metformine only. On her physical exam, she did not have any signs of endocrinopathy, BMI was 25 kg/m^2, however cortisol was not suppressible in the overnight dexamethasone suppression test, followed by the same result in low dose dexamethasone test. Since she did not have any signs of hypercortisolemia except a relatively newly diagnosed DMT2, and absorption of orally ingested drugs was questionable, we decided to perform an IV overnight suppression test with 4 mg of dexamethasone which confirmed diagnosis of Cushing disease (cortisol 421 nmol/l). Other hormone test showed tireotropic and gonadotropic insufficiency. Transsphenoidal surgical removal of tumor was performed and control MRI showed no tumor residua while patohistological finding confirmed diagnosis of corticotropinoma.

Our patient presented with macroadenoma producing ACTH which are rare especially when presenting as silent macrocorticotropinomas. This is an educative example to keep in mind IV dexamethasone suppression test which could be easy and accurate tool in distinguishing patients with Cushing disease and pseudo-Cushing syndrome while at the same time avoiding the potential difficulties of drug compliance and absorption with oral dexamethasone.

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EP319

Hair loss after transesphenoidal surgery in patient with cured acromegaly

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Hair loss after surgical treatment for acromegaly has been rarely described. We report a case of a patient with acromegaly that presented with hair loss after surgical treatment.

We describe a case of a 73-year female that was diagnosed with acromegaly. Transesphenoidal surgery was performed with complete tumour resection and no immediate complications. Postoperative IGF -1, GH and OGTT for GH were measured at 12 weeks confirming biochemical remission. The rest of the pituitary axis remained within normal range. Four months after surgery the patient presented with diffuse scalp hair loss, predominantly in the frontoparietal area, and complete loss of eyebrows. She was diagnosed of a telogen effluvium. At the same time she was diagnosed with depression. We performed a basic laboratory evaluation, which ruled out other etiologies than might cause hair loss. Three months after the initial evaluation, she did not show signs of recovery neither in the frontal parietal area, nor in her eyebrows.

Studies have shown that IGF-1 may play an important roll in the development and preservation of the hair follicle. Hair loss has been reported as an adverse effect of somatostatin analog therapy. Even though the mechanisms are still unknown, a drop in the IGF-1 levels could be implicated in both cases. Due to the association between hair loss and the drop of IGF-1 levels, this event could be considered as an indirect sign of remission. It is important to assess the initial hair status to prevent low self-esteem that can cause depression and improve the knowledge of this entity. Questioning patients about hair loss could help us make an early diagnosis, understand its natural history, frequency and risk factors.

Keywords: hair loss, acromegaly, transesphenoidal surgery

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EP320

A case of Cushing syndrome: long-time before being diagnosed ultimately in despite of abdominoplasty and reduction mammoplasty

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Introduction

Cushing's disease (CD) is rare systemic disease characterized by an endogenous hypercortisolism and it is the most common cause of Cushing's syndrome (CS). CS is encountered more often in women than in men, associated with an increased morbidity and mortality. Hence, early diagnosis and proper management of the condition is crucial. Here, we present a case of CD, who had abdominoplasty and reduction mammoplasty but went undiagnosed long time with correct diagnosis.

Case

A 43-year-old female patient applied to our outpatient clinic, complaining of obesity. Previously she had abdominoplasty and reductive mammoplasty operations for obesity. She had a BMI of 39.43 kg/m^2. She had such physical features as abdominal striae, moon face and buffalo hump, suggesting CS. Her basal levels of cortisol and ACTH were normal, but there were no suppression with overnight 1 mg and 2-days 2 mg dexamethasone tests. Daily urinary cortisol excretion was high (348 mg/day, ref. range: 36–137). Late-night cortisol level was 6.5 mg/dl. With 8-mg dexamethasone, serum cortisol decreased by 50% compared to basal level, suggesting a pituitary source. Then, MRI showed a left-sided pituitary mass, measuring 10 mm. Thereafter, the patient was underwent transphenoidal surgery. Pathological examination of the specimen was compatible with corticotroph adenoma. Three months after operation, the patient's weight decreased 15 kgs, and physical features suggesting CS disappeared significantly. Basal levels of cortisol and ACTH decreased, together with normal responses to suppressive doses of dexamethasone. Also, MRI showed no residual mass in the pituitary and the case ordered to have regular follow-ups.

Conclusion

CS is a systemic disease, manifested with mainly progressive central obesity. Although obesity is so prevalent health problem, the investigation for the presence of underlying CS is generally regarded as not cost-effective and often overlooked. Consequently, its associated obesity may not be improved substantially. Therefore, we may suggest that not all obese patients but having features suggesting CS should be evaluated for the presence of CS.

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EP321

Sellar hemangiopericytoma mimicking non-functional pituitary adenoma

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Background

Hemangiopericytoma (HPC) is a malignant vasculary tumor originate from pericytes around the capillary and venules. İntracranial hemangiopericytomas

usually arise from meninges, rarely they locate periventricular, suprasellar or sellar. Because of the malignancy potential, the differential diagnosis is important. A rare case of sellar HPC mimicking non-functional pituitary adenoma will be presented.
Case report
A 45 years old woman has admitted to our hospital complaining about two year's ongoing amenorea, spontaneous galactorea and one month ongoing headache. Hypocortisolism was detected at the hormonal tests and ACTH stimulation test was performed. The hypocortisolism was verified and we gave steroid therapy to the patient. The other hormonal tests were normal. The 3×2 cm suprasellar, well demarcated, predominantly solid with multiple cystic areas mass lesion extending into the sellar was shown at the MRI images. Because of the sudden vision loss, the patient was operated as an emergency, the prediagnosis was pituitary apoplexia. Because of the bleeding, the mass could not been totally resected at the procedure. There was residual mass at the post-operative MRI images but the visual examination was improved postoperatively. Central hypothyroidism was seen after the operation so we gave the patient levotyhroxine therapy. The pathological diagnosis was HPC. The patient developed acute vision after 2 months, so another surgical procedure was performed. The pathological diagnosis was HPC again.
Discussion
HPC arising from central nervous system (CNS) form less than 1% of intracranial tumors and less than 2.5% of the meningeal tumors and are rarely diagnosed preoperatively. HPC relapses in many cases and metastasizes to other parts of the body. Because of the aggressivity of this tumor, it relapses locally even after total resection and metastasizes to CNS or other parts of the body. Patients that received radiotherapy (RT) have better local control, disease-free survival, and overall survival rates. În selected cases chemotherapy can be discussed at the patients who had recurrence after RT.

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EP322

Malignant giant pituitary tumor

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Introduction
Malignant tumors of pituitary are very rare diseases.
Case report
We present the case of a 37 years male that progressed in 6 months from normal life to erectile dysfunction and severe panic attacks. The lab panel showed severe insufficiency of testosterone and thyroid hormones. MRI examination revealed a large pituitary tumor, extending to hypothalamus and temporal lobe, also to cavernous sinus. The tumor was treated for 30 days with Cabergoline 3.5 mg/week, then successfully resected without diabetes insipidus or neurologic defects. Patient recovered from panic attacks and needs substitution with 50 mcg/day of Levothyroxine, 5 mg/day Prednisone and 80 mg/day of Undestor. Pathology revealed a malignant pituitary tumor on IHC.
Conclusions
Patient's evolution was better than the evolution we predicted initially, with good quality of life, except for persistent tinnitus.

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EP323

Pituitary and legg calvé perthes syndrome – is there a connexion?

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Introduction
Legg calvé perthes (LCP) is a disease characterized by idiopathic avascular necrosis of the proximal femoral epiphysis caused by decreased blood flow. More frequently in boys between 2 and 12 years of age. LCPD is of unknown etiology. We present two male patients of LCP associated with pituitary disorders.
Case presentation
Case 1: g.i.c., 8 years 8 month, was first addressed to the endocrinology department for investigations of growth retardation. Clinical examination revealed: short stature (-3.2 ds), facial dysmorphism, uneven legs (right $<$ left with 2 cm), right hip pain, no sign of pubertal onset. Radiological examination revealed osteonecrosis of the right femoral head and delayed bone age of $\sim$ 7 years. Somatotropic axis investigations revealed low igf-1 (48 ng/dl, $n=64$–345). Case 2: n.g.a., 20 years 11 months, with significant orthopedic medical history (6 years: left *proximal femoral epiphysiolysis*, 19 years: LCP disease of the left hip), was addressed to the endocrinology department for bilateral galactorrhoea, obesity, intermittent headache. The clinical examination revealed: obesity (bmi $=$ 36 kg/mp), shorter left leg compared to right leg, right coxa valga, bilateral genu valgum, pubertal stage iv–v (loss of pubic and facial hair, thin voice, erectile dysfunction, reduced testicular volume). Biology confirmed hyperprolactinemia (prl $>$ 150 ng/ml, $n=2.5$–17) with hypogonadotropic hypogonadism (fsh $=$ 0.492 mUI/ml, $n=0.7$–11.1, l h $=0.764$ mUI/ml, $n=0.8$–7.6, testosteron $=1.3$ ng/ml, $n=2.8$–8); the other pituitary functions were normal. Mri described a pituitary macroadenoma (23/23/22 mm). Cabergoline treatment was started with good results (prl <0.5 ng/ml).
Discussion
LCP is associated with short stature and decreased growth velocity, some literature data considering igf1 deficiency as a causal factor of the osteonecrosis. This affirmation is controversial since GH treatment may induce femoral necrosis. Whatever the causal association, the presence of LCP impose caution in the short stature treatment. We did not find connexions between LCP and prolactinoma, however the concomitance of the two lesions may suggest a yet unknown correlation.

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EP324

Hirsutism and adrenocortical carcinoma (acc): a particular case report

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Introduction
ACC is a rare tumour with a incidence of 0.7–2.0/per million, more common in women between 40 and 50 years. Can be diagnosis as a incidentaloma or for clinic of abdominal pain and autonomous o hormone secretion symptoms (Cushing syndrome and hirsutism). We present the management of a particular case of hirsutism for ACC.
Case report
Sixty four year old woman referring increase hair and a deeper voice for 1 year. As personal antecedents include hypertension (treated with four drugs) and kidney stones. On physical examination she presents BMI 31 kg/m^2, blood pressure 157/87 mmHG, Ferriman Galway WITH 14 points, and no signs of hypercortisolism. In the hormonal profile highlights: DHEA 8.01 μg/ml, androstenedione >10 ng/ml, testosterone 3.83 ng/ml, cortisol after 1 mg of dexamethasone 12.2 μg/dl, urinary cortisol 34.2 μg/24 h, 17-OH progesterone 8.28 ng/ml and 11 dexosicortisol 27 ng/ml. Catecholamines, metanephrines and renin/aldosterone axis were normal. Body CT with contrast shows a heterogeneous mass adrenal of 8 cm maximun diameter with a density of 75 H, without lymphadenopathy or metastasis. The patient is operated by laparotomy performing right adrenalectomy with complete resection. Corticosteroid replacement downward is performed. The pathology reaches four criteria Weiss (nuclear grade III, multifocal necrosis, venous invasion muscular wall and capsular invasion). Ki 67 (+) was 10–15%. It is diagnosed of ACC completely respected stage II. The patient refuses adjuvant treatment with mitotane and decided closely monitored. At one year follow hormonal markers were normal and CT hadn't show signs of recurrence. Gradually returned hirsutism and hypertension is controlled with dual therapy.
Conclusions
The ACC is a malignant and aggressive tumor with poor prognosis especially in advanced. Complete resection is the best guarantee of cure. Mitotane is the first line drug as adjuvant therapy, but its role is unclear when complete resection can be performed. In our case it was decided to closely monitor whitin signs of recurrence at 1 year. Finally, more studies are needed to improve and clarify the role of adjuvant therapy in ACC.

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EP325

Association of TSH secreting adenoma and meningioma: a case report

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Introduction
TSH-secreting pituitary adenomas are rare pituitary functioning tumors accounting for $<2\%$ of the pituitary adenomas. Their association to meningiomas is a very rare condition.
We report a case of 55-year-old woman who had multinodular goiter with mild symptoms of hyperthyroidism. Blood tests showed inappropriate secretion of TSH and magnetic resonance imaging (MRI) revealed a pituitary tumor with maximum diameter of 13 mm that was extirpated through transsphenoidal route. After operation fT4 levels were still high and MRI showed persistence of residual tumor and a right parasagittal meningioma was detected. Treatment options are discussed.
Conclusion
Association of meningioma to TSH secreting adenoma is rare but can make difficult the treatment of persistence adenoma. Radiotherapy as well as somatostatin receptors agonists can stimulate the growth of meningioma.

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EP326

Anomalous venous drainage another difficulty for the diagnosis of Cushing's Syndrome

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Introduction
It is known that about 75% of cases of endogenous Cushing síndorme to a pituitary adenoma (HA) ACTH-producing, 15% to ectopic ACTH and 10% is due to adrenal adenoma.
Case
The patient was 64 years old, derived from Diabetes Mellitus type 2 of about 16 years of history with an unwieldy + hypertension diagnosed in 2007 with no physical signs compatible with hypercortisolism and incidentally detected a left adrenal adenoma 2 cm. Hormonal blood studied found: Nugent test:20.9. Morning Cortisol: 11.2; morning ACTH.: 21.7; evening Cortisol.: 11.3; evening ACTH.: 14.7; Free cortisol 24 h urine(UCF): 713 (36–137). After supression 2 mg of dexametasona four 6 h: UCF 24H: 483 and morning cortisol 10.3. Finally, after 8 mg. DXM at 23 h: Morning Cortisol: 23. In MRI pituitary microadenoma left 3 mm. so petrosal sinuses catheterization there is no clear lateralization and showed anomalous venous drainage. To rule ectopic Cushing, scan were performed with somatostatin receptors (negative), In CT existence of a millimeter thoracic nodule in the LSI without observing other injuries suprarrrenal adenoma and left unchanged in size.
After many studies, we decided to repeat like pituitary MRI, so after pharmacological control: Ketoconazole 200 mg (2-1-1), metopirone 250 mg (3-2-2) intervention was decided transsphenoidal with disappearance of injury in MRI.
Discussion
Petrosal sinus catheterization is the most effective means of diagnosis of pituitary Cushing vs ectopic. But it should not be considered definitive for the diagnosis because i like in this case had an abnormal venous drainage not help the diagnosis. Moreover, as in this case the size of AH <1 cm detection depends interobserver variability. Therefore, as in this case we must evaluate the results together to reach the final diagnosis.

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Clinical case reports – Thyroid/Others

EP327

A rare case of infertility – SRY positive, 46,XX testicular disorder of sexual differentiation

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Introduction
The testicular disorder of sexual differentiation (DSD) is a rare clinical condition with a reported incidence of 1:20 000 newborn males. It is characterised by a male phenotype with 46,XX karyotype. There are three clinical phenotypes: normal male phenotype, males with genital ambiguities and males who are true hermaphrodites. SRY positive 46,XX testicular DSD results from the translocation of a Y chromosome segment containing the SRY gene during spermatogenesis. In rare cases, the SRY gene may be misplaced onto a chromosome other than the X chromosome.
Case report
A 33 years old male presented with his wife to the fertility clinic with a 3 years history of primary infertility. The patient's wife had no significant past medical history, her clinical examination was unremarkable and her biochemical and hormonal investigations were all normal. The patient had a past medical history of appendicectomy, lumbar discopathy and undescended testes in childhood. There was no significant family history. He had normal libido and sexual function. Clinical examination revealed a normal height and bilateral small testes. His total testosterone was 6.7 nmol/l, LH was 4.4 IU/l and FSH was 43.1 IU/l. A sample was sent for sperm analysis which revealed azoospermia. His viral screen was negative. Genetic analysis for cystic fibrosis was negative. The patient was sent for chromosomal analysis and karyotyping using fluorescence *in situ* hybridization (FISH) technique. This revealed a 46XX SRY positive karyotype through translocation of the SRY gene between the X and the Y chromosome – 46,XX der(X)t(X;Y)(p22.3;p11.3)(SRY+).
Conclusion
Patients with azoospermia should be karyotyped. Sperm donation remains a fertility treatment option for patients with DSD and had a successful outcome in this patient. Such patients require lifelong follow-up led by an endocrinologist with regular imaging of their gonads, bone density measurements, and testosterone supplementation.

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EP328

Diabetic gastroparesis – a pregnancy in jeopardy

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Introduction
Diabetic gastroparesis (DGP) is defined by delayed gastric emptying in the absence of mechanical obstruction caused by autonomic neuropathy. Only 5% of type 1 and 1% of type 2 diabetic patients combine the delay of gastric emptying with typical gastroparesis symptoms. This entity is usually identified in patients with least 10 years of diabetes evolution and is presented typically in the 4th to 5th decades of life in type 1 diabetes mellitus (T1DM). It is associated with marked glycemic lability and it has significant morbidity.
Case report
A 32-year-old woman with a history of T1DM with 13 years of evolution, with poor metabolic control due to noncompliance with A1c 8–9%. After one year of functional insulin therapy she has improved her median A1c to $\approx 6.5\%$. No target organ lesions were known. In the previous 6 months she was hospitalized two times due to nausea and vomits. She performed a scintigraphy that revealed serious gastric emptying delay (100% radiopharmaceutical retention at 3 hours) and an endoscopy that showed gastric stasis with large amount of food in the gastric cavity (11-hours fasting). She was diagnosed with DGP and initiated treatment with domperidone before meals. Although she was advised about the pregnancy contraindication, she became pregnant and presented with significant worsening of symptoms with food intolerance and electrolyte disturbances and was admitted to the hospital at 7 weeks + 6 days (estimated gestation) of pregnancy. She started combined therapy with metoclopramide, domperidone, ondansetron, droperidol, erythromycin and dexamethasone. As she kept food intolerance and developed malnutrition, parenteral nutrition was initiated at 8 weeks + 6 days. Given the lack of therapy response, pregnancy interruption at 10 weeks + 2 days was decided after multidisciplinary assessment.
Conclusions
DGP can be associated with significant morbidity with weight loss, malnutrition and severe acid-base and electrolyte imbalances. Pregnancy in these patients can lead to death in extreme cases.

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EP329

Improvement of glucose metabolism by pioglitazone in a patient with lipoatrophic diabetes, increased plasma leptin and adiponectin levels, and subcutaneous axillary lipomas

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Introduction
Generalized lipodystrophies are rare disorders characterized by almost total loss of adipose tissue, and they are often accompanied by metabolic complications such as severe insulin resistance, diabetes mellitus, hypertriglyceridemia, and fatty liver.
Case report
We diagnosed a 17-year-old woman whose subcutaneous adipose tissue began to decrease in her late elementary school days with the acquired and generalized types of idiopathic lipoatrophic diabetes. She had no family history of lipoatrophy. She had extreme insulin resistance, fatty liver, hyperlipidemia, and an increased basal metabolic rate in addition to a decreased subcutaneous fat mass, partial white hair, acanthosis nigricans, hyperkeratinized skin of the fingers and toes, and arachnodactyly. On first examination, height was 164 cm, weight was 43 kg, fasting plasma glucose level was 100 mg/dl, glycated hemoglobin (HbA1c) level was 6.7%, and fasting immunoreactive insulin level was 80 IU/ml. Her serum insulin level gradually decreased, her glycemic control worsened, and her HbA1c level increased above 12% even with 1000 U of insulin per day. To overcome this severe insulin resistance, we added pioglitazone hydrochloride to the insulin therapy. Her glycemic control successfully improved along with an increase in the serum leptin (before and after pioglitazone medication: 4.5 and 9.6 ng/dl, respectively) and adiponectin levels (1.24 and 3.10 mg/ml, respectively). After starting pioglitazone, subcutaneous axillary lipomas on both sides of her body (right 9.7 × 7.6 cm, left 7.1 × 6.4 cm) were found, and fatty liver was improved.
Conclusions
Pioglitazone (thiazolidinedione) is a ligand for peroxisome proliferator-activated receptor-γ a nuclear receptor expressed mainly in adipocytes that promotes their development. In the present case, pioglitazone caused proliferation of the rest of the adipocytes and subcutaneous axillary lipoma growth. The current case also demonstrated that the metabolic complications of lipoatrophic diabetes can be partially resolved with pioglitazone treatment.

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EP330

Importance of levothyroxine absorption test in identifying malabsorption as a cause of inadequate substitution for hypothyroidism

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Introduction
The most common cause for persistent elevation of TSH levels in hypothyroid patients treated with levothyroxine is poor compliance. The levothyroxine absorption test (LAT) is usually confirmed this phenomenon called "pseudo-malabsorption".
Case report
Sixty-year-old female, weight 60 kg, BMI 24.3 kg/m^2, presented with sleepiness, tiredness, fatigue and forgetfulness. Her skin was very dry and flaky. She had low tolerance of effort, poor appetite with weight oscillation around 2 kg, constipation and sometimes heartburn. Hypothyroid for ten years after radioiodine treatment of Graveś disease. Her TSH levels were higher than normal, TSH 20–70 mIU/l, in spite of efforts to adjust the dose (different LT_4 preparations). In last two years her daily LT_4 dose was 900 μg (15 μg/kg), 3×300 μg then 500+400 mcg. She is also under treatment for depression, angina, hypertension, absolutely arrhythmias (with inadequate INR in last two months). Before testing TSH 33.6 mIU/l, FT_4 4.25 pmol/l. Standard (1 mg) LAT was performed under supervision. TSH, T_4 and FT_4 were measured 2 h, 4 h, 6 h and 24 h upon LT_4 administration. Baseline values were TSH 26.92 mIU/l; FT_4 4.4 pmol/l; T_4 41.5 pmol/l. Cmax T_4 88.6 pmol/l was in 120′. The end point values were TSH 29.37 mIU/l; FT_4 7.2 pmol/l; T_4 61.9 pmol/l. The lack of TSH fall and slight increase in T_4 and FT_4, significantly below expected AUC, pointed an inadequate absorption. After testing, it was started with 300 μg LT_4 oral suspension. The presence of fat in the stool and positive antiparietal antibodies increased suspicion to malabsorptiv syndrome. EGDS was performed and PH finding confirmed H. pylori positive chronic atrophic gastritis with micro focal intestinal metaplasia without morphological elements for GSE. Eradication treatment and IPP were introduced. After 4 weeks her thyroid hormones were TSH 1.63 mIU/l; FT_4 26.6 pmol/l, FT_3 3.87 pmol/l.
Conclusion
LAT is useful for identifying much rare malabsorption, so the adequate treatment could lead to proper substitution and avoidance of no rationale increase of levothyroxine dose.

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EP331

Overdiagnosis of osteoporosis in a patient with short stature and partial growth hormone insensitivity due to misinterpretation of dual-energy X-ray absorptiometry (DEXA)

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Introduction
Bone densitometry is currently one of the mainstays in the evaluation of systemic bone diseases. The most frequently assessed densitometric parameter is areal bone mineral density (BMD), measured by dual energy X-ray absorptiometry (DEXA) and expressed as g/cm^2. However BMD is a bone size-dependent measure and may be found inappropriately low in children and adults with short stature. Osteopenia/osteoporosis have been described in patients with short stature due to growth hormone insensitivity syndrome (GHIS) caused by mutations in the GH receptor gene or its downstream mediators. Estimated volumetric bone density (BMAD), expressed as g/cm^3, is thought to be more accurate than DEXA in interpreting areal bone density in GHIS patients.
Case report
A 47-years-old woman was admitted to our clinic for investigation of premenopausal osteoporosis. She had performed a DEXA due to bone pains, which revealed severe osteoporosis (lumbar spine *T*-score: −2.9, femoral neck *T*-score: −3). On physical examination she had short stature (1.47 cm) with normal BMI, thin lips and small chin. She had no previous history of intrauterine growth retardation. Hormonal investigation for short stature, revealed elevated level of basal serum GH concentration in repeated measurements, while IGF-1 and IGF-BP3 values were low, supporting a diagnosis of partial growth hormone insensitivity syndrome. No other hormone disorders were identified except mild elevation of FSH/LH and mild vitamin D insufficiency. The rest of the laboratory tests were normal. X-ray of lumbar and thoracic spine revealed no fracture. Estimated BMAD at the spine and femoral neck indicated osteopenia (lumbar spine *T*-score: −1.94, femoral neck *T*-score: −2.32). She was treated with vitamin D and calcium supplements.
Conclusion
The described case highlights the difficulties in the appropriate assessment of bone density in patients with short stature and partial GHIS. The use of the right technique is of great importance in order to avoid over treatment of these patients.

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EP332

A novel clinical phenotype of acquired partial lipodystrophy associated with intensive childhood cytostatic treatment

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Context
Lipodystrophy is characterized by subcutaneous fat loss, fat maldistribution, and metabolic syndrome. We present a novel phenotype of partial acquired lipodystrophy, possibly associated with childhood chemotherapy.

Case reports
Two adult female patients that had been exposed to intensive cytostatic treatment in childhood for leukemia and aplastic anemia, respectively, were referred for therapy resistant diabetes. Both patients had distinct partial lipodystrophy at the hips and distal extremities with severe hypertension, insulin resistance, dyslipidemia, and steatohepatitis. BMI was normal. Leptin levels were increased in both patients without evidence for auto-immunity or known pathogenic DNA mutations. Pioglitazone treatment reversed all features of the metabolic syndrome in the first patient. Pioglitazone could not be initiated in the second patient due to myocardial ischemia.
Conclusion
Lipodystrophy may be associated with intensive cytostatic treatment in childhood, since this phenotype, characterized by loss of fat tissue of the extremities and buttocks in the presence of elevated (instead of low) leptin levels, did not match previously reported types of lipodystrophy. As the number of patients that survive childhood cancer increases, this association might well become relevant.

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EP333

Renal form of pseudohypoaldosteronism type I in suckling: clinical case

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Pseudohypoaldosteronism is one of the least explored questions in clinical endocrinology. That leads to complexity in diagnosis and differential diagnostics of disease. A boy, aged 13 days was admitted to the hospital with complains: vomiting, low weight gain, constipation. Biochemical blood assay (BBA) and acid-base balance of blood: level of sodium −127 mmol/l (*N* 132 – 145 mmol/l), potassium −6.6 mmol/l (*N* 3.1 – 5.1 mmol/l), chlorine – 94.7 mmol/l (98–107 mmol/l), pH – 7.42 (*N* 7.35 – 7.45). Clinical blood analysis, clinical urine analysis, thyroid hormones, coagulation profile were within normal limits. Values of 17-pregnenoldione in blood −4.09 and 2.57 nmol/l (*N* 0.7 – 2.3 nmol/l), adrenocorticotropic hormone (ACTH) −9.61 pmol/l (*N* 7.2 – 63.3 pmol/l), cortisol – 76.5 and 324 nmol/l (*N* 140 – 600 nmol/l), dehydroepiandrosteronum-sulfate – 252.1 μg/dl (*N* 31.6 – 214 μg/dl). Diagnosis was made: salt-losing form of congenital adrenal cortical hyperplasia. Fludrocortisone and hydrocortisone were given. BBA after treatment: level of sodium – 127 mmol/l and potassium – 6.8 mmol/l. Values of ACTH in blood (34.9 pmol/l), aldosterone (2772 ng/l, *N* 300 – 1900 ng/l), renin (128 pg/ml, *N* 4.66 – 31.9 pg/ml) were measured. Resistance of electrolyte disturbances was marked on glucocorticoid and mineralocorticoid treatment. The final clinical diagnosis was made: renal form of pseudohypoaldosteronism type I (based on complains, level of sodium and potassium, values of ACTH, aldosterone and renin in blood, resistance of electrolyte disturbances was marked on treatment of glucocorticoid and mineralocorticoid). Gradual dose decline of fludrocortisone and hydrocortisone to full drug withdrawal; solution of Sodium Chloride 0.9% peroral (100 ml within 24 hours) were recommended. The child (2 months 13 days) was discharged from the hospital in compensated condition.
Conclusions
Early diagnosis of pseudohypoaldosteronism permits to start treatment timely and to improve prognosis, to reduce the risk of physical and psychomotor retardation.

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EP334

Erdheim-Chester disease and papillary thyroid carcinoma: case report of a common association in a rare disease

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Introdution
Erdheim-Chester disease is a rare multisystemic form of Non-langerhans cell histiocytosis CD67 positive, with approximately 550 published cases. Papillary carcinoma is the most common thyroid cancer with BRAF V600E the most common mutation. Both diseases may be associated to BRAF V600E mutation. If Erdheim- Chester disease is positive to this mutation on histiocytes, a specific pharmacolgical treatment is available, (vemurafenib), with better results.
Case report
We present a 69 years old woman with previous diagnosis of negative BRAF Erdheim-Chester disease. During follow up of the disease, a hypodense nodule without suspicious signs was identified in the thyroid. The patient had a fine needle aspiration of the nodule, being diagnosed a papillary carcinoma. The patient was submitted to a total thyroidectomy, having been discharged at day four without any complication. She was submitted to radioative iodine. Papillary carcinoma was positive for BRAF V600E mutation. Follow up of 1 year without recurrence of thyroid cancer.
Conclusion
With this case report we want to alert and suggest, that if the patient has a diagnosis of Erdheim-Chester disease and a thyroid nodule, that lesion should be biopsied, even if it's clinical aspect is not suspicious.
With this case we concluded that if the papillary carcinoma cells are positive to the BRAF V600E, it doesn't mean that the Erdheim-Chester histiocytes are positive to this mutation. Although it's the same mutation, if a papillary carcinoma is present, the mutation shouldn't be searched on papillary cells and the introduction of the new armamentarium should be based on mutation in the histiocytes cells.

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EP335

Orbitopathy as a manifestation of Immunoglobulin-G4-related disease – case report

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Introduction
Immunoglobulin-G4-related disease (IgG4RD) is a multidisciplinary problem due to plasmatic cells infiltration and areas of fibrosis in the affected tissues. In IgG4RD, elevation of serum IgG4 immunoglobulins is present. Clinically, the disease is mainly manifested as: autoimmune pancreatitis, salivary gland involvement, sclerosing cholangitis, lymphadenopathy, lachrymal gland enlargement, retroperitoneal fibrosis or orbital pseudotumor. The simultaneous involvement of multiple organs is common. Treatment is based on glucocorticoids in case of recurrence or resistance to steroids, immunosuppresive therapy, involving disease-modifying antirheumatic drugs or rituximab are used.
Material and methods
The aim of the study was to present a case of a patient with orbitopathy in whom in the course of diagnostic procedure, IgG4-related ophthalmic disease was detected.
Results
A 68-year old man, without past history of any chronic diseases, was admitted to the outpatient endocrinology clinic because of increased protrusion of both eyeballs with swallowing conjunctivitis, eyelids redness and retro orbital pain. The MRI scans revealed enlargement and swallowing of all periorbital muscles. The thyroid function was normal with negative all anthythyroid immunoglobulins thus excluding Graves orbitopathy. Since elevated serum total IgG and IgG4 was stated, systemic glicocorticosteroid therapy followed by oral prednisolone treatment was introduced. The evident regression of symptoms and protrusion of eyeballs was achieved. The above therapy was repeated one year later because of recurrence of symptoms. Yet, at that moment it was followed by methotrexate treatment (20 mg/week). Until now, 5 months after second glucocorticoids pulse, the patient does not present any symptoms of orbitopathy; well tolerated metotrexate therapy is continued.
Conclusion
Presented case highlights the importance of considering IgG4RD in the differential diagnosis of orbitopathy.

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EP336

Mixed gonadal dygenesia report of a mosaicism 45,X/46,XY, mexican case report

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Introduction

The Disorders of Sex Development (DSDs) may arise from various genetic disorders therefore cytogenetic studies are necessary to determine the chromosomal sex. The 45,X/46,XY karyotype is considered a mixed gonadal dysgenesis (MGD) and the mosaicism in this condition has a low incidence: 1.5 per 10 000 newborns, characterized by a broad phenotypic spectrum.

Objective

The aim of this report is to present a mexican newborn female patient with a phenotype of ambiguous genitalia and a mos 45,X/46XY karyotype. Product of the IV pregnancy, of non-consanguineous parents. Mother of 39 years and father of 42. They refer threatened abortion during the first trimester. Born at 37 weeks of gestation, normal delivery. At birth: weight 3500 gr, height 53 cm. Physical examination: dolichocephalism, low posterior implanted hair, narrow forhead, sparse eyebrows, hypertelorism, epicanthic folds; depressed nasal bridge, long philtrum, wide mouth, high arched palate; posteriorly rotated ears, narrow chest; genital shown micropenis, right and left hypoplasic gonads. Histopathological studies: right gonad 1.7×0.8 cm with histological evidence of testicular dysgenesis; left gonad 7×5 mm with histological data of testicular dysgenesis with fibrous band. Both were compatible with mixed gonadal dysgenesis. Cytogenetic analysis of peripheral blood lymphocytes revealed a karyotype with mos 45,X[63]/47,XY[7] with a 400 bands resolution level according to ISCN 2013.

Discussion

There are few Latin American cases reported in the literature with Mixed Gonadal Dysgenesis and a mos 45,X/46,XY karyotype. Cases of newborns with genital ambiguity occur most frequently in mosaicism 45,X/46,XY and this proportion should be correlated with the phenotype. Clinical features were recently reported in this patients including peculiar fascies, renal, cardiac and neurologic anomalies.

Conclusion

The Mixed Gonadal Dysgenesis includes congenital anomalies including citogenetic, gonadal and genital alterations. The mosaicism is rare and in this case all the results correspond to those reported in other literature. These cases require complete clinical examination, cytogenetic and histopathological findings, and the performance of new diagnostic methods such as screening of microdeletions in sexual chromosomes.

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EP337

Management dilemma in papillary carcinoma arising from struma ovarii

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A rare ovarian teratoma consisting mainly of thyroid tissue, Struma ovarii accounts for up to 3% of all ovarian tumors. The thyroid tissue may demonstrate the same spectrum of pathological features as in the normal thyroid including benign and malignant changes.

A 46-year-old woman was referred to our clinic in July 2015 by the oncologist, with the diagnosis of struma ovarii with carcinomatous transformation (follicular variant of papillary carcinoma).

The patient known with morbid obesity, candidate for gastric sleeve surgery, had been followed up for about one year for a right ovarian cyst of 44/34 mm revealed at the preoperative echography. Further follow-up IRM examination showed an increased cyst volume-79/66/72 mm and her CA 125 was slightly elevated at 85 U/ml (0–35 U/ml). At that time, she was euthyroid: TSH = 1.21 uIU/ul, fT_4 = 0.94 ng/dl and her anamnesis revealed no sign of hyperthyroidism.

Suspecting a neoplasia, she underwent exploratory laparotomy and total abdominal hysterectomy with bilateral salphingo-oophorectomy On histopathology examination, the large ovarian mass was a Struma ovarii with malignant papillary architecture and thyroid follicles. On immunohistochemistry, the tumor cells were positive for TTF1.

Subsequently, the patient underwent prophylactic total thyroidectomy followed by the administration of 90 mCi of 131I therapy. The WBS examination showed small uptake in the area of the right ovary. The Tg values were in normal range-0.04 ng/ml (<0.04 ng/ml) under the administration of a suppressive dose of L-thyroxine. A pelvic IRM investigation was asked to complete our investigation and a close follow-up will establish the management in this rare disease.

Case particularities

Being this fairly uncommon tumor there is a lack of diagnostic and treatment guidelines. The management of the struma ovarii like any other thyroid cancer permitted us the attentive follow up of eventual secondary disseminations.

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EP338

Diabetes mellitus and ataxia with anti-glutamic acid decarboxylase antibodies

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Introduction

Glutamic acid decarboxylase (GAD65) is expressed by pancreatic beta cells and also by GABA (gamma-aminobutyric acid)-secreting neurons. Cerebellar ataxia associated with anti-GAD65 antibodies (antiGAD Ab) is a rare neurological disorder that frequently coexists with other autoimmune conditions, namely Diabetes *Mellitus* (DM).

Case reports

We describe two cases of ataxia associated with antiGAD Ab. The first case is a 69-year-old obese man with DM known for 5 years, initially medicated with oral antidiabetic agents and with premature need for insulin therapy, 4 years after diagnosis, for chronic inadequate metabolic control. At age 65, he developed dysarthria and ataxic gait and after extensive investigation was diagnosed with antiGAD Ab ataxia, and underwent treatment with intravenous immunoglobulin. Levels of antiGAD Ab were 13.3 U/ml (<1.0), ICA (*Islet-cell cytoplasmic antibodies*) and anti-insulin Ab negative, anti-IA2 Ab (*insulinoma 2-associated*) 1.30 U/ml (<1), C-peptide 6.7 ng/ml (1.0–7.6). The glycemic control was improved after intensification of insulin therapy. The second case is a 68-year-old woman, paraplegic after vertebromedullary traumatism, with DM since she was 60. The metabolic control was difficult with oral antidiabetic medication for 5 years, so insulin was added in 2012, but she mantained significant glycemic lability. In 2015 she was diagnosed with antiGAD Ab ataxia after presenting with progressive positional vertigo, dysarthria and diplopia. AntiGAD Ab 239.07 U/ml (<1.0), ICA (*Islet-cell cytoplasmic antibodies*) positive, anti-insulin Ab negative. Considering the analytical results and glycemic lability, oral antidiabetic agents were suspended and she initiated multiple daily injections of insulin.

Conclusion

The autoimmune etiology of DM can be considered in any age group, especially when other autoimmune conditions are present. An accurate DM classification allows therapeutic adjustment and metabolic control optimization. In patients with DM and positive autoimmunity, with neurologic disorders not explained by diabetic neuropathy and after exclusion of other causes, ataxia associated with antiGAD Ab can be considered.

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EP339

A rare case of sex reversal during puberty

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A 34-year-old refugee from Somalia was referred because of a suspected DSD. Due to ambiguous, but predominantly female external genitalia at birth he was raised as a girl, whereas his subjective gender identity has always been male. Puberty led to a significant virilization of the body but only to a very limited virilization of the external genitalia. The patient presented himself with an undoubtedly male-type body composition. External genitalia were now predominantly male with micropenis and hypospadia glandis. Small testes could be palpated in both labia between which a small perineal orifice appeared. Sex hormones LH, FSH, testosterone (T), dihydrotestosterone (DHT) DHEAS and androstenedione lay within normal male ranges. Estradiol level was borderline elevated (54 pg/ml, *n* 27.1–52.2), whereas Müllerian inhibiting hormone was remarkably increased (35.48 ng/ml, *n* 1.5–4.3). Chromosome analysis showed a regular male karyotype. Highly increased T/DHT-ratio of 54 (*n* 8–16) in combination with the masculinization defect strictly limited to external genitalia led to the clinical diagnosis of steroid 5 alpha-reductase 2 deficiency (SRD).
SRD is an autosomal recessive, 46, XY DSD leading to an impaired virilization during embryogenesis due to defective conversion of T to DHT. In affected subjects, 5-alpha-reductase activity is reduced in genital skin fibroblasts. Clinical presentation is highly variable from almost entirely female to almost entirely male external genitalia. Pubertal increase in T can be sufficient for virilization of the remainder body at the time of expected puberty as seen in our patient. Consanguinity of patient's parents suggests a homozygous mutation in the SRD5A2 gene and a molecular genetic analysis is ongoing in order to identify the mutation. Over 50 different mutations have been described in the past.
Conclusions
This case of a rare DSD elucidates impressively how an enzyme deficiency affects the mechanisms of androgen action in the process of sexual differentiation.

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EP340

Unknown cause of non-PTH mediated hypercalcemia in Pregnancy

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Introduction
Calcium metabolism during pregnancy changes significantly but ionized calcium level remains normal. During pregnancy, there is two-fold increase in intestinal calcium absorption mediated by increase in 1,25-dihydroxyvitamin D. Hypercalcemia in pregnancy is uncommon and most reported cases are primary hyperparathyroidism.
Case report
A 18-year-old 10 weeks' pregnant African American female presented to hospital with epigastric pain, nausea, vomiting for 2 days. She was not taking any calcium supplements. She had mild epigastric tenderness.
Lab showed hypercalcemia with corrected calcium of 13.1 mg/dl (normal 9–10.8) and ionized calcium of 6.7 mg/dl (normal 4.7–5.3). PTH was undetectable. PTHrP, thyroid function test, serum immunoelectrophoresis, vitamin A, ACE were normal. 25-hydroxyvitamin D was low, 9 (normal 30–100 ng/ml) and 1,25-dihydroxyvitamin D was inappropriately normal 51 (Normal 19.9–79.3 pg/ml). Her 24-hour urinary calcium was 436.8 mg (normal 50–150). MRI of neck, chest, abdomen, pelvis showed a 1.4 cm sized lymph node in right hilar region. Foetal ultrasound revealed singleton pregnancy, clubbed left foot. Due to persistent hypercalcemia, she had PICC placed and discharged with iv hydration.
Lab from first pregnancy (medically terminated) two years ago showed corrected calcium of 13.5. Her calcium in between these pregnancies was 9.9. With intravenous hydration at home, her ionized calcium was between 5.5 and 6.9.
Conclusion
Our case represents a unique case of non-PTH mediated hypercalcemia. Extensive work up did not reveal any definite aetiology. Another consideration is CYP24A1 gene mutation. As CYP24A1 metabolizes 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D, patients have high levels of both and kidney stones. Our patient did not have high levels of 25-hydroxyvitamin D and no renal stones. Normally, PTHrP level steadily rises throughout the pregnancy. Our patient had normal levels of PTHrP. A normal calcium level in between pregnancies suggest that this hypercalcemia is related to pregnancy. Hence, we suspect there is/are unknown calcium regulators.

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EP341

Multiple endocrine disorders in Werner syndrome

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Background
Werner syndrome is a rare autosomal recessive disease caused by a mutation of the DNA helicase gene (WRN), characterized by the premature onset of multiple age-related disorders.
Objective
To describe unusual multiple endocrine and metabolic disorders in three unrelated clinical cases of Werner syndrome.
Methods
Three patients with obvious clinical features of premature ageing were referred to an endocrinologist due to endocrine disorders. Mutations of the *WRN* gene were found using a custom Ion Ampliseq panel and PGM semiconductor sequencer (Ion Torrent).
Results
All patients had short stature, grey hair since youth, a beaked nose, BMI deficiency and lipoatrophy, two of them had had their lenses replaced. Patient 1, 41 years, was referred to an endocrinologist due to uncontrolled diabetes mellitus type 2 (DM2) with marked insulin resistance (200 U insulin daily) and late-onset complications (microalbuminuria, polyneuropathy, trophic foot ulcers), marked hypertryglyceridemia and arteriosclerosis, recurrent acute pancreatitis and follicular adenoma of the thyroid gland. In Patient 1 homozygous mutation c.3957dupT p.I1320Y*fs*X12 was found. Patient 2, 35 year, was referred to an endocrinologist due to hyperparathyroidism, which was secondary to Werner syndrome as no parathyroid tumour was found and vitamin D levels were normal. He had milder DM2 and dyslipidemia, foot ulcers, primary hypothyroidism and osteoporosis. Patient 2 – heterozygous mutation c.1165del. p.R389E*fs*X4. Patient 3, 43 year, was referred to an endocrinologist due to severe osteoporosis and hypogonadism, and he also had mild DM2. In Patient 3 heterozygous transition p.L687V (registered as a rare polymorphism rs185468906) was found.
Conclusion
Patients with Werner syndrome develop multiple endocrine and metabolic disorders, which may vary, possibly due to different genetic backgrounds, but this should be recognised and diagnosed by endocrinologists as soon as possible in order to provide patients with required symptomatic therapy and proper follow-up.

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EP342

A young woman with a giant cystic parathyroid adenoma presenting with myelofibrosis

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Introduction
Parathyroid adenomas are rarely large in size. Here, we present a giant cystic parathyroid adenoma presented with pancytopenia.
Case report
Twenty two years old female presented with fatigue, bone pain, polyuria, a lump in the neck and pancytopenia. She had a pulsatile mass on the right side of the neck which compressed her trachea. She was evaluated by Hematology since her Hb was 4.7 g/dl, WBC was 2200 u/l platelet count was: 69 000 u/l. Bone marrow

biopsy revealed myelofibrosis. During her evaluation, she was found to have a brown tumor on her right mandible with Ca: 12 mg/dl (8.6–10), *P*: 2.2 mg/dl (2.3–4.7), ALP: 135 U/l (35–104), PTH: 327 pg/ml (15–65), 25(OH)D: 6.8 ng/ml (30–80) and 24-h urine Ca: 320 mg/day. She was referred to Endocrinology. Her bone survey revealed diffuse osteoporosis, and brown tumor of right mandible. *T* scores obtained by DXA were: Lumber vertebra: −4.3 Femur neck: −3.4 Distal radius: −5.6. Glomerular filtration rate was calculated as 72 ml/min. She had no history of renal stones and renal ultrasonography reveled no stones. Her parathyroid ultrasonography and scintigraphy confirmed the presence of giant parathyroid adenoma 8×8×14 cm in dimensions, extending into the mediastinum. She received iron and vitamin D for three months followed by adenoma excision. Her surgery was unique among other surgeries performed to patients with giant adneomas since it was only performed by a servical incision without the need for thoracotomy. After the excision, intraoperative PTH level was measured as 87 pg/ml. Three months after the operation her Ca, P, ALP and PTH levels and her blood count were normal.

Conclusions

Animal and human studies suggest a myelofibrotic role for high PTH levels. However, very few patients present with pancytopenia due to myelofibrosis. This patient with chronic primary hyperparathyroidism presented with myelofibrosis that resolved after paratahyroidectomy.

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EP343

Parathyromatosis following endoscopic parathyroid surgery: a rare case report

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Parathyromatosis, a rare cause of recurrent hyperparathyroidism, consists of ectopic hyper-functioning parathyroid tissues scattered throughout neck. Two forms of parathyromatosis have been reported, type-1 due to hyperplasia of parathyroid rests from embryologic development and type-2 occurs due to spillage, seeding of parathyroid tissue during parathyroid surgery. Repeated surgery often is necessary. Preoperative diagnosis is rarely made, may be due to lack of awareness of entity.

We present a case of recurrent hyperparathyroidism occurring 2-years after parathyroid surgery in a patient with primary hyperparathyroidism. We attribute this to spillage of tumour cells during previous endoscopic parathyroidectomy. A 55-years old male presented with bony pains and nausea for 1 year. He had focused left superior endoscopic parathyroidectomy done 2-years back for adenoma. Physical examination was unremarkable. The laboratory results showed elevated serum calcium 3.5 mmol/l, PTH 1400 ng/l and 24-h urinary calcium, suggestive of recurrent hyperparathyroidism. Ultrasonography, MIBI and PET scans failed to localise lesion. Possibilities of incomplete removal, hyperplasia, multiple/ectopic adenoma, malignancy and parathyromatosis were considered. On exploration, multiple nodules (<5 mm) were found in the left side neck compartment embedded in strap muscles, sternocliedomastoid, thyroid surface and left central compartment. Opposite parathyroid glands were normal. The surgical procedure included left hemi-thyroidectomy, removal of ipsilateral straps, parts of sternocleidomastoid, berry picking of superficial nodules and clearance of tissue close to entry of ports. Post-op laboratory results showed serum calcium 2.4 mmol/l and undetectable PTH levels (<2.5 ng/l). The histopathology findings indicated parathyromatosis. Serum calcium is normal on 1-year follow up. This is first case report to show parathyromatosis occurring following endoscopic surgery for benign parathyroid adenoma. So, Utmost care should be taken to avoid parathyroid spillage during surgery and make every effort to not rupture parathyroid capsule, even of benign tumour of the gland.

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EP344

Type 1 diabetes mellitus and acquired hemophilia

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Introduction

Type 1a Diabetes (DM1) is a challenging disease with a rising incidence (up to 40 per 100 000 in Finland and Sardinia) being less common in the African population. It is believed to have an autoimmune basis and has been associated with other autoimmune diseases namely autoimmune thyroiditis and celiac disease. Acquired hemophilia is a rare clinical entity characterized by bleeding diathesis induced by circulating inhibitors to coagulation factors (VIII ou IX) that compromise hemostasis. The authors describe a case of a patient with DM1 with concomitant acquired hemophilia.

Case report

A 23 year old female patient with previous hospitalization for severe urinary tract infection and no regular medication, allergies or previous pregnancy or transfusions was admitted to the Hospital for Diabetic Ketoacidosis. Autoantibodies (Anti-insulin, islet cell and Glutamate decarboxylase) were positive and a favorable glycemic response was obtained with an intensive insulin regimen. On the 3rd day of hospital admission the patient presented with severe hematuria. There was no significant hemoglobin fall but activated plasma thromboplastin time was prolonged (120 seconds). No changes in prothrombin time or platelets were found. Mixing clotting studies showed a failure to correct aPTT and Factor VIII activity was reduced (<0.5% – Normal Range 50–150%). Inhibitors to FVIII were detected (2.68 Bethesda Units). Full autoimmune panel and Rheumatology consult were inconclusive. Due to treatment failure of Cyclophosphamide and corticosteroids the patient was treated with Rituximab with improvement of both the hemophilia and DM1.

Conclusion

In this case no secondary cause of the hemophilia was found, being DM1 the only autoimmune comorbidity possibly contributing to the onset of hemorrhage. Only a few cases of acquired hemophilia have so far been described to affect DM1 patients. Interestingly Rituximab improved both conditions being the patient currently hemorrhage free despite still requiring insulin.

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EP345

Intravenous omega 3 treatment in a pregnant patient with acute pancreatitis and lipoprotein lipase deficiency

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Introduction

Acute pancreatitis induced by hypertriglyceridemia is a severe condition and its management is complicated.

Case report

We present a case of severe acute pancreatitis induced by hypertriglyceridemia secondary to lipoprotein lipase -LPL- deficiency (188 Gly-Glu mutation, LPL undetectable activity) in a pregnant patient with gestational diabetes.

The patient was sent to our Lipid Unit in the 13th gestation' week. The triglyceride levels were 5337 mg/dl at the beginning. Our patient was initially managed with diet (very low fat diet and low carbohydrates because of gestational diabetes) and omega-3 supplements but it was necessary to carry out artificial nutricional support: total parenteral nutrition (TPN) because she presented acute pancreatitis secondary to hypertriglyceridemia. We used a omega 3 enriched TPN. Meanwhile the patient was supported with TPN the triglycerides levels were 537 mg/dl (the lowest level in her medical history). She had a healthy female baby.

Conclusions

LPL deficiency might cause severe hypertriglyceridemia, repetition acute pancreatitis which is an unwieldy and severe situation during pregnancy. Acute familial hypertriglyceridemia pancreatitis accounts for 5% of cases, including LPL deficiency.

The goal of treatment is to reach triglycerides levels below 500 mg/dl, being very low fat diet the treatment of choice, drugs or plasmapheresis techniques can also be associated. Clinical guidelines do not recommend to supplement with lipids de TPN composition in pancreatitis induced by hipertrygliceridemia, but we decided to use w3 fatty acids (20% of total kilocalories were fats) in the parenteral nutrition because it is a source of essential fatty acids and because of its hypolipemiant and inmunomodulatory effect. With this treatment, patient achieved the lowest triglyceride levels in her life. So we could say that TPN enriched in w3 fatty acids and glutamine was safe and effective in our patient with significant decrease in triglyceride levels. This is the first case in the literature that describe this evolution in a patient with hypertriglyceridemia induced severe pancreatitis.

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EP346

Stiff-person syndrome and type 1 diabetes mellitus

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Stiff person syndrome (SPS) is a rare disease characterized by progressive muscle rigidity and spasms, which can lead to functional disability. This condition can be challenging to diagnose if there is no high index of suspicion. Its etiology is unknown, but one of the most likely causes is autoimmune aggression, which is corroborated by that fact that it is associated with other autoimmune diseases in half of the cases described in literature.

We will present here the case of a boy in which SPS is associated to type I diabetes mellitus.

The 15-year-old patient was diagnosed with type I diabetes 5 years ago, when he presented with altered level of consciousness and capillary glucose of 32.22 mmol/l. Three years ago he started presenting with episodes of muscle stiffness and spasms, triggered by touch and lying down position, which led him to sleep sitting on a chair. After thorough investigation, including a electroneuromyography exam showing continuous motor stimulation and immunological testes indicating high levels of anti-GAD antibodies (50 IU/ml), SPS became the main diagnostic hypothesis.

The patient has been currently using Clonazepam, with overall improvement of the symptoms. He also uses NPH and regular insulin for the diabetes, and does not suffer from any chronic complications.

The presence of type I diabetes on this patient, who already suffered from a neuromuscular disease of unknown etiology, brought to light the hypothesis of SPS, later confirmed by laboratory exams. This allowed appropriate treatment in time. Therefore, this case illustrates the importance of having a broader view in clinical practice, taking co morbidities into consideration in order to reach the correct diagnosis.

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EP347

A case of complicated course of type 1 diabetes mellitus due to Graves' Disease manifestation

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Introduction

The prevalence of autoimmune thyroid diseases in patients with type 1 diabetes mellitus (T1DM) is high. Thyroid hormones have a pronounced effect on the regulation of glucose homeostasis. We report patient with well controlled T1DM and good compliance, presented with severe diabetic ketoacidosis (DKA) due to thyrotoxicosis.

Case report

A 15-year-old girl with well-controlled T1DM for 5 years (HbA1c $<$ 8%) had no tissue complications of diabetes and episodes of DKA. The daily dose of insulin was 0.7 units/kg. She presented to the emergency room feeling unwell with severe weakness, nausea, abdominal pain, vomiting and polyuria. She was dehydrated and shocked with blood pressure 120/50 mmHg and heart rate 160 beats/min, temperature was 37.3°C. She had heavy glycosuria and ketonuria, capillary blood glucose 18.6 mmol/l, HbA1 14.5%, arterial blood pH 6.8, bicarbonate 3.9 mmol/l. Full blood count, liver and renal function, chest X-ray, and electrocardiogram were all normal. Admission diagnosis of DKA was confirmed and patient was started on intravenous fluids and insulin infusion. Patient show improvement, blood sugar levels decrease, bicarbonate also improved. However, tachycardia and expressed weakness remained, fine tremor and goiter (volume of thyroid gland 28 ml) were noted. The thyroid function test showed TSH of 0.057 mU/l (norm 0.25–5 mU\l), fT_4 of 44 pmol/l (norm 12–23) and the TSH receptor antibodies were high (17.8 U\l) confirming the diagnosis of Graves' disease. Tiamazole 30 mg orally with betablockers was started. The daily dose of insulin increased to 1.1 units/kg. The girl responded well to treatment with normalization of the overall health and positive dynamics at laboratory inspection and went home after 14 days.

Conclusion

All patients with T1DM must periodically assess thyroid function. In patients with unexplained DKA is necessary to investigate the levels of thyroid hormones.

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EP348

A rare case of dermoid cyst of the neck – clinical presentation and surgical treatment

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Introduction

Dermoid cysts are usually presented as solitary hamartomatous tumor, containing all skin adnexa. They can be found in the skin and subcutis of the face and neck; or can be intracranial, intraspinal, or intra-abdominal, localized in the ovary or omentum. Cutaneous cysts most commonly appear on the forehead, around eyes, as well as on the floor of the mouth, rarely on the neck.

Case report

We present a 24-year-old female patient with a dermoid cyst in the jugulum that was operated in our Institution. Patient initially noticed painless tumor mass lower on the neck. Physical and ultrasonical examination showed well-marginated, semi-solid, semi-cystic tumor mass in the jugulum, approximately 50 mm in size, localized anteriorly to infrahyoid muscles and trachea, with no connection to thyroid gland. Patient was asymptomatic. No fine-needle aspiration biopsy was done. After adequate preparation, patient was operated in general anaesthesia. Through minimal skin incision on the anterior of the neck, just above the tumor mass, the cystic lesion was completely removed from the front of trachea and infrahyoid muscles, with the intact wall. Frozen section histopathology analysis showed dermoid cyst. On definite histopathology these findings were confirmed. The cyst was $46 \times 42 \times 25$ mm (CCxLLxAP) in size, with keratinized stratified epithelium covering the cyst wall, and sebaceous and sweat glands, as well as hair follicles and hair within. Patient was released from hospital on first postoperative day, with full recovery.

Conclusions

Dermoid cysts of the neck are rare and can often be misdiagnosed with thyroid tumors. Ultrasound and magnetic resonance imaging are helpful in making the correct differential diagnosis. Surgery is the treatment of choice, especially due to possible malignant alteration. However, surgical manipulation has to be delicate, since cyst content, especially if with bacterial infection, may spread into the surrounding tissues and cause severe complications.

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EP349

High testosterone causing virilisation from a right polycystic ovary

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Introduction

Polycystic ovarian syndrome (PCOS) is a common cause of hyperandrogenism in women of reproductive age but rarely causes very high testosterone levels and frank virilisation which is associated with ovarian or adrenal tumours. We present a rare case of progressively increasing testosterone levels causing virilisation from a histologically confirmed right polycystic ovary. Complete cure was achieved by right salpingo-oophrectomy.

Case

A 32 year old lady diagnosed with PCOS four years previously, presented with worsening extensive hair growth forcing her to shave daily, receding thinning hair line, deepened voice with male stature and amenorrhoea of 8 years duration despite Metformin and spironolactone therapy and weight loss. On examination she had a BMI of 36, and Ferriman-Gallwey score of 30 with evidence of virilisation. Testosterone was 12 nmol/l (0 – 2.8) from 5.6 nmol/l at the time of diagnosis of PCOS with marginally raised androstenedione level 13.5 nmol/l (up to 12.9). LH, FSH, oestradiol, DHEAS, 17-hydroxyprogesterone and CA125 levels as well as MRI adrenals were all normal. She was under surveillance for a 3×4 cm right dermoid cyst and she then underwent a right salpingo-oophrectomy. Histology showed ovarian follicular cysts and no malignancy. Testosterone levels 3 days and 6 weeks postoperatively were $<$ 0.6 and 1.4 nmol/l respectively and she continues to notice marked improvement in her symptoms.

Discussion

PCOS, the commonest cause of ovarian hyperandrogenism has moderately elevated testosterone levels. The presence of virilization is rare in PCOS and warrants consideration of solid ovarian malignancies such as teratomas. The

unusual features of this case were; firstly the degree of virilisation was greater than expected for PCOS raising suspicion of an underlying ovarian malignancy which was the presumed dermoid cyst. Secondly, the slowly progressive nature of her symptoms leading up to virilisation is unusual. Lastly her imaging was of a unilateral cystic ovary not bilateral.

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EP350

Improvement in acute intermittent porphyria symptoms after bilateral oophorectomy: a case report

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Acute intermittent porphyria (AIP) is an uncommon monogenic autosomal dominant disorder with a defect in the haem biosynthesis pathway at the level of the enzyme porphobilinogen deaminase. The disease has low penetrance; most patients could stay asymptomatic throughout life. Clinical manifestation depends on various precipitants, which increase hepatic haem production and cytochrome activity. We report a case of a female patient who had regular moderate-to-severe cyclic AIP attacks, which started usually during the premenstrual period and ended after the menstruation. During the attacks she was treated with intravenous dextrose load, gabapentin, tramadol and intravenous hemin, which could not be used regularly due to high costs. Combined oral contraceptive drug therapy was unsuccessful. Gonadotropin releasing hormone agonist treatment was impossible since it was too expensive for the patient. Chronic complications progressed, including sensory, motor and autonomic neuropathy and chronic kidney disease. After the last severe AIP attack, a laparoscopic bilateral oophorectomy was performed. The surgery was successful with an uneventful postoperative recovery. Four years have passed, during this time AIP attacks have become milder and infrequent with one attack-free year during the last two years. The improvement in patient's quality of life is evident. Endogenous sex steroid hormones, mostly progesterone, play an important role in precipitating AIP attacks in women. Our case shows that the choice of therapy needs to be made individually for each patient. During the last forty years, only a few similar cases have been reported.

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EP351

Saint John's wort not so saint

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Introduction
In addition to the medication prescribed by their doctors, patients may recourse to natural medicine and take herbal medications without thinking about their potential side effects and interactions with other drugs.
Case Report
A 39-year-old female, with personal history of iron deficiency anemia, regular menses but long-standing dysmenorrhea and polymenorrhea and reactive anxiety-depressive disorder, complained of frequent intermenstrual spotting during the last four months. She had also increased emotional lability with several episodes of tremor, chills, sweating, nausea and vomiting. The patient was taking sertraline and oral contraceptive. She was initially diagnosed with anxiety crisis. Except for anxious mood and central obesity (BMI 31.2 kg/m^2), no pathological signs were found on physical examination. Lab tests were normal, except for LH 2.04 mUI/ml, FSH 1.45 mUI/ml and 17-β-estradiol 17 pg/ml. When the patient was asked about taking any other additional medication, she said that she had been taking a herbal antidepressant for the last four months. This herbal medication was based on Hypericum perforatum (Saint John's wort), which is a potent inducer of cytochrome P450 and P-glycoprotein. Saint John's wort is implied in many drug interactions, including with antidepressants of the selective serotonin reuptake inhibitor family and oral contraceptives. Hypericum was withdrawn and, during the follow-up, the patient did not present new episodes of breakthrough bleeding or anxiety crisis.
Conclusions
Our patient was finally diagnosed with episodic serotonergic syndrome and breakthough bleeding due to interactions between Hypericum and sertraline and oral contraceptive. An exhaustive medication lookup should be performed in every patient in order to find out if they are taking any herbal medication with potential severe side effects or drug interactions.
What's new
Self-medication with natural medicines is increasing, so every treatment must be reviewed, even in case of unreported or alternative drugs.

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EP352

Echinococcal cyst as rare cause of increased lumbar bone mineral density

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Introduction
An 80-year old female with known osteoporosis was reassessed for BMD measurement. Her baseline BMD and *T*-score of lumbar spine (L1–L4) measured in 2004 were 0.699 g/cm^2, −3.5 s.d., *T*-score of total left hip was 0.618 g/cm^2, −2.7 s.d.. She was treated with alendronate 70 mg, cholecalciferol 7000 IE per week and calcium supplements.
Case report
At follow-up in 2013, DXA scan, BMD of lumbar spine L1–L4 was 0.910 g/cm^2, *T*-score was −1.2 s.d. BMD and *T*-scores for lumbar vertebrae: L1 1.384 g/cm^2, +4.2 s.d.; L2 0.667 g/cm^2, −3.3 s.d.; L3 0.654 g/cm^2, −3.9 s.d.; L4 0.785 g/cm^2, −3.0 s.d. BMD and *T*-score of neck and total hip were 0.463 g/cm^2, −3.5 s.d., and 0.590 g/cm^2, −2.9 s.d., respectively. On image examination, we identified a calcified mass in the projection of the L1 vertebra. Upon the reanalysis of the DXA scan, we excluded the calcified formation and L1. BMD of lumbar spine (L2-L4) was 0.701 g/cm^2, *T*-score was −3.4 s.d.. BMD and *T*-scores were: L2 0.614 g/cm^2, −3.8 s.d.; L3 0.642 g/cm^2, −4.0 s.d.; L4 0.785 g/cm^2, −3.0 s.d. In 2016, BMD of lumbar spine (L3–L4) was 0.722 g/cm^2, *T*-score was −3.4 s.d. BMD and *T*-scores were: L3 0.667 g/cm^2, −3.8 s.d.; L4 0.778 g/cm^2, −3.1 s.d., and superposition of calcified formation was on L1+L2. We checked previous examinations: 3 years before she underwent an abdominal CT, which revealed a 3 cm large calcified Echinococcal cyst (EC). In 2013, a DXA scan EC was projected on L1, in 2016 on L1+L2 due to the collapsed L1, developed kyphosis and height reduction.
Conclusion
Artifacts can interfere with BMD measurements. The study showed that bra-wires and calcium carbonate pills positioned lateral to the spine can modify BMD. Several medical conditions, such as osteophyte formation, osteoarthritis, ankylosing spondylitis, vertebral fractions, and aortic calcifications can also increase BMD. However, after review of the PubMed literature, to our knowledge there were no cases of falsely increased BMD of lumbar spine due to calcified EC.

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Malignant struma ovarii causing thyrotoxicosis

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Introduction
Struma ovarii (SO) is a specialized monodermal teratoma predominantly composed of mature thyroid tissue (>50%). It accounts for ∼5% of all ovarian teratomas. Thyrotoxicosis is seen in about 8% of patients with SO. Most struma ovarii are benign with only 5–10% being malignant. Malignant SO causing thyrotoxicosis is very uncommon.
Case presentation
A 64-year-old woman had been diagnosed with thyrotoxicosis 2 years ago. The thyroid gland is palpable with micronodular texture and the patient is euthyroid under carbimazole. She presents abdominal pain and progressive enlargement of the abdomen over a two-month period. An abdominal ultrasonography (U/S) revealed a pelvic mass and a large fluid collection. Subsequently, Computed Tomography (CT) of the abdomen and Magnetic Resonance Imaging (MRI) of the pelvis confirmed the presence of a complex right ovarian mass measuring 13 cm. The patient underwent total abdominal hysterectomy and bilateral salpingo-oopherectomy, omentectomy and appendectomy. Histological examination of

multiple sections from the excised tumor revealed the presence of 'follicular thyroid-type carcinoma arising in struma ovarii of the right ovary. Metastatic infiltration was seen in the tissue fragments submitted from the pouch of Douglas. The immunohistochemistry analysis showed positivity for TTF1, TH6, HMBE1, focally positive for NSE and negative for panCK and CK19'.
Anti-thyroid treatment was discontinued one month post-surgery, in light of the pathology result. During the 4-year follow-up the patient remains euthyroid.
Conclusion
There has been controversy about the management of malignant SO which is a very rare entity. Even more uncommon is malignant SO causing thyrotoxicosis. As clinical signs are non specific other causes of thyrotoxicosis must be considered for differential diagnosis. Our case is one of the very few cases ever reported.

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An unusual case of adult onset multi-systemic Langerhans cell histiocytosis with perianal and subsequent incident thyroid involvement

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Introduction
Langerhans cell histiocytosis (LCH) is a rare sporadic disease characterized by histiocytic neoplastic infiltration of various organ systems and a wide spectrum of clinical manifestations, ranging from benign and self-limiting to lethal.
Case report
We report a rare case of adult onset multi-systemic LCH in a 36-year-old male patient with an initial perianal presentation and incidental finding of subsequent thyroid gland involvement in the follow up period. The patient with history of perianal LCH treated with surgical excision and local radiotherapy was referred to our endocrinology department upon detection of hypermetabolic nodular lesions in the left lateral lobe of thyroid gland on Positron Emission Tomography - Computed Tomography (PET/CT) scan in the 9th month of follow up. Current evaluation revealed euthyroid status, a hypoechoic solid lesion of 13×9 mm in size with irregular borders in the left thyroid lobe on thyroid USG and diagnoses of suspected oncocytic lesion, Hashimoto thyroiditis or LCH based on cytologic assessment of thyroid nodule fine needle aspiration of biopsy. The patient underwent total thyroidectomy and pathological assessment confirmed the diagnosis of Langerhans cell histiocytosis. Assessments in the 6th month of postoperative follow up revealed euthyroid status with no thyroid tissue remnants or pathological lymph node on thyroid USG. In view of the multifocal lesions indicating multi-system disease, a systemic chemotherapy protocol with combination of prednisone and vinblastine has been planned by the hematology department.
Conclusion
Our findings underscore the importance of awareness of this rare condition associated with low index of suspicion among practitioners for LCH as well as the significance of ensuring proper follow-up in adult onset LCH to rule out systemic disease. Along with implementing a treatment plan matching the prognostic stratification of the patient, multidisciplinary approach and long-term close follow up with PET/CT scan in the management of adult onset LCH seem crucial given its rarity and varied presentation.

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EP355

Amiodarone - induced type 2 thyrotoxicosis in patient with ESRD treated with hemodialysis

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Introduction
Type 2 amiodarone-induced thyrotoxicosis (AIT2), resulting from the release of thyroid hormones, is a rarer form of side effect of this drug. Treatment of thyrotoxicosis in patients with end stage renal disease (ESRD) is difficult because hemodialysis alters renal clearance of drugs and iodine, may impact the results of assessment and treatment and can increase the medical instability of patients.
Aim
The aim was to present the difficulties of AIT2 treatment in a patient with ERDS.
Case report
Forty seven-year-old man treated with hemodialysis four times a week for 3.5 years. Because of recurrent episodes of atrial flutter and fibrillation amiodarone was applied by 1.5 months. Due to arrhythmias recurrence, evaluation of thyroid function was performed and thyrotoxicosis was recognized. Amiodarone was withdrawn and thiamazole and prednisone have been applied. After slight improvement, the concentrations of thyroid hormones significantly raised with TRAb-0.4 U/l ($n < 1.5$), a/TPO-86U/l ($n < 60$), a/TG-89U/l ($n < 60$). In ultrasound thyroid goiter [47 ml] with heterogeneous structure and reduced vascularization was detected. The lack of 99 mTc uptake in scintigraphy was found. The patient received thiamazole, prednisolone and lithium carbonicum again together with sodium perchlorate. After another short-term of an improvement, deterioration of the disease appeared ($FT_4 - 60.8$ pmol/l ($n < 22$), $FT_3 - 39.2$ pmol/l ($n < 7$), TSH < 0.04 mIU/l). The results of imaging studies justified AIT2 recognition. Antithyroid drugs and sodium perchlorate were withdrawn. High dose of prednisolone was continued. In order to accelerate the elimination of the free thyroid hormones three cycles of plasmapheresis were conducted. Normalization of hormones was reached after five months of onset of the disease.
Conclusions
Similarly as in the case of patients without renal failure, only prednisone is effective in treatment of AIT2 in ESRD. Hemodialysis is ineffective and plasmapheresis is slightly effective in the elimination of free thyroid hormones. Monitoring of thyrotoxicosis and assessment of the effects of treatment in patients with ESRD are difficult.

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EP356

Transient amenorrhea: a very rare complication of radioactive iodine ablation therapy for papillary thyroid carcinoma

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Radioactive iodine (RAI) treatment has been used in the treatment of differentiated thyroid cancer (DTC) since 1946. RAI treatment is recently used as adjuvant treatment for ablation of residual tissue following thyroidectomy and in the treatment of metastases of thyroid cancer. Some acute (nausea, vomiting, ageusia, salivary gland swelling and pain) and long-term side effects (sialadenitis, pulmonary fibrosis, second primary malignancies) may be observed following RAI treatment. In 12–31% of young women, menstrual irregularities have been reported after high dose radioactive iodine treatment applied for the treatment of DTC. In this report, we presented two patients with DTC treated by RAI ablation, in whom transient amenorrhea had occurred. Basal FSH and LH levels elevated in these two patients within 3 months after RAI treatment, but all normalized within 6 months (table 1). We suggest that it is important to evaluate premenopausal patients with DTC for the development of RAI related menstrual irregularity and inform these patients for the possibility of treatment related ovarian dysfunction.

Table 1

		Patient 1	Patient 2
Age		42	41
RAI dose (mCi)		100	150
3 months after RAI	LH (1.9–12.5 IU/l)	72.75	39
	FSH (2.5–10.9 IU/l)	95.17	50.5
	E_2 (19.5–144.2 IU/l)	2.19	<5
6 months after RAI	LH (1.9–12.5 IU/l)	30.9	14
	FSH (2.5–10.9 IU/l)	7.17	17
	E2 (19.5–144.2 IU/l)	130.61	128

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Postpartum osteoporosis associated with hypercalcemia and hypoparathyroidism

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A lactating 31-year-old woman who developed L5 vertebral compression fracture 2 months after the delivery of her first child is presented. Serum concentrations of Ca was 10.24 mg/dl (8.6–10.2 mg/dl), phosphorus was 4.1 mg/dl (2.7–4.5 mg/dl), albumin was 4.6 mg/dl, ALP was 210 U/l (35–105 U/l), PTH was 13.8 pg/ml (15–65). There was axial osteoporosis, as assessed by dual-energy X-ray absorptiometry. *Z* score; L1 (−3), L2 (−3.8), L3 (−3.8), L4 (−3.6). CCr 127 ml/min, 24 h Ca excretion was 153.4 mg. 25-hydroxyvitamin D was 10.9 ng/ml. Causes for secondary osteoporosis were excluded. She was diagnosed as postpartum osteoporosis associated with hypercalcemia and probable parathyroid hormon-related protein (PTHrP) hypersecretion. Studies have established that the exogenous production of vitamin D requirements fall during breast-feeding through a PTHrP and prolactin mediated mechanisms. PTHrP is known to be physiological present in some tissues, especially in brest milk. Production of PTHrP from the mammary gland in response to elevated prolactin and lower estradiol levels leads to calcium and phosphate mobilization from bone. Its role in control of total milk calcium content is postulated, and PTHrP may also regulate mammary blood flow through vasodilatory mechanisms. Our case highlights the importance of the possible aetiological role for parathyroid hormone-related peptide in derangements in calcium metabolism with postpartum osteoporosis during lactation.

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EP358

An acute gout attack following parathyroidectomy

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Gout is an arthritis characterized by the deposition of monosodium urate cyristales in the joints because of chronic hyperuricemia. Infections, intravenous contrast materials, acidosis, trauma, surgical interventions can be counted as common causes of acute gout attack. The aim of this study was to present postoperative gout attack at a patient with parathyroidectomy.

Case

Sixty five year old man presented with back pain and fatique was admitted to our endocrinology clinic with hypercalcemia (12.4 mg/dl) for further investigation. He had a previous history of gout disease 5 years before admission but he said never treated for gout. In the laboratory examination, her urine was 136, creatinin was 3.5, albumine was 4.1, calcium was 12.4 mg/dl, fosfor was 3 mg/dl, parathormone was 1386 ng/ml. In 24-hour-urine, calcium was measured as 365 mg/day. In his neck ultrasound, it was determined a 12×16×14 mm hypoechoic lesion consistent with a parathyroid adenoma on right inferior posterior at the inferior of gland. In urinary ultrasound, there was multiple stones. Patient transferred to generel surgery department for parathyroidectomy operation. After right inferior parathyroidectomy operation,in the second postoperative day, patient had high fever raised to 39°C, pain, swelling, limitation in movements and redness in metatarsopharyngeal joint at right foot. Other physical examinations were normal. The uric acid level was studied and measured as 11.5 mg/dl. In the diagnosis, a gout attack was thought and colchium 0.5 mg 3×1 was began for treatment. The response to that therapy was fast. About in 24 h fever was lower, pain was decreased and the general situation of patient gone well

Discussion

The likely reasons for postoperative flares include fluid shifts that alter the serum urate level and may favor new medications that may elicit increases or decreases in serum urate. Gantes *et al.* From Spain presented two cases with pseudo-gout cases after parathyroidectomy. In their cases, gout symptoms began at second post-operative day (like our cases) and they reported that acute attack symptoms regressed with calcium replacement, using nsaid and 1 mg/day colchium.

In peri-operative term, the gout attack can begin with many factors. Catobolic process in operative term, starvation or dehydration can induce the hyperuricemia and gout. Postoperative gout appears in generally 8 day after surgery. The affected joint part is same with the affected joint before surgery. If patients have previous gout history prepare for a surgery, examination of uric acid levels should be done and prophylactic colcium treatment should be given if needed.

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EP359

Postmenopausal women with hyperandrogenism: case reports of three patients

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Introduction

Androgen excess in women usually is presented as hirsutism and alopecia. Androgens could be expressed from adrenal or ovarian origin.

Case reports

Female, 57 years (yrs) old, presented with hirsutism (Ferriman Galwey score, FGS 18), weight gain, type 2 diabetes mellitus (DM2), hypertension, hyperlipidemia and obesity (BMI 38.5 kg/m^2). Diagnostic evaluation revealed normal prolactin, SHBG, DHEAS, IGF-1, ACTH, TSH, serum cortisol in overnight 1 mg dexamethasone test (19 nmol/l); total testosterone (6.0 nmol/l; ref. < 2.6), free testosterone (94.8 pmol/l*;* ref. < 30) and androstendion (14.1 umol/l; ref. < 12) were increased. MRI of abdomen and pelvis showed fatty liver and myoma uteri. Bilateral ovariectomy was performed; PHD: hyperthecosis. Signs of hyperandrogenism regressed.

Postmenopausal woman, 59 yrs, presented with perennial DM2, diabetic retinopathy, nephropathy, hypertension, hyperlipidemia, hyperuricemia and obesity (BMI 39.8 kg/m^2). She had weight gain for last 5 yrs, with expressed hirsutism (FGS 28). Despite basal-bolus insulin therapy glycemic control is poor (HbA_1c 9.6%). Diagnostic evaluation revealed normal serum cortisol in overnight 1 mg dexamethasone test (63.5 nmol/l), normal prolactin, TSH, SHBG, DHEAS, IGF-1, ACTH. Total testosterone (4.1 nmol/l) and free testosterone (72.9 pmol/l) were increased. MRI of abdomen and pelvis showed normal adrenal glands, myoma uteri (25.2×21.7×18 mm), left ovary solid, enlarged 29.3×19.5 mm, and right ovary 14.4×8.6 mm in size. Tumor marker CA125 was normal. The patient refused suggested gynecologic surgery, applying only cosmetic treatment.

Female, 58 yrs, presented with postmenopausal hirsutism (FGS 14) and alopecia; DM2, hypertension, hyperlipidemia, obesity (BMI 31.2 kg/m^2).Total testosterone was 2.9 nmol/l and free testosterone 58.2 pmol/l. MR of abdomen and pelvis revealed enlarged ovaries. Bilateral ovariectomy was performed; PHD: Cellular steroid ovarian tumor. Signs of hyperandrogenism regressed, DM2 is well controlled with metformin.

Conclusion

Resolving the origin of androgen excess is important for adequate treatment. Ovariectomy in described cases resulted in regression of signs of hyperandrogenism.

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EP360

Pretibial myxedema in a euthyroid patient without history of autoimmune thyroid disease

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Introduction

Pretibial myxedema (PM) is a rare extrathyroidal manifestation of Graves' disease, with most patients being in hyperthyroid state. PM has also rarely been described in Hashimoto thyroiditis.

Case report
A 61-year old Caucasian woman attended our outpatient dermatology clinic for evaluation and management of bilateral erythema, involving the lower two-thirds of the pretibial regions. She reported appearance of the same lesion 11 years ago. Medical history was remarkable for subtotal thyroidectomy due to non-toxic multinodular goiter, breast cancer, type 2 diabetes mellitus and arterial hypertension. There was no history of thyrotoxicosis or ophthalmopathy. No smoking or alcohol was reported.
Clinical examination revealed the presence of itchy bilateral, edematous pretibial erythema, with 'peau d'; orange' appearance. No signs of ophthalmopathy or acropathy were observed.
Laboratory investigation showed: TSH: 0.89 mIU/l (normal range: 0.4–4) and free-thyroxine: 1.32 ng/ml (normal range: 0.8–1.5). Thyroid peroxidase and thyroglobulin antibodies were negative, as well as, thyroid stimulating and inhibitory immunoglobulins (TSI and TBII, respectively).
Neck ultrasonography revealed the presence of significant thyroid remnant, with mild heterogeneity regarding its echogenic structure, without nodules.
A skin biopsy from the pretibial skin was performed which showed edema of the reticular dermis presenting as empty slit-like spaces separating collagen fibers, with normal fibroblasts. Stellate fibroblasts (myofibroblasts) in papillary dermis and perivascular infiltrate of lymphocytes were observed. The histochemical stain Alcian blue pH 2.5 showed mild increase of acid mucopolysaccharides in papillary dermis. These findings were consistent with PM.
The patient was successfully managed with topical application of corticosteroids, with significant amelioration of her lesions one month later.
Conclusions
This is a rare case of PM in a euthyroid patient, with no evidence of thyroid autoimmunity. Six other euthyroid PM cases have been reported (one with positive TSI, two with negative TSI and not measured in the other cases).

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EP361

131I uptake in nonlactating breast related to papillary thyroid carcinoma

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Introduction
Radioiodine whole-body scintigraphy (WBS) has been widely used for detection of differentiated thyroid cancer (DTC), based on the marked storage of iodine in functioning thyroid tissue. However, radioiodine uptake is not specific for thyroid gland. Iodine accumulation in lactating breast has been demonstrated, but it is rare in nonlactating breast.
Case report
A 74-year-old-woman who underwent near-total thyroidectomy in 1988 due to a multinodular non-toxic goitre, presented during the surveillance a suspicious left thyroid nodule. Ultrasound (US) guided fine needle aspiration (FNA) was performed and the cytologic examination showed a follicular proliferation with atypia. A total thyroidectomy and selective lymphadenectomy was realised because of macroscopic lymph node affectation. Pathology examination showed a 1.1 cm papillary thyroid carcinoma and regional lymph node metastases. Radioiodine ablation with 100 mCi ^{131}I was realised after the surgery. WBS was negative for extrathyroidal metastases. Patient presented progressive elevation of thyroglobulin (34 ng/ml) and increasing antithyroglobulin antibodies (307 UI/ml). US identified left III cervical compartment lymph node involvement. 150 mCi ^{131}I were administrated after recombinant human thyrotropin injection. Postablative WBS showed focal intense uptake in left cervical region and increase uptake in bilateral breasts. Hyperprolactinemia (serum prolactin 110 µg/ml) was found in biochemical test and a magnetic resonance imaging detected a pituitary microadenoma (6 mm). Medical treatment was rejected due to the postmenopausal condition.
Conclusions
Radioactive iodine uptake in functioning thyroid tissue is mediated by enhanced expression of sodium-iodide symporter (NIS). This case illustrates that not only lactating breast can concentrate iodine, but also in nonlacting mammary gland the presence of prolactin hypersecretor pituitary gland tumour can induce increased NIS expression and therefore prominent accumulation of iodine.

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EP362

Lenalidomide-induced hyperthyroidism during treatment for anaplastic multiple myeloma: a case report

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Lenalidomide a *thalidomide derivative* has immunomodulatory, antiangiogenic and anticancer properties.Lenalidomide has significantly improved survival in myeloma although toxicity,side effects do occur.
We report a case of thyroiditis with hyperthyroidism in a patient receiving lenalidomide in treatment for Anaplastic multiple myeloma.
Case Presentation
Sixty four year old female with anaplastic multiple myeloma but no history of thyroid disease received Lenalidomide 25 mg once daily orally for 21 days of repeated 28-day cycles. She developed hyperthyroidism during the course of the treatment, with TSH of 0.003 mIU/ml (0.35–4.94 mIU/ml) decreasing from a normal baseline of 0.93 mIU/ml two months prior. Free T4 and Free T3 was elevated at 2.25 ng/dl (0.7–1.8 ng/dl) and 5.01 pg/ml (1.7–3.7 pg/ml) respectively. There were no interim medication changes, recent contrast CT, viral illness, amiodarone or interferon treatment. Patient denied overt hyperthyroid symptoms, with stable vital signs,unremarkable physical exam (no exophthalmos, thyromegaly or palpable thyroid nodules, normal reflexes). The creatinine went up to 1.7 mg/dl from baseline of 0.6 mg/dl (0.6–1.1 mg/dl).Lenalidomide was implicated and was discontinued for 6 weeks. After 6 weeks, TSH spontaneously normalized to 1.34 mIU/ml, and creatinine improved to 1.1 mg/dl, lenalidomide was restarted at reduced dose of 20 mg daily. Two weeks later, TSH dropped to 0.005 mIU/ml, FT4 increased to 2.27 ng/dl.
Further work-up
TSH receptor antibodies (Trabs): normal, thyroidperoxidase antibodies and thyroglobulin antibodies: normal Thyroglobulin 800 ng/ml (1–50 ng/ml).
ESR 82 ($<$30). Thyroid ultrasound showed a heterogeneous gland and findings were suggestive of thyroiditis. Thyroid pertechnetate scan showed minimal uptake, suggesting Lenalidomide-induced thyroiditis.
Her hyperthyroidism again spontaneously resolved after Lenalidomide was stopped following completion of 6 cycles of chemotherapy.
Conclusion
Lenalidomide is increasingly used in the treatment of myelodysplastic syndromes. Treating physicians must be aware of potential thyroid dysfunction associated with lenalidomide treatment. Checking thyroid function before starting the treatment and throughout the course is recommended.

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EP363

Ovarian Leydig cell hyperplasia – an unusual cause of hyperandrogenism in a post-menopausal woman with a possible familial link

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A 60-year-old lady was referred with male pattern hair loss and facial hirsutism of 5–7 years duration. She was otherwise well and had two children in their 30s. She was not taking any medication and reported a normal menstrual cycle prior to menopause at the age of 50.
Her androgen profile showed a high testosterone level of 6.1 nmol/l (range $<$2.5), androstenedione 3.8 nmol/l (0.7–3.8), DHEAS 5.7 µm/l (0.80–4.9), SHBG 33 nmol/l, FAI 17.9% (0.1–2.6). LH was 22 IU/l and FSH 59.6 IU/l consistent with post-menopausal state. Thyroid function was normal.
CT of adrenals showed no evidence of tumour. Pelvic US showed a normal right ovary, left ovary not visualized.
She subsequently underwent laparoscopic bilateral salpingo-oophorectomy. Ovarian histopathology indicated Leydig cell hyperplasia, an uncommon cause of hyperandrogenism in post-menopausal women. Her testosterone level normalized to 1.3 nmol/l 3 months after surgery.
Interestingly her elder sister had also undergone bilateral salpingo-oophorectomy 3 years earlier. She had been found to have a testosterone level of 7.0 with clinical evidence of virilization. Her ovarian histology was unremarkable. In light of family history slides from 2013 were recently re-examined by a Histopathologist. No evidence of Leydig cell hyperplasia was seen but it was suggested that this could be focal and therefore not present in the tissue sampled.

Leydig cell hyperplasia causing hyperandrogenism in women is rare with several case reports only in the literature. This case raises the possibility of a genetic component which has been described in males due to LH receptor mutations but never reported in females to the best of our knowledge. Our patient has not yet had genetic testing. Normal ovarian imaging does not exclude an ovarian source of hyperandrogenism and bilateral oophorectomy is a safe and effective procedure after excluding an adrenal source.

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EP364

Ectopic thyroid of young child with severe dysphagia: a surgical indication

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Introduction
Ectopic thyroid tissue can be found anywhere along the normal path of thyroid descent, but is most commonly found at the base of the tongue, in which case it may be referred to as a lingual thyroid. Although the patients are usually asymptomatic, it can lead to symptoms such as dysphonia and dysphagia. We present a child patient with a lingual thyroid resulting in severe dysphagia that was cured surgically.
Case reports
An 4-year-old male child presented to our department for failure to thrive estimate at less 2 DS. He Present a severe dysphagia to food, some episodes of transitional dyspnea, hypothyroidism treated since 1 year with lévothyrox. Examination of the neck revealed no palpable thyroid gland in the normal prétrachéale position, no cervical adenopathy and normal oral cavity.
Thyroid hormone tests showed elevated TSH, TG (thyroglobulin) concentrations and decreased FT3, FT4 concentrations. The ultrasound exam shows an oval mass lobed echogenic and homogeneous measuring 1.4×1.0 cm without discernable isthmus. The thyroid scintigraphy with 99mTc-Pertechnetate showed an uptake region at the base of the tongue representing a lingual thyroid. There was no thyroid uptake in the usual site in the neck. CT image showing intensely enhancing mass in the base of tongue and absent native thyroid issue in the thyroid bed.
Increased dose L-thyroxine was started and surgery because sever dysphagia was performed. The patient made a good post-operative recovery and the clinically symptoms decreased.
Conclusion
An ectopic thyroid should be considered in any child with presence of hypothyroidism and surgical indication is to be expected after exploring all dyspnea and/or dysphagia.

Keywords: lingual thyroid, hypothyroidism, child, dysphagia, surgical indication
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EP365

Graves' orbitopathy and Graves' disease after bone marrow transplant in a patient with Fanconi anemia

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Introduction
Endocrinopathies are a common late effect of haematopietic stem cell transplantation, resulting in thyroid dysfunction, impaired growth and pubertal development during childhood and metabolic syndrome. Because of the possible endocrine complications, transplanted patients need life-long endocrine follow-up.
Case report
A 14-year-old male patient with a history of Fanconi anemia (7 years), bone marrow transplant (10 years) and Graves Disease (13 years) was admitted in our endocrine department for evaluation in November 2015. He was diagnosed six month ago with hyperthyroidism (TSH < 0.004 uIU/ml, FT4 = 4.44 ng/ml, ATPO = 324 IU/ml, TRAb = 28 U/l) and started treatment with metimazole (MMI). On antithyroid drugs his symptomatology improved, with normalization of FT4 and TT3 (TSH remained suppressed), but when we tried to decrease the dose of MMI, FT4 and TT3 became elevated again and the dose of metimazole was increased again at 20 mg/day. At present admission the physical exam revealed goiter, H = 151.6 cm (−1.25 S.D.), W = 49 kg, BMI = 21.32 kg/m^2, upper eyelids swelling, retraction of the lower eyelids, discrete eyelids erythema, mild exophtalmia, especially at his left eye-signs that were not present in September, at his last visit in our hospital. The ophtalmological consultation diagnosed evolutive orbitopathy and suggested considering glucorticoid therapy. The level of TSH receptor antibodies decreased during antithyroid treatment, but they were still elevated (14.2). He started a 6-month course of selenium supplementation (100 µg/day) and pulsetherapy with methyprednisolone 125 mg/week for 3 weeks and 250 mg/week for the next 3 weeks with a good clinical outcome.
Conclusion
Graves' orbitopathy is a rare complication in transplanted patients and was not present in our patient from the start. In this situation, euthyroidism is essential for improvement of eye changes, but sometimes other therapeutic interventions are needed.

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EP366

Case report: endoscopic ultrasonography can be used as an adjunctive procedure in atypically localized and conventional ultrasound negative parathyroid adenoma

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Introduction
Ectopic and atypically localized parathyroid adenomas such as in the anterior mediastinum, paraesophageal or retrotracheal position, although rare, can be seen in clinical practice. Ultrasound (US) which is a frequently used and one of the best conventional imaging modality sometimes fails to identify the lesion especially in atypically localized adenomas. Endoscopic US (EUS) is a new technique that can be used for localization of parathyroid lesions. We reported a case with paraeosophageal parathyroid adenoma which was localized accurately with EUS.
Case
A 55-year-old woman with papillary thyroid microcarcinoma (PTMC) (0.8 cm in size) was operated 5 years ago. After the thyroid surgery her Ca levels (10.5–11 mg/dl) were found as elevated. She had been evaluated for hypercalcemia and PTH level was also found elevated. In her neck ultrasound (US) and parathyroid scintigraphy no pathology was found. Since she had no operation indication for asymptomatic hyperparathyroidism she had been followed for 5 years. Bone mineral densitometry revealed osteoporosis in lumbal vertebraes. Neck US found no pathology. Recent parathyroid scintigraphy revealed parathyroid adenoma in the posterior of the trachea in the inferior thyroid region. Neck and upper mediastinal computerised tomography showed heterogenous solid nodular lesion in the superior right paraeosophageal region 11 mm in size. In order to determine the exact localization of the parathyroid adenoma EUS was performed and detected a hypoechoic lesion close to esophagus on the right parathyroid localization. The patient underwent parathyroidectomy with minimally invasive procedure, parathyroid adenoma was detected and excised.
Conclusion
Preoperative localization of parathyroid pathology is important in appropriate cases of minimal invasive surgery. EUS can be accepted as a tool for detection of parathyroid adenoma. When the other imaging methods are negative or conflicting, EUS can be considered in these patients.

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EP367

A case with atypical parathyroid lipoadenoma presented with severe hypercalcemia and skeletal deformities

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Introduction
Parathyroid lipoadenoma (PLA) is a rarely seen, benign variant of parathyroid adenoma (PA). However, PA usually consists of uniform, polygonal chief cells with a few nests of oxyphil cells, PLA consists of similar histologic features, but with an abundance of fat cells. Additionally, PLA may be functional with the secretion of parathyroid hormone (PTH) or non-functional. Here, we present a case of atypical PLA presented with severe hypercalcemia and skeletal deformities.
Case
A 41-year-old male referred to emergency department due to the cranial trauma following the syncope episode. In his cranial magnetic resonance imaging no pathology was found. He had no chronic disease except hypertension. His laboratory evaluation revealed elevated creatinine and calcium (Ca) levels (1.7 and 14.3 mg/dl, respectively). PTH level was found 735 pg/ml, urinary calcium excretion was found 348 mg/24 h. Neck ultrasound (US) revealed an isoechoic mass with 18.5×29.5×38.7 mm in size in the left inferior part of the thyroid gland which was consistent with parathyroid scintigraphy. Grade I hypertensive retinopathy was detected in ophtalmological examination. Bone mineral densitometry revealed severe osteoporosis, especially in lumbal vertebraes. Pathologic fracture was not determined in vertebral graphics. He had severe scoliosis and pectus excavatum. Ca levels were regressed to 12 mg/dl with intravenous hydration and diuretic treatment. He had underwent left hemithyroidectomy and parathyroidectomy and pathology was revealed atypical PLA and benign thyroid disease. Also the surgical specimen was revealed a large size mass with a 5 cm in diameter and neoplastic cells were seen in one area in the capsule.
Conclusion
Although PLAs are benign lesions, our case had atypical features. He had severe osteoporosis and skeletal anomalies in addition to severe hypercalcemia. However, there has been no known malignant PLA, the cases which show atypical features should be followed closely.

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EP368

Is β2-microglobulin a specific marker of anaplastic thyroid carcinoma?

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Anaplastic thyroid carcinoma (ATC) is the most aggressive and lethal thyroid malignancy. The median survival time following diagnosis is typically 6 months or less. β2 microglobulin (β2-MG) is a component of MHC class I molecules, which exists in all nucleated cells except red blood cells and placental trophoblast cells. Levels of beta-2 microglobulin can be elevated in multiple myeloma, lymphoma and amyloidosis. In few studies on anaplastic thyroid cancer, β2-MG levels were found to be elevated especially in the subjects with lymph node metastasis.
A 71-year-old woman presented with a rapidly enlarging neck mass present for the last 4 weeks. Physical examination revealed a 3 cm sized tender thyroid mass on the right lobe and 2 cm sized lymph nodes on right cervical region. Anti-thyroglobulin antibody and anti-TPO were positive, TSH, FT4 and FT3 levels were normal. Leukocyte: 4730 μl (*n*: 3980–10 040), hemoglobin: 10.6 (*n*: 12–15) gr/dl, thrombocyte: 210 000 μl (*n*: 150 000–450 000), sedimetation: 44 mm/h (*n*: 0–20), CRP: 0.11 mg/dl (*n* : 0–0.34), urea: 36 mg/dl (*n*: 15–43), creatinin: 1 (*n*: 0.57–1.11), LDH: 622 U/l (*n*: 125–220), calcitonin < 2 pg/ml (*n*: 0–10) and β2-MG levels obtained at different time points were 3418, 3296 and 3882 ng/ml (*n*: 1010–2500). On neck ultrasonography, thyroid parenchyma was heterogeneous and there were multiple, macrocalcific, hypoechoic nodules, the biggest one was being 35×28×30 mm in size in the right thyroid lobe. There were 2 cm sized, multiple, spherical lymph nodes with irregular borders and invisible fatty hilum in the right anterocervical region. Lymphoma and thyroid cancer were considered as differential diagnoses. Peripheral blood smear and protein electrophoresis were found to be normal. Tru-cut biopsy samples obtained from lymph nodes in the right anterior cervical region and nodule in the right thyroid lobe detected anaplastic carcinoma with rhabdoid variant. The patient was referred to the department of oncology for chemo-radiotherapy.
In conclusion, further studies are required to confirm whether β2-MG can be used as a specific marker for thyroid cancer.

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EP369

Simultaneous diagnosis of type 2 diabetes mellitus and insulinoma: diagnostic pitfalls

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Introduction
Co-morbidity of DM t 2 and insulinoma is extremely rare. There are only some case reports of diagnosing insulinoma but they concern patients already diagnosed with DM t. 2. We present patient diagnosed at the same time with DM t. 2 and insulinoma.
Case report
A 69-year-old female patient was admitted to hospital because of high blood pressure. Since 2 years she reported attacks of weakness, tachycardia and sweating within the day, usually several hours after food intake or directly after physical effort or rarely while fasting. The food intake resolved the symptoms. Physical examination revealed blood pressure 200/100 mmHg, BMI 26 kg/m^2, abdominal obesity, waist circumflex 89 cm. By prolonged 5-hours OGTT diabetes with reactive hypoglycemia at hour 5 of test was diagnosed. Abdominal US revealed hepar steatosis. Antibodies: anti-GAD, ICA, IAA were negative. During hospitalization fasting glycaemia levels were within range of 3.22–6.33 mmol/l and postprandial levels were: 3.61–8.94 mmol/l. Hypothyroidism, adrenal insufficiency, kidney and hepar failure were excluded. Screening cancer exams were negative. We performed fasting test. After 14 h symptomatic hypoglycaemia: 2.44 mmol/l was observed with inadequately high levels of insulin and C-peptide. Endogenic hyperinsulinaemia was diagnosed. CT scans revealed pancreatic tumor diameter 17 mm. The patient underwent surgical treatment. Histopathological examination confirmed well differentiated endocrine tumor. 3 months after operation she was treated with metformine and remained euglicaemic. C-peptide level was normalized.
Conclusion
1. Diagnosis of DM t 2 should not be followed by abandoning diagnosis of fasting hypoglycaemia when there are morning or frequent postprandial hypoglycemia episodes within the day.
2. Hypoglicaemia must not be always typical sign of the early stage o the diabetes mellitus. Other causes should be considered even insulinoma.

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EP370

Apolipoprotein B deficiency

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Introduction
Family hypobetalipoproteinemia (HBF) is a rare genetic disorder, in 50% of cases are due to mutations APOB gene, which leads to decreased values of total cholesterol, low density lipoprotein (LDL-cholesterol) and apo-B. It is inherited as an autosomal dominant and heterozygous carriers are usually asymptomatic.
Clinical case
Thirty-two-year-old male with abdominal pain and diarrhea associated with food, no relevant history and physical examination standard, which hypolipidemia is detected. Once discarded hypolipidemia secondary causes of decreased cholesterol (85 mg/dl), triglycerides (20 mg/dl), c-LDL (32 mg/dl), apo-B (23 mg/dl) with slightly elevated levels are confirmed TGP (50 U/l) and lack of vitamin E (473).The family proceeded to study lipid and other affected cases with an autosomal dominant inheritance pattern detected suspect mutation in the gene

for apoB. The genetic study of the index case confirmed the presence of a mutation in compound heterozygosity for the ApoB gene. With low-fat dietary treatment the patient's symptoms disappeared are currently taking supplements of vitamin E.
Discussion
The HBF affects lipoproteins containing apo-B, so that heterozygous carriers have decreased levels of apo-B 25–30% of normal, while asymptomatic but most often present as hepatic steatosis and our homozygous paciente.Los compound heterozygotes have a similar clinical picture Abetalipoproteinemia also frequently presenting our case as diarrhea and index deficit soluble vitamins, mainly A, D and E.
Conclusions
The presence of LDL cholesterol and ApoB below P5 for the population should make us suspect the presence of HBF. The genetic study differentiates heterozygous and homozygous forms allowing family counseling and appropriate treatment.

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EP371

A girl with Cornelia de Lange syndrome with good response on GH therapy: case report

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Introduction
Cornelia de Lange Syndrome (CDLS) a relatively uncommon genetic disorder diagnosed mainly by clinical features: distinctive facial features, developmental delay, hirsutism, mental retardation and structural abnormalities. Most cases are due to spontaneous mutations (NIPBL on chromosome 5, SMC1A on X chromosome, and SMC3 on chromosome 10). Short stature in CDLS is due to GH deficiency and resistance.
Case report
We present a 9-year-old girl, B.A., which was addressed to the Endocrinology Department for growth retardation, with severe short stature (86 cm, −3 S.D.) and underweight (11.5 kg, −3 S.D.), delayed bone age (2 years), but normal GH profile. She was an only child of non-consanguineous marriage, naturally delivered on term, Apgar score of 8, small for gestational age (birth weight of 1850 g) and delays in milestones during development. Clinically diagnosed with Cornelia de Lange syndrome (CDLS) at the age of 3: low anterior hair line, bushy eyebrows meeting in mid-line, low set ears, maxillary hypoplasia, small hands, clinodactyly, and hypertrichosis. One year later, because of the stationary height, she was reevaluated for GH deficiency: GH was not stimulated (4.93 ng/ml), with low IGF1 (85.1 ng/ml, *n*: 49–283) and GH therapy was started. After 5 years of treatment she gained 38 cm (7.5 cm/year of treatment, actual height 124 cm, −2.9 S.D.), with ameliorated bone age (7 years).
Conclusions
CDLS has been characterized by small gestational age, growth retardation, distinctive facial dimorphism, primordial short stature, psychomotor delay, behavioral problems. Patients suffering from CDLS have a normal puberty but without growth spurt (final stature is approximately 155 cm in men and 133 cm in women). Despite the bKIGS data which did not find an apropriate response at GH treatment at short term, our patient showed a satisfactory growth velocity, probably due to the associated GH deficiency.

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EP372

Recurrent pancreatitis and an ectopic parathyroid - an unsavoury combination

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Introduction
Pancreatitis due to hypercalcemia from primary hyperparathyroidism is rare with an incidence of 1–1.5%. We report on a case of recurrent pancreatitis secondary to an ectopic parathyroid adenoma with co-existing severe vitamin D deficiency with its management difficulties.
Case report
A 45-year-old male admitted to the hospital with abdominal pain and attendant nausea had investigations ruling out structural lesions for his symptoms but ultrasound evidence of acute pancreatitis. He was noted to have severe hypercalcemia with raised amylase. He was managed conservatively and further evaluation revealed elevated parathormone levels. An ultrasound of his parathyroid failed to localize any adenoma while the sestamibi scan showed activity in the right para sternocleidomastoid region consistent with an ectopic parathyroid tissue. He has had two further admissions with acute pancreatitis secondary to hypercalcemia. Co-existing severe vitamin D deficiency was discovered which required correction to optimize his chances of a successful outcome post-surgery. This case was challenging because of its rarity. Vitamin D deficiency correction attempts frequently led to severe hypercalcemia which in itself posed additional risk of recurrent pancreatitis. The patient was referred for urgent consideration of surgery for removal of his ectopic parathyroid.
Conclusion
Primary hyperparathyroidism may rarely provoke acute pancreatitis but for recurrent pancreatitis to occur is indeed very unusual save for hereditary primary hyperparathyroidism. Our patient in question had an ectopic parathyroid which was revealed by adopting a more intensive investigation approach following initial negative ultrasound. Correcting severe vitamin D deficiency with careful management of severe hypercalcemia presents its own treatment challenges especially with stone formation in the urinary tract but recurrent pancreatitis triggered by hypercalcemia presents a management nightmare which involves close monitoring of numbers as a prelude to ensuring an optimal outcome following surgery.

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EP373

A rare cause of hypoglycemia in a diabetic woman: insulinoma

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Insulinoma is generally a rare benign tumor of the pancreas islet cell. The typical clinical symptom of insulinoma are repetitive hypoglycemia attacks. Insulinoma with coexisting diabetes is extremely rare condition, We aim to present a case with insulinoma conmomittant with type 2 diabetes mellitus.
Case report
A 65-year-old woman diagnosed with type 2 diabetes mellitus was admitted by our internal medicine clinic. She complained from perspiration and tremor when she was hungry. She was taken metformin 2000 mg/day for 3 years. In the first laboratory analysis, plasma glucose was 62 mg/dl and HBA1c was 4.4%. Plasma glucose maintained to decrease, although metformin treatment was quitted because of hypoglycemia. Plasma glucose during hypoglycemia was detected 47 mg/dl, insulin 35.3 mIU/ml (2.4–23.3) and C peptide 3.51 ng/ml (0.9–4). It was performed abdominal CT for the possibility of insulinoma. In the abdominal CT, it was monitored a well-circumscribed mass, approximately in the size of $21\times20\times17$ mm in pancreas caudal part. Distal pancreatectomy was performed in the patient. Pathological outcome of the patient was reported as insulinoma. There was no hypoglycemia in the patient after the operation.
Conclusions
It is not easy to diagnose insulinoma for hypoglycemic symptoms in diabetic patients are associated with diabetes treatment. When diabetic patients have frequent hypoglycemia, insulinoma is also thought.

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EP374

From Horner's syndrome to primary hyperparathyroidism: a case report

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Introduction
Horner's syndrome represents a clinical symptom that may result from a variety of lesions both in the central and peripheral nervous system. It is a combination of

ipsilateral ptosis, pupillary miosis and anisocoria, enophthalmos and facial anhydrosis induced by disruption of the sympathetic innervation of the eye anywhere along its three-neuron trail. Tumors are the most frequent causes of Horner's syndrome.
Aim
Aim of the study was to present a rare case of Horner's syndrome caused by parathyroid adenoma.
Case report
50-year-old man was initially diagnosed in neurology ward because of right Horner's syndrome in the form of ptosis, pupillary miosis and enophthalmos. CT of the neck disclosed 30×26×16 mm homogenous solid tumor strictly adhering to the posterior contour of the right lobe of the thyroid with initial density 56 HU. Differential diagnosis included: atypical part of the thyroid gland, parathyroid adenoma or paraganglioma (in MRI). 99mTc-MIBI parathyroid scintigraphy revealed an area of increased tracer accumulation that could correspond to enlarged right parathyroid gland. PTH level was 347–426 pg/ml ($n<72$), total calcium level 11.8–12.9 mg/dl ($n<10.4$), ionized calcium 1.64–1.67 mmol/l ($n<1.32$). Low concentration of serum phosphorus (2.3 mg/dl) and increased urine calcium excretion (570–950 mg/24 h, $n<300$) were also observed. 25(OH) D3 blood level was 14.39 ng/ml ($n>30$). Due to the suspicion of PTH-secreting paraganglioma daily urine excretion of methoxycatecholamines (913 and 742 µg/24 h; $n<1000$) and biopsy of the lesion (parathyroid tissue) have been done. During surgery a tumor of the right upper parathyroid gland has been removed. The postoperative pathologic examination revealed 4.5×2.5×21.3 cm parathyroid adenoma. The Horner's syndrome symptoms did not resolve after surgery.
Conclusion
Among the many causes of Horner's syndrome, parathyroid tumor should be taken into account in the differential diagnosis.

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EP375

Parathyroid adenomas: critical appraisal of surgical therapy in 18 cases

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Background
Parathyroid adenomas represent the most common anatomoclinical variety of hyperparathyroidism.
Material and method
From our experience of 84 cases of hyperparathyroidism – 20 primary and 64 'renal' (CKD-MBD) – 18 patients underwent surgery for solitary adenomas of these glands. Clinical data, laboratory and imaging test results, surgical procedures and outcome were comprehensively analysed.
Results
We registered 16 women and only two men, aged between 16–58 (mean 46) years. From the clinical point of view bone manifestations prevailed in six cases, those of urolithiasis in nine cases and pancreatic phenomena in two cases. One patient was asymptomatic being discovered incidentally during a thyroidectomy. The mean serum calcium at the time of diagnosis was 11.5±2.2 mg/dl but serum phosphorus was 4.4±0.5 mg/dl. The mean parathyroid hormone (PTH) level (measured in only 12 patients) ranged between 127–778 pg/ml. Ultrasonography acurately identified lesions in 16 cases and Technetium=99 m sestamibi scintigra-phy in only five cases. Eighteen adenomectomies were performed of which bilateral neck exploration was done in 16 patients and minimally invasive approach in the remaining two cases. In seven situations concomitant thyroid exeresis were done for associated lesions or imposed by tactical purpose. Pathologic examination revealed single adenoma consisting of main and oxyphil cells in 17 cases. In one patient an atypical adenoma was identified and in another case 3 years after removal of a benign adenoma the subject presented a homolateral clinical recurrence, which proved to be a carcinoma (new lesion or erroneous initial diagnosis?). Postoperative clinical and humoral outcome was favorable in all situations excepting the case with carcinoma which died after 14 months.
Discussions and conclusions
Parathyroid adenomas produced evident systemic clinical features but not always easy to diagnose. They benefit significantly from surgical treatment which is considered the gold standard of respective lesions.

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EP376

To be or not to be … male

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Introduction
Pats with Klinefelter Syndrome (KS) have elevated morbidity and mortality due to several reasons. Yet, there is no connection between KS and male-to-female sex change.
Case
A 74-year-old man was sent for endocrine work-up prior to surgery due to gynecomastia. The patient had lived as a man-to-woman transgender for many years. He was told not to qualify for a transgender surgical approach when he was 55 years old. He took estradiol substitution for several years, but by age 60 after developing recurrent severe pulmonary embolism he stopped substitution. After that he lived 'asexual' and bilateral, non-painful gynecomastia developed. Gonadal examination revealed small testes, bilateral Gynecomastia (Tanner IV) and signs of chronic venous insufficiency. The biochemical analyses showed hypergonadotropic hypogonadism with otherwise normal values. The molecular analyses revealed a 47XXY Karyotype. Osteodensitometry showed low peak bone mass. We started topical testosterone replacement and calcium/vitamin D3 substitution.
Discussion
KS affects about 1 in 660 men, but remains often undetected with only about 25% of patients receiving the correct diagnosis. Age at diagnosis is around 35. The phenotype is thought to be linked to non-inactivated genes from the extra X-chromosome, but alternative mechanisms are possible.
The excess morbidity and mortality may be explained by endocrine dysfunction and diseases of the cardiovascular and of respiratory systems. Only few studies have examined the association of KS and transsexuality. One study found an association of gender dysphoria with KS. Yet, no significant increase in KS was reported in previous studies looking at men-to-female transgender populations. Still, this hypothesis has to our knowledge not systematically been investigated to make firm conclusions.
Thus, in patients with male-to-female sex change, further work-up towards KS should only be envisaged if there is additional clinical suspicion – such as small testes or hypergonadotropic hypogonadism as found in our case.

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EP377

Changing of thyroid status in an autoimmune polyglandular syndrome type 2

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Introduction
Autoimmune polyglandular syndrome type 2 (APS2) is the most common form of the polyglandular failure syndromes. Seventy-five percent of cases occur in women. Adrenal insufficiency is the principal manifestation occurs with autoimmune thyroid disease or type I diabetes mellitus. The incidence of autoimmune thyroid diseases in APS2 is 70%; 30% Hashimoto's thyroiditis, 20% non toxic goiter, 20% hypertyroidism is seen. We will discuss about a patient with APS2, who previously had hypothyroidism, but now presenting with adrenal crisis and hyperthyroidism.
Case
A 25-year-old male patient admitted to out-patient clinic for nausea, vomiting and non specific abdominal pain. Biochemical results were as follow; sodium 130 mmol/l (135–146), potassium 5.13 mmol/l (3.5–5.1), free T4 2.8 ng/dl (0.9–1.7), free T3 3.97 pg/ml (2.5–3.9), TSH 0.02 µIU/ml (0.34–5.6). In his medical history, he has been diagnosed APS2 with adrenal insufficiency and hypothyroidism for 8 years. At the time of diagnosis TSH, ACTH were 21.8 µIU/ml, and 2000 pg/ml respectively and anti TPO was positive. He was on prednisolone 5 mg/day, fludrocortisone 0.1 mg/day and levothyroxin (LT4) 150 mcg/day treatment. We thought thyrotoxicosis factitia, so we stopped LT4 and increased prednisolone dose. After 2 weeks, despite cessation of L-thyroxin treatment, thyrotoxicosis was persisted, anti TPO antibody and anti thyroglobulin antibody were negative, but TSH receptor antibody (TRAbs) was high (315 U/l (0-14)) and thyroglobulin was 90.4 ng/ml (0–80). Thyroid ultrasonography revealed heterogeneous parenchyma with minimal increase in vascularity.

Thyroid scintigraphy with Technetium showed non homogeneous increase uptake. The patient diagnosed as Graves disease.
Conclusion
TRAbs is responsible for two distinct clinical syndromes. Stimulating antibodies (TSAb) cause thyrotoxicosis where as blocking antibodies (TBAb) cause hypothyroidism. Antibody switch can occur. The etiology of this process remains unknown but hemodilution of TRAb titer can be one of the possible mechanisms. Also LT4 treatment in unusual patients can induces or enhances thyroid autoantibody levels. The occurrence of 'switching' emphasizes the need for careful patient monitoring and management.

	TSH	fT4	fT3	AntiTPO
Time of diagnosis (8 year before)	21.63	1.13	2.98	52.4
Initial result	0.02	2.80	3.97	5.8
2nd admission (2 weeks later)	0.08	3.87	5.63	–

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EP378

Safely operated two patients in pregnancy with primary hyperparathyroidism

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Introduction
Primary hyperparathyroidism (pHPT) during pregnancy is rare and associated with increased morbidity for both mother and fetus. Maternal complications of pHPT include nepfhrolithiasis, pancreatitis, cardiac arrhytmias, hypertension, nausea and vomiting. pHPT is caused by a solitary adenoma in 85–90% of patients, and the curative treatment is parathyroidectomy. Here, we presented two women who have diagnosed pHPT and operated without complications in pregnancy.
Case 1
She was 20 years old and presented with abdominal pain at 8th weeks gestation. Her laboratory tests were revealed 12.2 mg/dl Ca levels, 2 mg/dl Phosphorous (P) levels and 136 pg/ml parathyroid hormone (PTH) levels and her urine Ca level was 810 mg/24 h. Her neck ultrasonography (US) revealed a hypoechoic lesion with $6.3\times6.3\times14.5$ mm size consistent with parathyroid adenoma in the left superior of the thyroid gland. No thyroid nodule was detected. Nepfhrolithiasis was not determined. The left superior parathyroid gland was excised with minimal invasive surgery in the 9th weeks of gestation and parathyroid adenoma was excised.
Case 2
Thirty-eight years old woman who was 9th weeks gestation was referred to our clinic for the high serum Ca levels. Her Ca level was 11.5 mg/dl, P level was 1.4 mg/dl, PTH level was 344 pg/ml. Her neck US revealed parathyroid adenoma in the right inferior part of the thyroid gland $2\times1\times1$ cm with size. Also she had a nodule in the right thyroid gland. She had underwent right hemithyroidectomy and parathyroidectomy in the second trimester and parathyroid adenoma was excised.
Conclusion
Since the symptoms are often non-specific in the PHPT, it can be easily misdiagnosed during pregnancy. Early recognition of pHPT, followed by appropriate management and treatment may reduce the maternal and fetal complications. Therefore pregnant women with biochemical hypercalcemia or any clinical presentation associated with hypercalcemia must be evaluated for pHPT.

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EP379

Calcific uremic arteriolopathy (Calciphylaxis): case report

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Introduction
The calcific uremic arteriolopathy (CUA) is one of the several types of extra-osseous calcification that may occur in patients with end-stage renal disease (ESRD). CUA is a serious disorder characterized by calcification of the arterioles that leads to ischemia and subcutaneous necrosis. The pathogenesis is poorly understood, and the optimal treatment is not known.
Case report
We present the case of a 64-year-old female with ESRD on hemodialysis since 2010, is hypertensive, had a heart attack in 2006. She was referred to our hospital with extensive two ulcers on the left leg with necrotic eschars.
Laboratory investigations showed elevated levels of phosphorus 2.46 mmol/l, calcium 2.73 mmol/l, $[Ca]\times[P]$ 6.7 mmol/l, iPTH 2529 pg/ml. Ultrasound revealed multiple enlarged parathyroid glands, DEXA revealed osteopenia. The clinical diagnosis was severe secondary hyperparathyroidism and CUA.
Considering the severity of CUA, was recommended a total parathyroidectomy. However, due to the patient's cardiovascular status, there were certain contraindications. Initially, we cancelled the warfarin, recommended a hypophosphatic diet, analgesics, intravenous antibiotics, assessment by surgeons for wound care. She started intensive dialysis on a daily: 3-h-sessions with low calcium (1.25 mmol/l) dialysate for 2 weeks, later three times a week, followed by 24 mg of sodium thiosulfate intravenous administration at the end of every session. She was also started on phosphate binders (sevelamer 2400 mg/day) and calcimimetics (cinacalcet 30–60 mg/day) for better control.
Laboratory investigations were done during the treatment – phosphorus 2.14 mmol/l, calcium 2.13 mmol/l, $[Ca]\times[P]$ 4.55 mmol/l, iPTH 2086 pg/ml. We added other phosphate binders Almagel for a short period. Six months later, the first CUA lesion was healed, a year later – the second one.
Conclusion
Our case study shows that only a multi-interventional strategy is likely to be more effective in treating CUA in patients on hemodialysis and with several secondary hyperparathyroidisms.

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EP380

Unusual presentation of primary hyperparathyroidism with coexisted thyroid carcinoma

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Introduction
Brown tumor is a rare benign bone lesion with incidence ranging from 1.5% in primary hyperparathyroidism to 13% in secondary hyperparathyroidism. Common sites of involvement are pelvis, femur and ribs, but may appear in any bone. Since the incidence of thyroid disease is higher among patients with hyperparathyroidism than the general population, these lesions must be distinguished from metastases from thyroid carcinoma.
We present a patient with a complex clinical picture of primary hyperparathyroidism with multiple destructive skeletal lesions suspicious of bone metastases and concomitant multifocal papillary thyroid carcinoma with a metastatic central lymph node. To our knowledge, this is the second reported case of multiple brown tumors caused by primary hyperparathyroidism and coexisting papillary thyroid carcinoma.
Case report
A 38-year old male presented with progressively worsening right hip pain and restricted motion. MRI revealed multiple lytic bone lesions suggestive of brown tumors, but also suspicious for metastases. Biochemical tests were consistent with primary hyperparathyroidism. Neck ultrasound and parathyroid scintigraphy revealed a single parathyroid adenoma and a thyroid nodule, preoperative cytology of which confirmed papillary thyroid carcinoma, as did the final surgical specimen. Biochemical results, regarding hyperparathyroidism, declined to

normal levels and his complaints gradually decreased after surgery. Postoperative whole body bone scintigraphy showed increased tracer uptakes at multiple sites. However, post-RAI whole body scan and FDG PET/CT did not exhibit an abnormal uptake throughout the skeletal system, which proved these osteolytic lesions to be metabolically inactive.
Conclusion
Although the guidelines do not consider primary hyperthyroidism a risk factor for thyroid carcinoma, several data suggest that this risk may be increased when compared to the general population. As the concomitant thyroid carcinoma is not uncommon among primary hyperparathyroidism patients, all patients who present with a thyroid nodule should undergo FNAB, even if sonographic features are not suspicious for malignancy.

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EP381

Undetectable HbA1C in a case of Thalassemia major: misuse of diagnostics became a boon for the patient

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Objective
To report a case of thalassemia major diagnosed per chance when investigated for undetectable HbA1C.
Clinical Presentation
A 2-year-old male patient presented with fever since 3 days and moderate pallor. His blood was sent to Biochemistry laboratory for the estimation of HbA1C. Later on it was found that there was no indication for this test in this case. When assayed, his haemoglobin (Hb)A_{1C} was not detectable on a BioRad D10 HPLC system.
Discussion
To find out the cause sample was analyzed for hemoglobin variants in the extended mode which eluted with 95.2% HbF and 4.1% Hb A2 and 0.3% HbA. The likely diagnosis was beta thalassemia major which was later confirmed by hemogram and electrophoresis. Because there is very less (0.3%) HbA, ion exchange HPLC will not detect glycated Hb in such individuals. There are several other factors that affect HbA_{1C} results such as homozygosity for HbE, carbamylated Hb, any condition that decreases RBC survival.
Conclusion
A patient with undetectable HbA1C should be investigated for hemoglobinopathy with very low HbA.

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EP382

Tuberculous lymphadenitis mimicking nodal metastasis in follicular variant papillary thyroid carcinoma

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Background
Tuberculous (TB) lymphadenitis can mimic cervical node metastasis from papillary thyroid carcinoma (PTC) since the distribution and appearance of affected lymph nodes is similar.
Case
A 50-year-old Filipino presented with a gradually-enlarging anterior neck mass, with a solitary lymph node palpated at the left cervical area. The rest of the history, physical examination and blood workup were unremarkable. A thyroid ultrasound showed a 6.5×5×3 cm solid left thyroid mass plus a single 1.2×1×0.5 cm cervical lymph node. Fine-needle aspiration biopsy (FNAB) of the thyroid mass revealed PTC. The patient underwent total thyroidectomy with node dissection where histopathology confirmed follicular variant (FV)-PTC. Lymph node examination, however, revealed granulomatous inflammation with caseation necrosis and Langhans giant cells consistent with TB. A chest X-ray plus two acid-fast stained sputum samples were negative for concomitant pulmonary TB. The patient underwent standard anti-mycobacterial therapy.
Discussion
Our patient had an enlarging anterior neck mass with an associated lymph node. Due to the documented thyroid malignancy on FNAB plus lymph node proximity, primary consideration for lymphadenopathy was metastasis. However, the distribution and sonographic appearance of lymph nodes is identical in TB adenitis and cervical node metastasis. Since current guidelines do not recommend routine preoperative FNAB of lymph nodes in PTC (which is staged clinically and radiologically), the diagnosis of TB lymphadenitis can be easily missed. In retrospect, it could have identified TB preoperatively, leading to earlier anti-mycobacterial therapy and avoiding neck dissection. This is the first documented case in Southeast Asia, a high TB burden region. This is also the first report involving FV-PTC, which has features between those of conventional PTC and follicular thyroid carcinoma.
Conclusion
In endemic areas, TB should be a differential in the etiology of cervical lymphadenopathy in PTC patients. Proper preoperative evaluation is important, and guidelines may need to be revised.

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EP383

Hypertriglyceridemia induced pancreatitis

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Introduction
Hypertriglyceridemia is rare but associated cause of pancreatitis and accounts for 10% of cases. Hypertriglyceridemia induced pancreatitis may occur secondary to causes such as diabetes, pregnancy, hypothyroidism and obesity. Management of hypertriglyceridemia includes a change in dietary intake as well as lipid lowering agents, fenofibrates, statins and omega 3 fatty acids. To reduce the triglycerides acutely, intravenous heparin and insulin have been used. In the case reported, the use of intravenous insulin and heparin showed an 80% reduction in triglyceride levels correlating with a significant improvement in clinical symptoms.
Case
A 51-year-old gentleman who was visiting North Wales was admitted under the surgeons with a 1 day history of epigastric pain radiating to the back. His past medical history included hypertension, non-insulin dependent diabetes and previous pancreatitis. Admission bloods revealed a crp 287 mg/l, amylase 893 U/l, cholesterol 20.5 nmol/l, triglycerides of 87.2 nmol/l and a HbA1c 81. His CT showed pancreatic oedema and fat stranding suggestive of acute pancreatitis. Following this, an abdominal ultrasound showed no evidence of gallstones. There was no family history of hyperlipidaemia and he was teetotal excluding these causes, making hypertriglyceridemia the likely diagnosis. He was commenced on fenofibrate, Omega 3 and atorvastatin. Due to his clinical symptoms and the elevated levels of triglyceride, intravenous insulin with 10% dextrose and heparin infusion 0.6 ml/h was started. Within 24 h, the triglyceride level had reduced to 25.8 nmol/l. His pain improved and his was discharged on subcutaneous Lantus and Novorapid.
Conclusion
Hypertriglyceridemia is often associated with poorly controlled diabetes mellitus and can precipitate an acute pancreatitis. The use of intravenous heparin and insulin stimulates lipoprotein lipase activity and chylomicron breakdown, reducing triglyceride levels. Long-term treatment includes dietary modifications, statins and better control of diabetes.

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EP384

Riedel's sclerosing thyroiditis (RT): six case report

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Case 1
78-years-old female with progressive increase volume in cervical area with dysphagia, drowsiness, slowness, dispnea, and change in of voice. Hypothyroidism and a TPO >1000 UI/ml. Thyroid ultrasound: heterogeneous mass in the left lobe, vascularized with ipsilateral multiple lymph nodes of 0.8×0.6 cm. PAAF: Bethesda 1. Four weeks later course with major obstruction of the upper airway. In ER a near-total thyroidectomy is performed. Postoperatory without complications. Biopsy compatible with RT.
Case 2
58-years-old male. 15 weeks of dysphonia. Euthyroid. Studies identified left paralysis of the vocal cords. CT: node with an intrathoracic extension of the thyroid's left lobe. The cervical ultrasound revealed a suspicious thyroid nodule of 5×7 cm. A bilateral thyroidectomy was performed. Biopsy compatible with RT. Dysphonia continued after the late post operatory.

Case 3
85 years old female with hypothyroidism. Logic dysphagia for 15 days, dyspnea and increment in cervical volume. 2 PAAF obtaining Bethesda 3. The CT presented a 7 cm mass with and infiltration to the adjacent tissues in the thyroid's left lobe and left cervical adenopathies. She was admitted to perform a study and a corticotherapy. The mass diminished its size softening the obstructive symptoms. Biopsy showed RT treated with corticoids
Case 4
58-year-old female. Multinodular bocio. During surgery it was identified a strong mass very attached to adjacent tissues. Suspecting RT, the total thyroidectomy was finished. Biopsy confirmed RT. Postoperatory had no complications.
Case 5
Female 72 years old with increase nodular volume in thyroid and airway compromised. Byopse thyroiditis sclerosing and anaplastic carcinoma. Patient died for acute respiratory insuficience without therapy. Case 6: Male 77 years old with giant bocio with 30 years of evolution. Total Thyroidectomy: Riedel's thyroiditis and papilar carcinoma. Complementary therapy with radiotherapy and radioactive yodo in course.

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EP385

Thyroid, the Heart and Amiodarone

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Introduction
The hyperthyroidism is a risk factor for tachyarrhythmia and dilated cardiomyopathy. Amiodarone is an effective antiarrhythmic medication, however if coexisting thyroid pathology complicates the treatment of thyroid dysfunction. It presents a case of Graves' disease (GD) of long evolution, which illustrates the complexity of these associations. Clinical case: man, 44 years old, smoker, history of acute myocardial infarction and GD diagnosed at age 28. Has made treatment with propylthiouracil during 3 years, having abandoned the medical follow-up. Admitted for urgent care by signs and symptoms of hyperthyroidism and heart failure (class IV NYHA), with 1 month of evolution. He presented with tachyarrhythmia, tremor, visible and palpable diffuse goiter, slight active Graves' ophthalmopathy. Eletrocardiogram: ventricular tachycardia alternating with sinus rhythm, left anterior hemiblock, repolarization changes suggesting ischemia. Echocardiography:dilated ischemic heart disease, LVEF-32%, suspicion of intracavitary thrombus in the left ventricle. Laboratory tests: TSH <0.003 μU/ml; fT_4 2.18 ng/dl (0.7–1.48); fT_3 6.06 pg/ml (1.71–3.71); anti-TPO 514 UI/ml; anti-Tg 18.9 UI/ml; TRAb 12.4 UI/ml; pro-BNP 2146 pg/ml; troponina 33.8 ng/l (<15). Cervical ultrasound revealed GD. Established therapy in hospital:amiodarone, rivaroxaban, atorvastatin, furosemide, ramipril, spironolactone, bisoprolol, thiamazol and prednisolone. There was clinical improvement and normalization of thyroid function. It was decided to thyroidectomy about 2 weeks after the episode. After 6 months: Echocardiography: LVEF-55%, segmental hypokinesia; Coronary angiography: LVEF 60%, occluded coronary proximal left anterior descending, filling by collateral of the right coronary artery. Performed coronary artery bypass surgery.
Discussion
The effect of hyperthyroidism in the myocardium begins to be better understood. The euthyroid state allows the improvement/reversion of cardiac abnormalities. The amiodarone is effective, even in the context of thyrotoxicosis, contributing to normalization of thyroid hormones (Wolf-Chaikoff effect). However, in the long term may worsen the hyperthyroidism by escape of this mechanism. Thus, thyroidectomy in the short term is the best definitive treatment of the GD, being carried out without major surgical risk, when normalized thyroid hormones.

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EP386

A rare variant of hyperthyroidism: unilateral Graves' disease

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Introduction
Despite the fact that Graves' disease (GD) almost always presents as a diffuse hyperfunctioning goiter involving both lobes of the thyroid gland, it may rarely reveal at only unilateral lobe with bilobar thyroid gland. We herein present a case of unilateral GD involving the right thyroid lobe of a bilobar gland.
Case report
A 42-year-old woman presented with symptoms and signs of hyperthyroidism; thyrotropin (TSH) was undetectable, while free thyroxine (fT_4) and free triiodothyronine (fT_3) were increased. A color Doppler ultrasonography of the thyroid gland was revealed a nonhomogeneous, hypervascular and enlarged right lobe compared to the hypovascular and homogeny left thyroid lobe. Thyroid scintigraphy with Tc99m showed that uptake of the radioisotope was uniformly and unilaterally increased in the right lobe, with no uptake in the left lobe of thyroid gland, which was compatible with unilateral GD. Finally, thyroid autoantibodies were positive. Unilateral Graves' disease was diagnosed, and treated with methimazole and propronalol. In the nineth month, the complaints and laboratory of the patient were improved by antithyroid therapy, and the treatment was gradually discontiuned. Two months later, because her complains and laboratory were consistent with overt thyrotoxicosis, the antithyroid therapy was given again. As a conclusion, after the last medical treatment, she will be referred for radioiodine ablation therapy due to the recurrent disease.
Conclusion
This thyrotoxic patient has positive thyroid autoantibody, hypervascular and heterogeneously enlarged right thyroid lobe on ultrasonography (compared to the hypovascular and homogeny left thyroid lobe),and the uniformly distributed,increased Tc99m uptake in the right thyroid lobe pointing to existence of unilateral GD as the diagnosis. Unilateral GD is a rare condition and its pathophysiology has not been clearly elucidated. In conclusion, clinicians should be aware that Graves' disease can present with unilateral involvement of the thyroid gland.

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EP387

4 years between diagnosis and insulin therapy in a case of slow onset type 1 diabetes mellitus

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Introduction
Type 1 diabetes mellitus (T1DM) is the most common form of diabetes in children and young adults. Though T1DM often presents in an acute manner, it may be preceded by a prodromal period, often extending over years.
Case report
A 19-year-old male, diagnosed with T1DM at the age of 15, with no insulin treatment, was admitted to our department for high glycemic value (G) of 365 mg/dl on a routine exam at his GP. At diagnosis the patient was asymptomatic, with a jeun G = 149–159 mg/dl, 2 h-OGTT = 386 mg/dl, A1c = 5.2%, high GAD antibodies, C peptide and insulin levels in the normal lower range. The lack of family history and the normal G of his parents excluded a MODY form and the absence of obesity or overweight excluded T2DM. His past medical history was consistent with: left popliteal deep vein thrombosis in the context of a moderate (27%) deficit of S protein, moderate thinness, mild dyslipidemia and mild normocytic, normochromic anemia. Six months after the diabetes diagnosis and on a diet the A1c = 7.28%. In our department, labs exams revealed: $G = 285$ mg/dl, mild hypokalemia, mild dyslipidemia, ketonuria (150 mg/dl), significant glycosuria (1 g/dl) and the A1c $>14\%$ was consistent with a sever glycemic imbalance in the last 3 months. A basal bolus regimen with glargine and lispro insulin was started, adjusted according to the glycemic values and carbs ingestion. The screening for other autoimmune diseases was performed revealing only slightly elevated circulating immune complexes.
Discussions
This case illustrates the complexity of diagnosis in a case of slow onset T1DM. The clinical judgment and immunological labs exams are essential for a correct diagnosis. From our knowledge, this case presents the largest period from the diagnosis of T1DM and initiation of the insulin therapy.

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EP388

Acute mania after levothyroxine replacement for hypothyroid-induced heart block

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Background
While psychiatric disturbances are well-documented manifestations of hypothyroidism, initiation of levothyroxine (LT_4) therapy can also present in a similar manner.
Case
A 34-year-old Filipino with Hashimoto's thyroiditis consulted for signs and symptoms of hypothyroidism. Thyroid function tests were severely deranged, and an electrocardiogram revealed high grade atrioventricular block. Twenty-four hours after a full replacement dose of LT_4, he developed manic symptoms, which were addressed with sedatives and neuroleptics with gradual restoration of euthymia the following day. He remained stable throughout his admission with no relapse of psychiatric symptoms. A comprehensive workup did not reveal other etiologies for the mania or the heart block. We ultimately attributed the mania to LT_4, and the heart block to hypothyroidism.
Discussion
The temporal relationship between LT_4 intake and onset of mania, plus the lack of other findings on workup, suggest that the mania was probably LT_4-induced. The pathophysiology is thought to be related to abrupt augmentation of catecholamine receptor sensitivity. In the few available case reports, manic symptoms were found to manifest in as short as one day after LT_4 initiation and can likewise resolve the following day. While most cases occurred at higher LT_4 doses, they can also occur at low doses and with gradual dose titration. We gave the full replacement dose for our patient due to his young age, profound hypothyroidism complicated by heart block, and absence of co-morbidities. Our case is significant in the sense that it is the first report involving a double-edged sword: dealing with psychiatric disturbances from LT_4 administration at the same needing to urgently correct severe hypothyroidism with cardiac complications.
Conclusion
Although rare, LT_4 therapy can present with psychiatric disturbances. An exhaustive workup is needed to rule out other diagnoses, and the pros and cons of treatment should be weighed.

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EP389

Graves' orbitopathy- When the going gets tough… the tough get going?

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Introduction
Thyroid disorders are common within the elderly population and are particularly challenging to diagnose and treat due to the presence of a wide variety of comorbidities. Graves' ophtalmopathy remains a therapeutic predicament despite all progress made in understanding its pathogenesis, especially in the elderly population with severe presentation.
Case presentation
We present the case of a 71-years-old female patient who was admitted in our clinic for diplopia, decreased visual acuity, visual field amputation, dysphonia and thyroid enlargement. She was diagnosed with Graves' disease 2 years prior her admission and had been on block and replace treatment ever since. Her medical history includes: class III NYHA heart failure, metallic mitral valve replacement, permanent atrial fibrillation, severe tricuspid regurgitation and severe secondary pulmonary hypertension. Clinical examination revealed bilateral exophthalmia, eyelid edema, conjunctival hyperemia, convergent strabismus and a large, compressive goiter. Lab tests revealed iatrogenic hypothyroidism (TSH = 36.7 uIU/ml, $FT_4 < 0.30$ ng/ml, TT_3- = 104.3 ng/dl).The orbit CT scan and ophtalmological examination discovered bilateral hypertrophy of orbital rectus muscles, disthyroid optic neuropathy, paracentral scotoma, very low motility and corneal edema in both eyes. The cardiologic examination pointed out her high surgical risk considering the heart failure and severe pulmonary hypertension. The Methimazol dose was adjusted and over the next 4 months, under multidisciplinary surveillance, our patient received three courses of pulse therapy with low-dose methylprednisolone (375 mg over two courses and 250 mg/one course, cumulative dose 1 g), well tolerated, with slight improvement in visual field defects and visual acuity and amelioration of symptoms. Considering the severe ophtalmopathy and the cardiac pathology, the patient continues treatment with Methimazol.
Conclusion
Treating Graves' disease/orbitopathy can be challenging when having a severe presentation, especially in the geriatric population where associated pathologies, concomitant medication, treatment tolerance must be considered.

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EP390

A rare case: co-occurrence of aplastic anemia and high-risk thyroid papillary carcinoma

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Aplastic anemia is an idiopathic/idiosyncratic or hereditary bone marrow failure characterized by hypocellular bone marrow and pancytopenia without abnormal infiltration and increase in reticulin fibers. Papillary thyroid cancer (PTC) constitutes 85% of all differentiated thyroid cancers. There is no data on the application of radioactive iodine treatment for the treatment of high-risk differentiated thyroid carcinoma detected in the subjects with aplastic anemia.
A-60-year old male patient was referred to our clinic for pancytopenia detected on the examinations performed for ecchymosis on the skin. Physical examination revealed ecchymosis on the skin and cervical lymphadenopathies. Leukocyte: 2170 μl (4230–9000), hemoglobin: 6.4 gr/dl (13.7–17.5), thrombocyte: 12 000 μl (150 000–400 000). Bone marrow aspiration biopsy demonstrated hypocellular bone marrow. The patient with the initial diagnosis of aplastic anemia underwent neck US examination, which revealed a $28 \times 30 \times 32$ mm sized, expansile and heterogeneous nodule with lobulated margins, microcalcification and intranodular vascularisation on the upper part of the left thyroid lobe and multiple pathologic lymph nodes on the cervical region. The patient was in euthyroid state. PTC metastasis was detected on lymph node biopsy and the patient underwent total thyroidectomy and central and lateral lymph node dissection. Histopathologic examination revealed PTC tall cell variant, tumor size of 3 cm, extrathyroidal invasion and carcinoma metastasis in seven of 25 lymph nodes. The patient was diagnosed with aplastic anemia and high grade PTC; radioactive iodine treatment was delayed until the 6th month of aplastic anemia treatment after hematology and nuclear medicine department consultations and TSH suppression treatment was commenced.
In conclusion, high dose radioactive iodine treatment is known to cause bone marrow suppression. As in our case, since radioactive iodine treatment may deteriorate pancytopenia in the patients with severe aplastic anemia, multidisciplinary approach is required in the management of such particular cases.

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EP391

The importance of an intraoperative revision of all parathyroid glands, which may reveal additional pathologic changes and lead to an operation extension

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We present two case reports of patients who were diagnosed with hyperparathyroidism based on a parathyroid gland adenoma (PTA). The pathological parathyroid tissue was precisely localised by ultrasonography and scintigraphy before the surgery. In both cases all four parathyroid glands were revised by the surgeon resulting in an operation extension. Another parathyroid gland was removed and histologically confirmed as PTA. This surgeon's approach was beneficial for the patient and the operation procedure was therefore curative.
The first patient (male, 72 years old) was diagnosed with hyperparathyroidism in 10/2012. Ultrasonography showed a goiter with a solitary cystic nodule in the right lobe. Scintigraphy did not show any hyperfunctional parathyroid tissue. In the cystic fluid from the nodule we measured very high concentration of parathormone. Next sonography after the evacuation of the cystic fluid showed a typical hypoechoic right inferior PTA. The patient was recommended for a total thyroidectomy and extirpation of the right inferior PTA. After the operation in 2/2014 the pathologist surprisingly did not describe any parathyroid tissue within

or next to the right lobe of the thyroid gland. Moreover, the surgeon found left superior PTA that was confirmed histologically!
The second patient (female, 77 years old) was diagnosed with a hyperparathyroidism in 6/2015. Ultrasonography showed two suspicious hypoechoic nodules under the left lobe. Scintigraphy revealed two PTAs – right inferior and left superior. The patient was recommended for a surgery too. The surgeon unsurprisingly removed left superior PTA, but he had doubts about the right inferior parathyroid gland that was only partially respected and histologically confirmed as a normal tissue! Moreover, the surgeon removed right superior PTA (confirmed histologically)!
Those two case reports highlight the important role of an intraoperative revision of all parathyroid glands.

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EP392

Hypothyroidism as a cause of precocious puberty

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Introduction
Hypothyroidism is a rare cause of early puberty in childhood. It reduces the growth rate by decreasing the amplitude of GH pulses. We report the case of a child who developed precocious puberty and reduced speed consequent to hypothyroidism growth. The treatment of thyroid disease with levothyroxine led to regression of pubertal development and resumption of growth.
Methods
A.J.S., female, 1 year and 5 months of age at first consultation. She to came the endocrinology service in March 2011, complaining about bilateral breast enlargement since birth. Her mother reported pregnancy without complications. Cesarean delivery, birth weight and height were 48 cm and 3.3 kg, respectively. Breast feeding up to 10 months; no use of medications. Physical examination in 2011 showed Tanner M2 P1, genitals and thyroid gland without changes on physical examination, 11 kg weight and 80 cm in height (50–75 percentile).
Results
In 2011, TSH was 7.48 U/l, LH: <0.71 U/l, FSH: 4.1 U/l, Estradiol: 15 U/l. Breast ultrasound showed stromal gland stimulation. Pelvic US showed no change. Bone age was 18 months to 2 years. The conduct was to prescribe levothyroxine 50 μg/day. When she became 2 years and 6 months old she had a Tanner M2P2. TSH: 1.69 U/l, Free T_4: 33.6 U/l. Growth rate of 11.5 cm/year. She came back in January 2013, with Tanner M2P2. On April 2014: Weight: 17.6 kg and Height: 105 cm, Tanner M2P1. Bone age: 2 years old. Growth rate 04/2014 to 04/2015: 8.5 cm/year, the patient was euthyroid. January 2016 she was asymptomatic, in use of levothyroxine 75 μg/day, Tanner: M2P1, Height: 116 cm, Weight: 23.8 kg.
Discussion
Treatment of the thyroid disease led to regression of the pubertal development and reduction of growth velocity as a consequence of primary hypothyroidism. Thyroid dysfunction may be associated with Precocious puberty in the clinical practice, demanding a specific clinical approach.

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Diaphoresis and palpitation like first syntoms a tumor

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Introduction
Hypoglucemia is one of the most common endocrine symptoms and supposes a challenging in endocrine clinical practise. In most cases, are produced in relation with diabetes (drugs and diet). In other cases, there was an endogenous insulin production which cause the symptoms.
Clinical report
A 58-year-old was attended in the Emergency Department with episodes of lightheadedness, diaphoresis, palpitation, tremulousness for month duration. In that moment, her glucose level was 45 mg/dl. The patient was admitted in Endocrinology Unit for study. The patient had obesity, hypertension in treatment with three drugs, hypercholesterolemia, aortic root dilatation and sleep apnea syndrome. The most episodes were in the evening and during prolonged fasting. The symptoms were relieved with eating something (not special food) or taking glucose water orally. She had no family history of diabetes. Physical examination revealed an obese woman weighing 118 kg and with a body mass index of 43.7 kg/m^2. Hypoglycemic symptoms occurred by Prolonged fast test, simultaneously taken blood showed the glucose 49 mg/dl, plasma insulin 66.1 μUI/ml, insulin/glucose ratio was 1.34 with hypophysis-hypophysial hormonal analysis normal. CT scan showed at pancreas a nodular lesion of 35×27 mm in uncinate process, suggestive for insulinoma.
She was treated with 60 mg of oral prednisone and 100 mg diazoxide until surgery. A lesion resection was performed. The glucose and insulin levels were normal at postoperative period.
Conclusions
Insulinomas are rare pancreatic is let cell tumors with an incidence of 1 case per 250 000 person-years. Most insulinomas are sporadic and benign. The diagnosis of insulinoma is confirmed by high serum insulin concentrations during episode of hypoglucemia and surgical excision is the treatment of choice and is curative in most cases.

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EP394

Subacute thyroiditis during pregnancy

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Introduction
Hyperthyroidism during pregnancy is a rare condition and occurs in 0.1–0.4% of all pregnancies. Graves' Disease and transient gestational thyrotoxicosis constitute the majority of emerging thyrotoxicosis during pregnancy. Subacute thyroiditis (SAT) may also cause temporary hyperthyroidism.
Case report
A thirty-three-year-old, 13-week pregnant patients was admitted with fatigue, pain and swelling in thyroid lodge. Thyroid function tests performed two months ago were found to be in the normal range. On physical examination of the patient, there was no symptoms other than pain in the neck, and bilateral thyroid gland was large with tenderness. In the laboratory tests carried out at the patient's admission, TSH was: 0.17 (0.4–4.2) μu/ ml, fT4: 2.67 (0.65–1.7) ng/dl, fT3: 4.58 (2.5–3.9) pg/ml C-reactive protein (CRP): 5.27 (0–0.8) mg/dl, erythrocyte sedimentation rate (ESR): 41 mm/h, anti-thyroid peroxidase (anti-TPO): 3.54 (1–16) IU/ml, thyroid receptor antibody (TRAb): 3.88 (0–14) U/l, anti-thyroglobulin (anti-TG): 1715 (5–100) IU/ml, WBC: 9800 μl In the thyroid USG both lobes were large and parenchymal blood flow was not increased. There was a distinct view of bilateral subacute thyroiditis and reactive bilateral cervical lymphadenopathy. Paracetamol 3×500 mg was started because of the pain. The patient's pain was significantly decreased 3 days later. Clinical and laboratory findings in patient was compatible with SAT. 10 days later, pain and tenderness in the thyroid lodge was completely relieved. After repeated laboratory tests, 50 mcg of levothyroxine was instituted. With levothyroxine treatment, patient did not experience any problem during pregnancy and when she was 38 weeks and 2 days pregnant, vaginally delivered a healthy baby boy who weighs 3740 gr.
Conclusion
When determining the differential diagnosis of thyrotoxicosis in pregnancy, subacute thyroiditis should also be considered and detailed history and physical examination of the thyroid should not be neglected.

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EP395

A rare presentation of anaplastic thyroid carcinoma: spontaneous intrathyroidal hemorrhage

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Anaplastic thyroid carcinoma (ATC) is one of the most aggressive and lethal human malignancies. The median survival time following diagnosis is typically 6 months or less. Spontaneous thyroid haemorrhage may occur following an increase in venous pressure after Valsalva manoeuvre, hemodialysis session along with the use of heparin, trauma and in the patients with hypertension, especially in those with coagulopathy. Intrathyroidal hemorrhage may develop from a previous silent lesion as in the case of an ATC.
A 67-year-old woman presented with dysphagia and dyspnea of 1-month duration and a rapidly enlarging neck mass for the past 3 weeks. She had been suffering from toxic multinodular goiter disease. She was on methimazole 20 mg/day and propranolol 20 mg twice daily treatment for the last month. Physical examination revealed a large, ecchymosed and mildy tender thyroid mass. On neck ultrasonography, thyroid gland was slightly larger than normal with heterogeneous parenchyma and there were multiple, heterogeneous and hypoechoic nodules, the biggest one was being $28\times32\times35$ mm in size in the left thyroid lobe. Neck tomography revealed a $183\times68\times70$ mm sized malignant tumoral lesion? of left thyroid lobe, placing trachea anteriorly and to the right side, infiltrating esophagus and retrosternal area and having hemorrhagic component. In addition, 1.5 cm sized multiple necrotic lymph nodes were visible. Laryngoscopic examination demonstrated externally compressed trachea with normal mucosa, the esophagus was also narrowed by external compression on esophagoscopy. Blood coagulation profile was normal. Tru-cut biopsy of left thyroid lobe detected anaplastic carcinoma with rhabdoid giant cell formation. Since emergency surgical operation was not required, the patient was referred to the department of oncology for chemo-radiotherapy.
In conclusion, although it is rare, anaplastic carcinoma should be considered in the patients presenting with spontaneous intrathyroidal hemorrhage.

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EP396

Untreated hypothyreoidismus can lead to serious consequences in all organ systems

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Aim
To present a patient with all manifestations of long-term unsubstituted hypothyroidism-from alopecia to myxedema megacolon.
Case
sixty-one-old year women was admitted in ICU due to disturbance of consciousness, respiratory failure and electrolyte imbalance. Sopor, expressed alopecia, dry, flaky, pail skin, generalized edema, lung stasis and pericardial friction. A laboratory parameters pointed to the presence of normocytic normochromic anemia, hyponatremia, acidosis and hypoxia, and hormonal analyzes expressed in primary hypothyroidism. In the immunological findings of elevated double-spiral DNA. Visualization techniques proved the presence of pleural effusion and atelectasis of the left lung parenchyma, the presence of pericardial effusion, a small amount of fluid in the abdomen, as well as expressed enlarged and filled with air both flexure and transverse section of the colon, and multi chemical changes in white matter of the brain. The patient was intubated, applied mechanical ventilation. We started substitution with levothyroxine, diuretics, corticosteroids and other sympthomatic therapy. She was treated with enema various times, repeatedly performed bronchoscopy treatment on four occasions, and tracheotomy was made. The treatment led to an improvement in the sense of lowering the parameters of inflammation, improving the acid-base parameters and reexpansion of the lung parenchyma, and general condition of the patient was getting better.
Discussion and conclusion
The lack of treatment of hypothyroidism can lead to serious consequences in all organ systems. Since the autoimmune process has never antigen completely sensitive, there is a possibility of affection more target tissues in autoimmune process and mutually overlapping signs and symptoms of various autoimmune diseases. Elevated levels of double-spiral DNA in combination with the presence of and criteria indicate the presence of lupus disease.

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EP396B

Unusual ectopic thyroid

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Case
A 34-year-old, Saudi male, known case of hypothyroidism with coarse (potato) voice, referred for isotopic thyroid scan. After withdrawing the Eltroxin for one month, thyroid scan was done and showed abnormal uptake rounded in shape and appears bi-lobar, seen highly in the neck, at the midline, between both submandibular glands. No evidence of any uptake at the normal anatomical position of the thyroid gland. Ultrasound of the neck was done and showed large submental mass. Patient was referred for CT scan with contrast of the neck that showed large midline suprahyoid mass lesion, mildly calcified measuring $70\times54\times50$ mm, that showing heterogeneous enhancement post contrast. An ectopic goitrogenic lingual thyroid tissue was the first impression diagnosis; underlying malignancy cannot be totally excluded. Patient was referred for MRI of the neck four months later by his treating physician that showed no interval changes regarding the size and extension of the mass.
Unfortunately, there was no feedback from the treating physician. Only lately I was informed that the patient was operated and the large lingual mass was excised, and the pathology result came to be an abnormal thyroid tissue. Patient recovered his voice and obviously he is under Eltroxin treatment.
Discussion
The thyroid scan plays most important role in diagnosing thyroid ectopy.
Other X-ray modalities are contributing and mandatory in some cases.
Lingual thyroid is the most frequent location of ectopy.

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Developmental endocrinology

EP397

Cross-sex hormone therapy affects body fat distribution in transgender persons

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Introduction
Fat distribution is an important secondary sex characteristic, which is generally peripherally or pear-shaped (gynoid) in females and centrally or apple-shaped (android) in males. Total body fat increases in male-to-females (MtFs) and decreases in female-to-males (FtMs) during cross-sex hormone therapy (CSHT), approaching body fat amounts of the desired sex. However, changes in android or gynoid fat distribution might be a better measure for masculinization and feminization than changes in amount of body fat per se. As yet, the exact effects of CSHT on fat in the android- and gynoid region are unknown.
Aim
To investigate the effects of CSHT on android fat, gynoid fat and waist-hip ratio (WHR) in MtFs and FtMs.
Methods
This prospective study (ENIGI) included 108 patients that completed one year of CSHT. 51 MtFs received anti-androgens and estrogen therapy, while 57 FtMs were treated with androgens. At the start and after one year of CSHT anthropometrics were measured and a whole body DEXA was obtained, in which android fat and gynoid fat were measured.
Results
In MtFs an increase of gynoid fat was seen of $+0.8$ kg (0.6;1.1) from 3.3 to 4.1 kg. Android fat tended to increase with 0.1 kg (-0.02;0.3) from 1.6 to 1.7 kg, but WHR decreased with -0.02 (-0.001; -0.01) from 0.86 to 0.84. In FtMs, gynoid fat decreased with -0.6 kg (-0.4; -0.8) from 4.8 to 4.2 kg. Android fat and the WHR tended to increase with respectively 0.05 kg (-0.06;0.2) from 1.89 to 1.94 kg and 0.02 (-0.01;0.04) from 0.81 to 0.83.

Conclusion
Fat distribution in MtFs changed towards a more female-like fat distribution with an increase in gynoid fat and a trend towards a decreasing WHR. The opposite tended to occur in FtMs with a decrease in gynoid fat and an increase in android fat and WHR.

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EP398

Evaluation of the series of adults with inborn metabolic diseases followed in endocrinology in Andalusia (Spain)

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Objectives
The transition from the paediatric age to the adult is a particularly vulnerable period in patients with metabolic congenital diseases (mcd). In andalusia two adults' units exist (seville and malaga) for the follow-up of these patients. Our aim in this study was to evaluate the current series of attended patients.
Material and methods
We evaluated all patients transferred to the adult units since 2008. The clinical records were analyzed retrospectively.
Results
At present 149 adults with mcd (98 seville and 51 malaga) are evaluated. Aged (14–65) 71 women and 72 men. 92 phenylketonura (pku) (70 in seville and 22 in malaga). Benign hyperphenylalaninemia (1), fructosemia (4), galactosemia (4), glycogenosis: ia (2), ib (1), iii (2), trimethylaminuria (2), tyrosinemia type 1 (1), type 2 tyrosinemia (2), aciduria 3 oh 3 metilglutárica (2), propionic acidemia (pa) (1), methylmalonic acidemia (mma) (4), methylmalonic acidemia with homocystinuria (1), acidemia methylglutaconic (1) maple syrup urine disease (1) classical homocystinuria (deficit cbs): (4), metilen tetrahydrofolatoreductasa (mthfr) deficiency (3), alcaptonuria (2) otc deficiency (1), deficit succinyl coa (1), beta fatty acid oxidation deficiency (cpt1): (4), carnitine transporter deficiency (ctd) (4), methylcrotonylglycinuria: (4) xanthomatosis cerebrotendinous: (2) hiperamoniemic- hyperinsulinism syndrome (1), adrenoleukodystrophy (2) 9 were diagnosed in adults (1 alcaptonuria 1 adrenoleukodystrophy, 2 metylmalonic acidemia (mma): deficit cblc and cbla, 2 cerebrotendinous xanthomatosis, 3 deficit mthfr) 5 were diagnosed in adulthood as a result of neonatal screening for children (3 ctd and 2 methylcrotonylglycinuria) 17 pregnancies (12 pku, 2 homocystinuria, 2 pa,1 mma).
Conclusions
The majority pathology in our series is pku. The most patients come from pediatric follow-up the multidisciplinary, coordinated and individualized treatment is the guarantee for optimum care and quality of life in these patients. It is a challenge for endocrinology training and knowledge of these diseases.

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EP399

Scanning electron microscopy of adrenal gland after laser ablation

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Purpose
The study evaluated the effects of laser ablation of adrenal glands and results of regeneration using low-vacuum scanning electron microscopy for modeling the effects of laser ablation on pathological focus in the adrenal glands.
Methods/design
A study performed on the rats ($n=19$, male, Wistar line) with weighing 335.3 ± 24.9 g. At 14 of them (control 5 intact rat) under general anaesthetic was performed local laser ablation part of left adrenal gland. For damages used surgical laser apparatus "Lami" with standard options for parenchymatous organs: point action quartz with polyamide-coated optics with a diameter of 400 μm (wavelength-1020 nm radiation power-2.5 watts). Energy exposure amounted to 70 DJ. The adrenal glands were researched without the laser exposure, immediately after it and 1 month later.
Results
Immediately after exposure occurs laser ablation crater with rough edges and melted surface. It is penetrated by equidistant pores which are footprints of blood vessels. Beneath of the surface are numerous vaporization bubbles. Around the crater the surface wrinkles and sags due to decreased ability to retain water. Through 1 month after the laser damages in the affected area is determined by a scar. Among the big bundles of collagen fibers determined by amorphous chunks of coal and caverns. Tissues with normal structure are detected near to the scar, both inside of the adrenal gland and the tissues around her. The wrinkling and the sagging are absent. The undamaged part of organ has retained the previous shape and structure without hypertrophy, the damaged part the adrenal gland reduced.
Conclusion
The nature of the regeneration processes indicates a low probability of a relapse after the destruction of a pathological focus in the adrenal after the surgical laser ablation.

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EP400

Acute exercise training and circulating irisin in adult mens

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Context
Irisin is secreted by skeletal muscles into circulation and proposed to regulate energy homeostasis and hold therapeutic potential in diabetes and obesity.
Objective
The aim of this study was to evaluate the effects of acute exercise training (6 week) on circulating plasma irisin in adult mens.
Design and setting
This was a cross-sectional study conducted in a university hospital.
Participants
A total of 33 healthy, untrained male (mean age 19) participated in the study.
Main outcome measures
Plasma irisin, insulin, high sensitive CRP (hsCRP), fasting blood glucose and lipids were measured before and after 6 week exercise training. Body composition was calculated by Tanita body composition analyser.
Results
There was no significant correlation between lipids, insulin levels, fasting blood glucose with irisin levels. ($r=0.06$ $P=0.973$, $r=0.184$ $P=0.305$, $r=-0.009$ $P=0.959$). All the participants had unsignificant weight gain (before exercise BMI $=23.39 \pm 2.81$, after exercise BMI $=23.70 \pm 2.72$, $P=0.111$). Irisin levels positively correlated with hsCRP ($r=0.352$, $P=0.044$). Irisin level change with acute exercise training was not significant. ($P=0.458$).
Conclusion
Acute exercise training can change the irisin level in untrained males but it was unsignificant in this study. Maybe longer period of exercise can change the levels of irisin stronger. We find that after the training program, all participiants irisin levels decreased. Untrained person response times to the exercise can be slower than trained persons.

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EP400B

Mouse paternal-RNAs initiate pattern of metabolic disorders in a strain dependent manner

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Several instances of RNA-mediated inheritance of phenotypic variation have been reported, among them metabolic disorders. We and others have observed

that microinjection into naive fertilized mouse eggs of total sperm RNAs of obese and diabetic males maintained on high-fat diet induce the same pathological variation in the offspring. A role of noncoding RNAs is currently the prevailing hypothesis.
The sperm RNA content is complex. It depends on environmental conditions, but another level of variability is illustrated by the distinct pathological features reported by different groups, a variability that we tentatively attributed to the use of different inbred strains. We investigated the effect of different genotypes on the response to high-fat diet and its transgenerational maintenance. To that purpose, we maintained in the same housing and diet conditions mice of two inbred strains, C57BL/6 and Balb/c and B6/D2 F1 hybrids. From F0 males raised on high-fat diet we derived three generations by sexual mating (F0, F1 and F2) and two generations (G1 and G2) by microinjection into fertilized mouse eggs (Balb/c) of sperm RNAs of different founders. All mice other than the F0 males were maintained on a normal diet and followed for body weights and metabolic health up to 22 weeks. We observed very little difference among founders of the three genotypes fed on high fat diet. During this period strain dependant difference of gain of weight are observed. Variations in body weight were noticeable in the F1 and perpetuated to F2 generation (follow-up so far). Glucose and insulin tolerance tests evidenced a pathology prominent in founder animals and showed stronger differences in a strain dependent manner in generations F1 and F2. These results suggests that the initial signals that program offspring health are differentially perceived in the germ line of the different genotypes and start a genetic anticipation process. Furthermore, strain dependent phenotypic variations of the disease spectrum (GTT and ITT) are transferable by microinjection into fertilized eggs (Balb/c) of total sperm RNAs from C57/BL6, B6/D2 and Balb/c males. Together, these findings uncover a novel area of RNA-mediated epigenetic hereditary variation. Work is still in progress, up-dated results will be presented in the meeting.

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EP402

Calbindin-D9k in hypoxia-induced diabetes mellitus like model

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It has been proposed that cellular Ca^{2+} signals activate hormone secretion. In pancreatic β cells, which produce insulin, Ca^{2+} signals have been known to contribute to insulin secretion. Prior to this study, we confirmed that Calbindin-D9k (CaBP-9k) was responsible for regulation of the distribution of free calcium in the cytoplasm. We also confirmed that insulin-secreting β cells express CaBP-9k, and assumed that CaBP-9k play a role in β cell insulin synthesis or secretion. Using CaBP-9k knock out (KO) mice, we demonstrated that ablation of CaBP-9k causes type 1 diabetes by reducing insulin secretion and increasing serum glucose. To compare the role of CaBP-9k with type 2 diabetes pathophysiological conditions, we exposed wt and CaBP-9k KO mice to hypoxic conditions for 10 days.
Results
Hypoxia induced endoplasmic reticulum (ER) stress, increasing both insulin signaling and insulin resistance. By exposing hypoxia, CaBP-9k KO mice showed an increased level of ER stress marker protein relative to wild type mice. Without hypoxic conditions, CaBP-9K ablation regulates calcium channels and causes ER stress in a CaBP-9K specific manner. Ablation of CaBP-9k also showed decreased levels of sulfonylurea receptor1 (SUR1) and inward-rectifier potassium ion channel 6.2 (Kir6.2), which are insulin secretion marker genes. Overall, the results of the present study demonstrated that CaBP-9k regulates synthesis of insulin and is part of the insulin-secreting calcium signaling. Therefore, impaired CaBP-9K signaling may be linked with diabetes mellitus and CaBP-9K protein is as a potential candidate for gene therapy of type 1 diabetes.

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Diabetes (to include epidemiology, pathophysiology)

EP401

Co-inheritance of PAX4 and BLK Mutations (MODY 7 and 9) in an 38-year-old African patient with ketosis-prone diabetes

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Introduction
Ketosis-prone diabetes (KPD) is an emerging and uncommon form of diabetes characterized by patients who present with diabetic ketoacidosis without any immunological autoantibody to islet antigens of classic type 1 diabetes. KPD is mostly observed in African-American populations. Multiple, severe forms of β-cell dysfunction appear to underlie the pathophysiology of KPD. The *PAX4* gene, causing Maturity-onset diabetes of the young (MODY) subtype 9, already has been associated with ketosis-prone diabetes.
Case report
A case report of a 38-year old male African patient with co-inheritance of PAX4 and BLK mutations (MODY 7 and 9) as a cause of ketosis prone diabetes is presented to illustrate the clinical manifestations and difficulties in management. The patient was hospitalized as an emergency with metabolic acidosis, partial respiratory compensation with hypocapnia and initial renal failure. Under intensive medical therapy the metabolic situation could be normalized. MODY genes type 1–11 were analyzed.
DNA-Sequencing revealed two mutations: *PAX4* gene, exon 1, PAX4,c.109C>T,p.(Arg37Trp); reference sequence NM_006193.2) and *BLK* gene exon 5, BLK,c.335T>C, p.(Phe112Ser); reference sequence NM_001715.2). The amino acid position 37 in the *PAX4* gene is located in an evolutionarily highly conserved sequence motif across many species boundaries and the amino acid position 112 in the *BLK* gene is located in the functional SH3-domain of the BLK protein. We describe clinical, biochemical and genetic features of the patient.
Conclusions
Identification of the underlying genetic causes of KPD will give a better view of the mechanisms that contribute to the pathophysiology of the disease. Furthermore, proper identification may improve options to prevent KPD.
The results of the genetic analysis are discussed in the context of the clinical findings.

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EP403

Prevalence of diabetes mellitus in patients with hypercortisolism

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Background
Early carbohydrate metabolism disorders (ECMDs) and diabetes mellitus (DM) are frequently associated with endogenous hypercortisolism (EG). Prevalence of secondary (sDM) in these cases are poorly investigated.
Aim
We aimed to assess the prevalence of ECMDs and DM in patients with EG (pituitary-dependent Cushing disease (CD)) and adrenal-dependent Cushing (AC) and ACTH-ectopic syndrome (ACTHs) depending on gender and age.
Patients and methods
Forty-two patients with hypercortisolism (CD – 32 patients, AC – 7 patients, ACTHs – 3 patients), (five men, 37 women; 42.0 (33.7–49.2) years, estimated duration of EG – 36.0 (24–70) month) were observed.
OGTT was done in those not yet diagnosed with DM to reveal asymptomatic DM or ECMDs. Comparisons were made between patients with hypercortisolism and participants from the general adult population (GP) ($n=838$) and an adult population with multiple type 2 diabetes risk factors (HR group) ($n=604$), matched for age and BMI.
Results
DM was diagnosed in 26 patients with EG (62%) and in 75 (8.9%) of the general population ($P<0.001$). The prevalence of ECMDs was comparable in patients with hypercortisolism (17%) and in the GP (15.2%) and in the HR group (23.7%); only 21% of patients with EG were normoglycaemic. The prevalence of newly diagnosed DM was more than two times higher in patients with EG compared with the HR group (38.1 and 16.1% accordingly, $P<0.05$).
The prevalence of DM in women from EG group was 1.5 times higher, than in men (64.8 and 40%, $P<0.05$), among their newly diagnosed DM was two times higher than in men (40 and 20%, $P<0.05$). The prevalence of DM increased with age (from 57% (in those younger than 45 years) to 88% (older than 55 years), ($P<0.05$).

Conclusion
In patients with hypercortisolism, the prevalence of DM and ECMDs considerably exceeds that of the general population and of a high-risk group.

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EP404

Alpha lipoic acid attenuates high fructose induced pancreatic toxicity

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Objectives
Chronic consumption of high fructose corn syrup (HFCS) causes several problems like insulin resistance. The goal of the study was to investigate pancreatic damages induced by chronic HFCS consumption and protective effects of alpha-lipoic acid (ALA) on pancreatic cells.
Methods
Wistar Albino, 4 months old, female rats and weighing 250–300 g were randomly distributed into three groups each containing eight rats. Groups were HFCS group, HFCS + ALA administered group and control group (CON). The prepared 30% solution of HFCS (F30) (24% fructose, 28% dextrose) was given in drinking water for 10 weeks. ALA treatment started 4 weeks later to first HFCS administration (100 mg/kg per oral, last 6 weeks). Rats were anesthetized and euthanized by cervical dislocation 24 h after the last ALA administration. Blood samples for biochemical (Amylase, Lipase, MDA, CAT) and tissue samples for histopathological and immunohistochemical examinations (Caspase-3, insulin and glucagon) were collected.
Results
Comparing the control and HFCS groups; serum glucose (150.92 ± 39.77 and 236.50 ± 18.28 respectively, $P < 0.05$), amylase (2165.00 ± 150.76 and 3027.66 ± 729.19 respectively, $P < 0.01$), lipase (5.58 ± 2.22 and 11.51 ± 2.74 respectively, $P < 0.01$) and pancreatic tissue MDA (0.0167 ± 0.004 and 0.0193 ± 0.006; respectively, $P < 0.05$) levels were increased while tissue CAT (0.0924 ± 0.029 and 0.0359 ± 0.023 respectively, $P < 0.05$) activity decreased in HFCS group significantly. Histopathological examination revealed degenerative and necrotic changes in Langerhans islet cells, slight inflammatory cell infiltration in pancreatic tissue in HFCF group. Immunohistochemically significantly decrease in insulin (2.85 ± 0.37 and 0.87 ± 0.64 respectively, $P < 0.001$) and glucagon (2.71 ± 0.48 and 1.00 ± 0.75 respectively, $P < 0.001$) secreted cell while increase in caspase-3 (0.14 ± 0.37 and 1.00 ± 0.75 respectively, $P < 0.05$) expression were seen in this group compared the controls. In ALA treated group all of these pathologic conditions were improved.
Conclusions
This study indicated that HFCS induced pancreatic lesions but ALA has ameliorative effects.

Keywords: High fructose corn syrup, oxidative stress, pancreas pathology, alpha lipoic acid

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EP405

A novel E108D mutation of AVP-NPII gene in a Turkish patient with central diabetes insipidus

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Familial central or neurohypophyseal diabetes insipidus (FNDI) results from insufficient production of antidiuretic hormone arginine vasopressin, which is caused by mutations in arginine vasopressin-neurophysin II gene (AVP-NPII). In this study, we present the clinical features of a male Turkish patient with autosomal dominant neurohypophyseal DI caused by a novel mutation (p.E108D). The prospective clinical data were collected for the proband patient and his family members. The patient had severe polyuria (10.9 l/day), polydipsia (12 l/day), fatique, and deep thirstiness from his infancy. While being performed water deprivation test, diagnosis of central diabetes insipidus was confirmed according to increase in urine osmolality from 139 to 431 mOsm/kg after desmopressin acetate injection. Some of family members of this patient had severe polyuria, nocturia, polydipsia, fatigue as well. The genomic DNA of the proband and the other family members were isolated and the amplification of the AVP-NPII gene was carried out with polymerase chain reaction. We were sequenced all exons and intron-exon boundaries of the gene. We detected a novel heterozygous missense mutation at codon 108, which causes the the substitution of Glu (GAG) by a Asp (GAT) in exon 3. A three-dimensional protein structure prediction was shown for the mutant AVP-NPII protein and compared with the wt. In our future studies we are planning to do functional analyses studies for understanding the function of the p.E108D mutation.

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EP406

Decreasing betatrophin levels during pregnancy in healthy women

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Introduction and aims
To date we have had some evidence that betatrophin is associated with insulin resistance. Some studies have demonstrated that betatrophin levels are elevated in type 2 diabetes, obesity and gestational diabetes. It has been shown that in mice betatrophin significantly improves beta cell function and glucose tolerance. This is the first study on betatrophin in which pregnant women were observed during all trimesters and in postpartum period to evaluate its role in increasing insulin resistance and physiological proliferation of beta cells.
Materials and methods
We examined 80 healthy pregnant women in each trimester (T1, T2, T3). Forty-five of them were additionally examined at 3MPP. We also examined 30 non-pregnant women of reproductive age without obesity as the control group. We measured betatrophin levels (ELISA), glucose (enzymatic method with hexokinase), insulin (immunoradiometric method), C-peptide (enzyme amplified sensitivity immunoassay), HbA1c (HPLC). We calculated HOMA-IR and HOMA%β. The oral glucose tolerance test was performed in T2 and 3MPP.
Results
In T1 betatrophin level was highest and it significantly differed from T2 and T3 (1.84 ± 1.51 ng/ml vs 1.46 ± 1.25 ng/ml, $P < 0.05$; 1.84 ± 1.51 ng/ml vs 1.23 ± 1.29 ng/ml, $P < 0.01$; respectively). In T3 median value of betatrophin reached lowest level and we observed significant difference with 3MPP (1.23 ± 1.29 ng/ml vs 1.49 ± 1.54 ng/ml, $P < 0.01$). In 3MPP betatrophin level was similar to the control group (1.49 ± 1.54 vs 1.47 ± 1.78). HOMA-IR and HOMA%β increased during the course of gestation. It reached a peak in T3 (2.3 ± 1.06; 227.7 ± 140.8, respectively) and returned to the healthy control values (1.53 ± 1.3; 88.86 ± 68, respectively) at 3MPP (1.35 ± 0.6; 92.5 ± 37.3, respectively). Data are shown as median and interquartile range.
Conclusions
Decreasing betatrophin concentration during pregnancy despite the physiological proliferation of beta cells throughout gestation can suggest that betatrophin plays an insignificant role in the expansion of beta cell mass and insulin resistant during pregnancy. Further studies are needed to establish what factors impact on betatrophin levels during each trimester of pregnancy.

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EP407

A rare form of pancreatic diabetes: a 25 year-follow-up

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Introduction
Fibrocalculous pancreatic diabetes is an uncommon type of diabetes mellitus due to chronic calcific non-alcoholic pancreatitis. It is associated to several particularities based on glycemic control and the occurrence of degenerative and metabolic complications, in addition to chronic pancreatitis complications.
Observation
A 17-year-old male, with no familial history of diabetes and no alcohol consumption, was hospitalized in 1989 for ketone prone diabetes. He has reported abdominal pain for about 2 years, in a chronic and relapsing mode associated with progressive weight loss. Physical examination revealed no particularities. Biologic investigation has shown a raised random blood glycemia level. The urinalysis showed massive glycosuria and ketonuria. The abdominal X-ray showed multiple pancreatic calcifications. The 25-year follow-up showed a difficulty to obtain a good glycemic control despite of a good treatment adherence. Improvement of glycemic control was obtained by the use of insulin analogues. No diabetic ketoacidosis has occurred during the evolution. Diabetic retinopathy has been diagnosed and treated after 10 year-duration of DM. In 2009, acute pancreatitis with worsening signs of malabsorption was documented. Abdominal computed tomography scans revealed chronic calcifiant pancreatitis with porto-spleno-mesenteric venous thrombosis. No pancreatic tumor was found. The etiologic exploration of thrombosis revealed a resistance of activated protein C. The patient was hence treated by pancreatic enzyme granules and a lifelong anti coagulation therapy. The last biologic control showed an improved glycemic control without any malabsorption sign. Abdominal CT showed a complete involution of pancreas and a portal cavernoma.
Conclusion
This case presentation highlights how important is to suspect fibrocalculous pancreatic diabetes especially in the presence of chronic abdominal pain. The follow-up of such patients should be focused not only on diabetes clinical and biological markers, but also on pancreatitis complications.

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EP408

Two neonatal diabetes cases with different mutations and treatments

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Neonatal diabetes, is monogenic and can be due to different mutations. Here we report two patients with neoanatal diabetes, with two different mutations and treatments.
Case 1 was a female infant of consanguineous parents born at 37 weeks of gestation with a birth weight of 1900 g. After birth she was followed for respiratory distress and hyperglycemia. Her blood glucose was controlled with glargine insulin and with rapid acting insulin when needed. Her physical examination was normal except hip dysplasia. A homoxygous g.23508363A > G mutation was identified which is predicted to result in decreased PTF1A expression during pancreatic development.
Case 2 was a male infant of nonconsanguineous parents born at 35 weeks of gestation with a birth weight of 3400 g. After birth he was followed for seizures and hyperglycemia. He had hypotonia and decreased muscle strength. Glargine insulin was started with Humalog insulin when needed. His convulsions continued unrelated with his blood glucose levels. A heterozygous previosly reported *KCNJ11* missense mutation, p.C166Y was identified which is predicted to affect the Kir6.2 subunit of the KATP channel. Glibenclamid belonging to sulfanylurea group was started. In the follow up his glibenclamid dose was increased while insulin dose was decreased. With this treatment regimen his blood sugar levels were controlled and although not very significant a relative improvement in his neurological status was observed.
In neonatal diabetes, genetic analysis is relevant, regarding to the mutation, treatment and prognosis can be determined.

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EP409

Functional analysis of G12E mutation of AVPR2 gene in Turkish patients with diabetes insipidus

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Diabetes insipidus (DI) is a rare disorder which is characterized with inability to concentrate urine because of severe liquid-balance impairment. Mutations in AVPR2 gene is one of the causes of DI. AVPR2 is a G protein coupled receptor (GPCR) and its specific agonist is arginine vasopressin (AVP). When AVP binds to the AVPR2, which locates on the basolateral side of collecting duct principal cells of the kidney, it triggers accumulation of cAMP in the cell as a seconder messenger. If AVPR2 has a mutation, receptor could loose its function which is important for liquid balance of the body. The aim of this study is making functional characterization of G12E mutation of AVPR2 gene. G12E mutation was seen in three cases in our study. Functional characterization of this mutant is important for the therapeutic studies. G12E mutation was generated by site-directed mutagenesis strategy. For this purpose, pLV2R (a mammalian expression vector) was used and the mutant construct was checked with DNA sequencing. Totally expression in the cell and cell surface expression of the mutant receptor was analyzed with ELISA experiments. In addition to this, cAMP accumulation assay was performed after stimulation of mutant receptor with different concentrations of AVP. According to the ELISA results, G12E mutation showed reduced expression in total and also on cell surface. The results of cAMP accumulation assay supported our ELISA results. Mutant receptor showed reduced E_{max} and it also has a shift for EC_{50} value according to the wild type receptor. In conclusion, *in vitro* studies revealed that this mutation yields partial expression in the cell surface.

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EP410

Prevalence of biochemical hypoglycaemia in everyday practice

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Oral glucose tolerance test (OGTT) is the main tool in population based screening for type 2 diabetes mellitus. Sometimes OGTT results are showing asymptomatic lowering of post-load blood glucose. Post-load plasma glucose (2hPG) level 3.9 mmol/l (70 mg/dl) and lower shows biochemical hypoglycaemia. Biochemical hypoglycaemia might be observed among individuals with abnormal glucose tolerance and in healthy population. The objective of the investigation was to assess a prevalence of biochemical hypoglycaemia during OGTT in routine outpatient practice.
Material and methods
We conducted an audit of 75 g standardized OGTT performed at Vilnius Antakalnio outpatient clinic from 3 January 2011 to 15 December 2014 and analysed data of 5575 adult patients. We applied 2006 WHO criteria for impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes. Patients with biochemical hypoglycaemia during OGTT, and with normal glucose tolerance (NGT) or IFG were compared using Student *t*-test.
Results
Mean patients' age was 53.64 ± 15.59 years (36.4% male and 63.6% female). Mean FPG was 5.87 ± 0.65 mmol/l, mean 2hPG was 6.20 ± 2.25 mmol/l. OGTT detected IFG in 1518 (27.2%), IGT in 778 (14.0%), diabetes in 286 (5.1%) patients. NGT was found in 2993 patients. Total 760 patients (13.6%) had biochemical hypoglycaemia: 547 (18.3%) patients with NGT and 213 (14.0%) patients with IFG. Within NGT group patients having biochemical hypoglycaemia were younger by 5.02 years ($P < 0.0001$) and had lower level of FPG by 0.07 mmol/l ($P = 0.001$) than those who did not present biochemical hypoglycaemia. Males experienced biochemical hypoglycaemia more frequently than women (24.4% vs 15.5%, $P < 0.0001$). Within IFG group patients with biochemical hypoglycaemia were younger by 3.61 years ($P < 0.0001$) and had lower level of FPG by 0.09 mmol/l ($P < 0.0001$) than those who did not present biochemical hypoglycaemia.

Conclusion
Prevalence of biochemical hypoglycaemia is about 14%. Biochemical hypoglycaemia is associated with younger age, male gender and lower fasting plasma glucose level.

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EP411

Inpatient glycaemic variability and long-term mortality: a neglected diabetic parameter?

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Aim
To determine the association between recorded inpatient glycaemic variability and long-term mortality in patients with diabetes mellitus.
Methods
Inpatient capillary blood glucose (CBG) readings from eight acute hospitals were included. Data was analysed from first admission within the dataset with >4 measured CBGs. 28 353 admissions were identified (24 181 type 2 DM, 4,172 type 1 DM). Matching parameters were: age, diabetes duration, admission duration, median CBG and interquartile range of CBG values. Mortality analysis was performed from 90 days post discharge over five years, investigating 1) those with CBG IQR in the top half of all IQR measurements (matched for all except IQR), vs those in the lower half and 2) those with the lowest quartile median glucose (matched for all except median).
Results
1) Glycaemic variability: 3099 matched pairs. Total mortality over the period of analysis: 31.2% (high IQR) vs 26.5% (low IQR) ($P<0.001$, HR 1.22 – Cox proportional hazard model of survival analysis). 2) Median glucose: 4177 matched pairs. Total mortality over the period of analysis: 32.4% (lowest quartile median glucose) vs 26.1% (top 3 quartiles median glucose) ($P<0.001$, HR 1.25 – Cox proportional hazard model of survival analysis).
Conclusion
Higher inpatient glycaemic variability is strongly associated with increased long-term mortality. With cohort IQR matching, lower median CBG is associated with higher long-term mortality. CBG variability may increase risk by increasing hypoglycaemia exposure. This will occur more frequently for any given variability level at lower median CBG. Variability *per se* has also been postulated to increase oxidative stress. This may act synergistically with hypoglycaemia increasing cardiovascular morbidity.
Glycaemic targets and treatment modalities for inpatients with diabetes should primarily aim to minimise glycaemic variability. Where greater CBG variability is unavoidable a less stringent CBG target should be considered.

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EP412

Reduction of autoimmune regulator Aire mRNA and number of Treg-cells in mesenteric lymph nodes in the offspring of rats with experimental gestational diabetes

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Introduction
Formation of immunological tolerance to self antigens is an important mechanism that prevents the development of autoimmune diseases.
Methods
With the help of molecular genetic and immunofluorescence techniques we investigated the effects of experimental gestational diabetes (EGD) on the level of mRNA expression of autoimmune regulator Aire and differentiation features of $Foxp3^+$ cells in mesenteric lymph nodes in the offspring of Wistar rats. To determine the level of Aire mRNA was performed RT-PCR in real-time by thermocycler CFX96 Real-Time PCR Detection Systems. The relative level of gene expression were studied with rat reference genes GAPDH by the method ΔΔCt. Statistical analysis were conducted using available software 'Bio-Rad CFX Manager 3.1' (Bio-Rad, USA). The immunopositive Foxp3+-lymphocytes were determined using an indirect immunofluorescence technique with using a monoclonal rat antibody.
Results
The offspring of EGD rats showed a reduction of autoimmune regulator Aire mRNA in 2,3-8,1 times ($P<0.05$) in MLN cells compared to control animals. The observed decrease in the transcriptional activity of Aire is accompanied by reduction in the number of regulatory $Foxp3^+$ lymphocytes in MLN in the offspring of rats with EHD, as well as reduction of concentration of the transcription factor Foxp3 in lymphocytes of cortical plateau.
Conclusions
The revealed changes evidence of abuse of formation of peripheral immunological tolerance and can trigger the development of AID in the offspring of mothers with EHD.

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Oral disposition index as a predictor of changes in glucose tolerance status over time

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Introduction
Type 2 diabetes (DM) is characterized by both insulin resistance and β-cell dysfunction. The oral disposition index (DIo), a measurement of β-cell function and insulin sensitivity, is considered the best predictor of progression to a worse GTS, although it was not well tested for regression to a better GTS.
Objectives
To assess the validity of DIo and determine whether DIo predicts regression to a better GTS.
Methods
At first evaluation of a longitudinal study, patients from an outpatient clinic ($n=103$; 54.8 ± 11.4 years; females 69.9%) were submitted to a 75-g OGTT and classified according to different degrees of glucose tolerance in (PDM ($n=49$) and DM ($n=54$)). Insulin sensitivity was estimated as 1/fasting insulin and β-cell function as the ratio of the change in insulin to the change in glucose from 0 to 30 (ΔI0–30/ΔG0–30). The DIo was calculated as (ΔI0–30/ΔG0–30 × 1/fasting insulin). Patients were followed-up by 25 (15–38) months (median (P25–P75)) and their data were recollected. Patients were classified as regressors and non-regressors to a better GTS.
Results
ΔI0–30/ΔG0–30 demonstrated a curvilinear relationship with 1/fasting insulin. The confidence limits for the slope of the log-transformed estimates included -1 for DIo for regressors and non-regressors, consistent with a hyperbolic relationship. While at follow-up 22.2 and 38.9% of patients with DM respectively regressed to NGT and PDM, 26.5% of patients with PDM regressed to NGT and 14.3% progressed to DM.
Conclusion
A total of 44.7% of patients regressed to a better glucose tolerance status while participating in a program with multiple interventions for the treatment of hyperglycemia. Although the DIo was not able to predict these changes, a composite measure of β-cell function was proved to be reproducible and could be applied for DM research in the Brazilian population.

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High prevalence of diabetes and pre-diabetes in psychiatry inpatients

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Objective
To determine the prevalence and characteristics of psychiatry inpatients with type 2 diabetes and pre-diabetes, compared to psychiatry inpatients without diabetes.
Research design and methods
Inpatients aged >30 years at the Austin psychiatry unit (February 2014–April 2015) had HbA1c measurements as part of the Diabetes Discovery Initiative. Patients were divided into three groups – diabetes (HbA1c ≥6.5%, 48 mmol/mol), pre-diabetes (HbA1c 5.7–6.4%, 39 mmol/mol-46 mmol/mol) and no diabetes (HbA1c ≤ 5.6%, 38 mmol/mol). Data on baseline characteristics, co-morbidities, psychiatric illnesses and treatment were collected.
Results
Of 335 psychiatry inpatients (median age 41 years) 14% ($n=46$) had diabetes and 19% ($n=63$) had pre-diabetes, more than threefold higher than the aged matched general population. The most prevalent diagnoses were schizophrenia, depression and substance abuse. Approximately 50% of inpatients were on atypical antipsychotics or anti-depressants. Compared to inpatients without diabetes, those with diabetes and pre-diabetes were older (median age 49 and 46 vs 40, $P=<0.001$). Patients with diabetes compared to those without diabetes were at least twice as likely to have hypertension, obesity and hyperlipidaemia (all $P\leq0.002$). Multivariable analysis revealed the main significant variables associated with diabetes to be age ($P=0.02$), substance abuse ($P=0.04$), hyperlipidemia ($P=0.03$) and aripiprazole use ($P=0.01$).
Conclusions
Despite relative youth, one third of all psychiatric inpatients have diabetes or pre-diabetes. Presence of diabetes in psychiatric inpatients is associated with older age and substance abuse. The management of glycaemic status in psychiatric inpatients following discharge is difficult and hence routine HbA1c measurement as an inpatient presents an opportunity to address glycaemic management.

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Twenty-four hour blood pressure monitoring in women with gestacional diabetes mellitus

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Gestational diabetes mellitus (GDM) is associated with an increased risk of pregnancy-induced hypertension (PIH). Ambulatory blood pressure monitoring (ABPM) has been used to screen for PIH and preeclampsia in normotensive type 1 diabetic women. To date, there are no data regarding ABPM in women with GDM. The aim of the study was to establish blood pressure (BP) profiles for pregnant with GDM, using ABPM and determine whether a BP pattern can define a population at risk for developing PIH. We analysed the relation between BP profiles and baseline characteristics, metabolic parameters, obstetrics and perinatal complications. We prospectively studied 62 women with GDM recruited at 26–32 weeks of pregnancy. ABPM was carried out for one 24-h period using the SPACELABS 90207 ABP monitor. Four groups based on nocturnal fall pattern: dippers, non-dippers, extreme dippers, and risers. The mean age 34±4.4 years, BMI 27 kg/m^2 and HbA_{1C} 5.05%. Forty-five percent had a family history of Type 2 Diabetes; and 33.9% of high BP. The mean systolic/diastolic BP was 107.9/65.7 mmHg. By ABPM, 20 (41.7%) patients were pattern dippers, 2 (4.2%) extreme dippers, 20 (41.7%) non-dippers, and 6 (12.5%) risers. Comparing dipper/non-dippers groups, 24 h microalbuminuria excretion was significantly higher in the dipper group (0.56 vs 2.03 ng/ml, $P<0.05$). We observed higher levels of night-time diastolic BP in non-dippers (62.9 vs 56.4 mmHg). Fifty-one women delivered to date, 5.8% had preeclampsia and 7.8% PIH. Caesarean delivery in 25% of women and 17.6% macrosomia, without significant differences between groups. We concluded that a higher rate of the non-dippers pattern were observed in women with GDM and it seems to be associated with other factors, such as 24 h microalbuminuria excretion. Thus, higher levels of night-time systolic/diastolic BP could be a useful predictor of PIH. Further studies will be needed to determine the relationships between BP alterations and baseline, metabolic characteristics and obstetrics/perinatal outcomes.

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EP416

Differences in the risk factors associated with diabetic retinopathy between type 1 and type 2 diabetes mellitus

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Introduction
The aim of the study was to examine the risk factors associated with diabetic retinopathy (DR) in adult patients with DM1 and DM2.
Design
The study group consisted of adults patients with DM1 and DM2, diagnosed according to the WHO criteria. Risk factors for diabetic retinopathy were evaluated on the demographic data, medical history, clinical and biochemical parameters related to metabolic control of diabetes. We collected also ophthalmic anamnesis: ophthalmic examination and the presence of diabetic eye complications before inclusion to the study. Statistical analysis was performed using the statistical package STATISTICA 10 GB and econometric program GRETL 1.9.9 cvs.
Results
We examined 1209 patients, age 54.9 (15.79) years, 315 (26%) DM1, age 37.0 (13.55) years, duration of diabetes 11.0 (8.60) years, and 894 (74%) DM2, age 61.2 (11.13) years, duration of the diabetes 10.5 (8.09) years. Patients were treated by Diabetologists (39%) and GP (61%). 42% were inhabitants of large cities, 28% small and medium cities and 26% from rural areas. HbA1c was significantly higher in DM1 8.44 (2.02)% vs. DM2 7.84 (1.67)%. DM1 patients were characterized by hyperfiltration and albuminuria. In DM2 albuminuria and low GFR were observed. Model of the logistic regression indicated following risk factors for DR: duration of diabetes, HbA1c, albumin/creatinine ratio, GFR, smoking and model therapy of DM.
Conclusions
1) We found differences in the risk factors associated with DR between DM1 and DM2. 2) Risk factors for DR in the DM1: duration of DM, HbA1c, G1 stage of diabetic nephropathy, smoking. 3) Risk factors for DR in DM2: duration of DM, HbA1c, G2 stage of diabetic nephropathy, smoking, late introduction of insulin therapy in the management of hyperglycemia.

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EP417

Abstract withdrawn.

EP418

MiRNA-binding site polymorphisms of MODY genes associated with lipid profiles in Chinese patients with gestational diabetes mellitus

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Objective
Both MODY and GDM are characterized by pancreatic beta cell dysfunction. The study aimed to first investigate the associations between miR-SNPs of *HNF4A*, *HNF1A* and *HNF1B* genes and the GDM susceptibility and lipid profiles.
Methods
The software PolymiRTS were used to screen miR-SNPs. Genotyping of SNPs was performed with TaqMan allelic discrimination assays in 839 GDM patients and 900 controls. Multivariable logistic regression analysis and multiple linear regression adjusted for age were used to analyze the association.

Results
A total of three miR-SNPs rs6130615 (T/C, HNF4A), rs1169309 (T/G, HNF1A) and rs2688 (C/A, HNF1B) were selected, and the SNPs were located in miR-130a, miR-19a and miR-96 binding site respectively. The rs6130615, rs1169309 and rs2688 were not associated with GDM in Chinese Han women ($P>0.05$). We observed HNF1A rs1169309 genotype TT exhibited increased total cholesterol and LDL-c levels compared with wild genotype GG ($P=0.003$ and $P=0.031$). After adjustment for age and pre-BMI, the minor allele T rs1169309 SNP was found to be positively associated with total cholesterol ($P<0.001$) and LDL-c levels ($P=0.010$). We also found rs1169309 genotype TT+CT exhibited higher ApoA1 levels ($P=0.029$), and rs6130615 genotype TT carriers had higher ApoA1 levels than CT+CC carriers.

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Association between 25-hydroxyvitamin D levels and diabetes

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Introduction
A significant body of literature supports that 25(OH)vitD deficiency is associated with insulin resistance. We studied the prevalence of 25(OH)vitD deficiency across the spectrum of glucose metabolism.
Design
The study participants (441 total, 362 females (82.1%) and 79 males (17.9%)) had a mean age (±S.D.) of 64.59 (±9.44) years, range: 32–92 years. The study population was divided into two groups: Individuals with diabetes ($n=184$, 33 males), and controls with normal glucose levels ($n=257$, 46 males).
Results
The mean 25(OH)vitD values for males and females patients was 22.9±11.6 and 21.6±11.9 ng/ml respectively, $P=0.815$. The mean 25(OH)vitD±SD levels were significantly lower in subjects with diabetes (18.6±10.6 ng/ml) compared to normal subjects (24.2±12.2 ng/ml), $P=0.035$. There was no difference in the mean age of patients and sex distribution between the two groups. 25(OH)vitD deficiency was observed in 49.7% of the entire study population and was significantly more frequent in patients with diabetes compared to controls (60.9 vs 41.6% respectively). Only 26 out of 184 (14.1%) of patients with diabetes had 25(OH)vitD sufficiency and levels above 30 ng/ml, compared to 74 out 257 (28.8%) of individuals with normal glucose ($P<0.001$).
Conclusions
This study illustrates the higher prevalence of 25(OH)vitD deficiency among patients with diabetes. From a clinical standpoint, specific advice needs to be provided especially to people with diabetes. Vitamin D supplements on a regular basis over the year and adequate sun exposure could be also recommended in order to achieve sufficient levels of 25(OH)vitD.

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Molecular and clinical identification of A45T mutation in AQP2 gene

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Diabetes insipidus (DI) is a disorder which is rarely seen and it is characterized by polydipsia and polyuria. Inadequate secretion of arginine vasopressin (AVP) from hypothalamus or inadequate response of kidney cells to AVP could be causes of DI. Therefore, any mutations in AVPR2, AVP and AQP2 genes which are the parts of that stimulation and response pathyway can cause DI. In this study, mutational analyse was performed for A45T mutation in AQP2 gene. We present a novel homozygous missense mutation at codon 45, which causes the substitution of Ala (GCC) by a Thr (ACC) in exon 1 in a male Turkish patient with nephrogenic diabetes insipidus (NDI). Some of family members of this patient had also polyuria, nocturia, polydipsia, fatigue as well. The patient had severe polyuria polydipsia, fatique, and deep thirstiness from his infancy. While being performed water deprivation test, diagnosis of NDI was confirmed according to increase in urine osmolality after desmopressin acetate injection. We also did some bioinformatical analysis and we predicted three-dimensional structure of the mutant AQP2 protein. We suggest that functional characterization studies will enlight the function of the mutant AQP2 protein.

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EP421

The prevalence of insulin resistance in the Turkish population

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Introduction
We aimed to investigate the homeostasis model assessment of insulin resistance (HOMA-IR) and relation of HOMA-IR with age, sex and body mass index (BMI) and the prevalence of diabetes in Turkish population of different regions.
Methods
Cross-sectional observational study was done in the frame of Turkish prevalence of insulin resistance multicenter study. The study sample consisted of volunteers from seven different regions of Turkey. Weight, height, waist circumference were determined. BMI, blood pressure, fasting blood glucose, fasting blood insulin was performed. Insulin resistance was calculated using HOMA-IR.
Results
The prevalence of DM, impaired fasting glucose and insulin resistance (IR) were, 11.1, 21.3, 26.2% respectively in seven regions of Turkey. IR was detected 28.9% in women, 25.1% in men. The difference between men and women were significant ($P=0.04$). The prevalence of IR in postmenopausal women (30.8%) was higher than premenopausal (25.1%) ($P<0.04$). According to age groups; prevalence of IR in the age of 50–59 (33.8% $P<.001$) was higher than the other age groups. The prevalence of IR was higher in BMI>25, in subjects with hypertension and in subjects with living in city center ($P<.05$).
Conclusion
The high prevalence of IR and DM in Turkey is one of the important public health problem. There is an urgent necessity to institute more aggressive nation wide public health measures and screening programs about obesity.

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The antropometric and metabolic parametres in women with previous gestational diabetes mellitus during a 30-month observation

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Introduction
The aim of the study was to assess antropometric and metabolic parametres in women with previous gestational diabetes mellitus (GDM) during a 30-month observation.
Design
Our prospective study cohort consisted of 367 women with GDM diagnosed according to WHO criteria. Oral glucose tolerance test (OGTT) was performed during 6-10 weeks and 12, 18, 24, 30 months after delivery. On every 6th month between 12th and 30th month after delivery we estimated: BMI, abdominal circumference, blood pressure and the lipid profile, fasting plasma glucose and insulin levels were assessed, from which the HOMA- IR was calculated. Yearly OGTT was performed.
Results
139 (37.9%), 85 (23%) and 43 (12%) women underwent OGTT after 6–10 weeks, at 12 mo. and at 24 mo. after the delivery respectively. BMI 12 mo. after delivery was higher than pre-pregnancy BMI (23.47 and 24.12 kg/m^2 respectively), 18, 24, 30 months after delivery BMI was lower than before pregnancy. Abdominal obesity was found in 44.7% women at 24 months and in 27.3% at 30 months after delivery. Systolic and diastolic blood pressure were within normal population

limits. Total cholesterol varied 201–172.5 mg/dl. HDL 67–63 mg/dl, LDL 112.6-96.2 mg/dl, triglycerides 78–85.5 mg/dl. HOMA IR was growing from 1.59–12 mo. to 2.09 mo. – 30 mo. after delivery. IFG was found in 12.96% women in 12 mo., 26.67% in 18 mo., 32.26% in 24 mo., 33.33% in 30 mo. IGT was found in 5% 12 mo., 24% in 24 mo., 28.57% in 30 mo. after delivery. We found no diabetes mellitus.
Conclusions
Insulin resistance is high and growing in women with previous GDM after delivery. The number of women with prediabetes status after delivery becomes an epidemiologic challenge. We also observed that women with GDM are very often lost to the follow up.

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Diabetes and glycemic control in acute heart failure: complications, hospital stay and prognosis

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Introduction
Few studies have evaluated the impact of type 2 diabetes on the prognosis of acute heart failure (HF). This study assessed the effect of diabetes and glycemic control on complications, hospital stay and prognosis in patients with acute HF.
Methods
Retrospectively, databases of 428 hospitalized patients by acute HF were analyzed, 201 diabetic patients and 227 controls. Statistical analysis was done using SPSS, considering statistical significance for $P<0.05$.
Results
Of all patients, 61.4% were female and the average age was 77.6 ± 9.6 years. The median of hospital stay was 8 days (interquartil range (IQR) 8). Glycosilated hemoglobin (A1c) (median 7.2%; IQR 1.8) was available in 136 diabetic patients. The median of glucose was 177 mg/dl in the diabetic group and 119 mg/dl in controls. Glucose was higher in patients that had a posterior re-hospitalization for acute HF ($P=0.034$) and a negative correlation was found between the glucose value and the length of hospital stay ($P=0.002$). It was not found a significant difference in respect to complications, hospital stay, re-hospitalization and death in diabetic versus non diabetic patients. However, diabetic patients with an A1c $<7\%$ had a significant higher proportion of deaths compared to those with an A1c $>7\%$.
Conclusion
At hospital admission, glucose seems to be related with the risk of re-hospitalization and the length of hospital stay in patients admitted for acute HF pointing out the need of an excellent glycemic control even in non-diabetic patients. The diagnosis of diabetes per se does not seem to be related with an adverse prognosis in acute HF. Nevertheless, a relative higher A1c seems to be related with a lower mortality in diabetic patients. These data call action to a thoughtful investigation in this area. Additionally, similarly to obesity and dyslipidemia, it raises the question of a possible diabetes paradox effect in patients with HF.

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Glycemic control improves in patients with diabetes type 1 after transition from pediatric to adult care

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Aim
The aim of the study was to compare HbA1c levels in patients with type 1 diabetes before and 3 months after the transition from pediatric to adult endocrinology clinic.
Methods
Retrospective analysis of the data from 88 young adults with type 1 diabetes was done. The consecutive patients were recruited in their last year of pediatric care and then transferred to the adult endocrinologist care. A group of 25 randomly chosen patients underwent structured 5-days educational program through group classes while 63 patients underwent usual care. We compared glycemic control using HbA1c levels before and 3 months after the transition in both groups.
Results
Median age of participants was 25 (17–42) years. Median HbA1c level at the time of transition was 7.5% (5.3–11.4). After 3 months median HbA1c of the whole group was 7.3% (5–10.8), $P=0.036$. Two subgroups of patients did not differ in age, HbA1c levels before (7.2% (5.3–11.4) vs 8.2% (5.9–10), $P=0.184$) and 3 months after transition (7.3 (5–10.8) vs 7.3 (5.5–9.4), $P=0.587$). Nevertheless, patients in the group with structured educational program had significant improvement in glycemic control 3 months after the transition (8.2% (5.9–10) vs 7.3 (5.5–9.4), $P=0.036$), while the other group with usual care did not improve the HbA1c level significantly.
Conclusion
Structured educational program significantly improves the glycemic control in patients with type 1 diabetes in transition period.

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Patients with impaired fasting glucose exhibit a more frequent non-dipper or riser blood pressure pattern compared with normoglycemic patients

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Objectives
To study blood pressure circadian pattern in patients with impaired fasting glucose (IFG) evaluated with ambulatory blood pressure monitoring (ABPM).
Methods
Cross-sectional study evaluating patients taken from the Spanish ABPM Registry. Normoglycemia was defined as glucose <100 mg/dl and IFG as glucose 100–125 mg/dl. All patients underwent 24-h ABPM with a Spacelabs ambulatory blood pressure system. ABPM was performed according to standardized conditions and conventional threshold for ABP measurements.
Results
A total of 24 708 patients were included in the study; 16 587 with normoglycemia (67.2%) and 8.121 with IFG (32.8%). Patients with IFG were older (60.2 vs 56.0 years, $P=0.001$) more obese (BMI 29.6 vs 28.2 kg/m^2, $P=0.001$), presented more elevated clinic systolic blood pressure (150.4 vs 147.3 mmHg) but similar diastolic blood pressure (87.8 vs 87.7). Non-dipper + riser pattern was found in 51.3% of patients with IFG and in 48.2% in those with normoglycemia ($P<0.001$ for the comparison).
Conclusions
Patients with IFG show a higher percentage of non-dipper + riser pattern in the circadian blood pressure evaluation.

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EP426

Diagnostic and therapeutic stratagies in maturity onset diabetes of the young

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Background
Maturity onset diabetes of the young (MODY) has an estimated prevalence of 1–5% in the diabetic population, but misdiagnosis as type 1 or type 2 diabetes is common. It comprises a heterogeneous group of monogenic diseases characterized by primary dysfunction of β cell, young onset, autosomal dominant inheritance, without autoimmunity and without ketosis. Early diagnosis remains a challenge with important future implications, since it allows treatment optimization, prognosis definition and genetic counseling of family members.
Objective
Characterize the parameters for the diagnosis of MODY.

Patients and methods
We studied nine cases in three successive generations of a family of 12 elements, with assessment of age at diagnosis, gender distribution, clinical manifestations, initial treatment and subsequent need for insulin. We analyzed the levels of glucose, HbA_1c, C-peptide, the presence of ketosis and anti-β cell antibodies. Molecular analysis of GCK (glucokinase) and HNF-1α (hepatocyte nuclear factor 1α) genes was performed to detect MODY mutations.
Results
The age at diagnosis was 26.1 ± 8.2 years (16–38 years), 67% females, with a disease duration of 12.7 ± 10.6 years. Glucose levels were 200 ± 48 mg/dl, HbA_1c 8.5 ± 1.5%. All patients had glucosuria. Four (44.4%) patients had nephropathy with albumin excretion rate of 215 ± 48 μg/min; 6 (66.7%) had non-proliferative retinopathy. C-peptide levels were 2.5 ± 1.1 ng/ml. The anti-β cell antibodies were negative in all patients and none had ketosis (no ketonuria and indetectable β-hydroxybutyrate). Genetic testing revealed a mutation in exon 6 *(stop mutation Ser 371 OCH)* of gene *HNF-1α* (MODY3). Only 2 (22.2%) patients, diagnosed at 16 and 19 years, required insulin therapy, at 32 and 25 years respectively. The remaining 7 (77.8%) patients kept up with glibenclamide treatment (2.5–15 mg/day).
Conclusion
The clinical presentation of hyperglycemia without ketosis, no anti-β cell antibodies and C-peptide levels allowed to exclude type 1 diabetes. Genetic testing enabled to confirm mutations in gene HNF-1a and guide treatment according to clinical evolution.
Keywords: MODY, type 1 diabetes, type 2 diabetes, HNF1α, GCK
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EP427

Characterization of a pediatric population with type 1 diabetes at transition to adult health care
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Introduction
Type 1 diabetes (T1D) is an important endocrine disease in the pediatric age group. The shift from pediatrics to adult health care providers is a critical period for adolescents with diabetes.
Objective
Characterization of a pediatric population with T1D moved to adult health care between January/2001–April/2015.
Methods
Cross-sectional study with retrospective analysis of medical records.
Results
We evaluated 195 patients, 82 girls (42.1%) with a mean age of 7.94 ± 3.40 years at diagnosis. Follow-up time was 9.50 ± 3.50 years, with a mean number of visits of 30.60 ± 11.40. At transition, the mean age was 17.96 ± 0.93 years, with 10.03 ± 3.56 years of disease. Mean BMI was 23.63 ± 3.32 kg/m^2 (SDS 0.74 ± 1.01), with overweight in 57 (29.2%) and obesity in 8 patients (4.1%). Mean A_1c in the last appointment was 8.7 ± 1.6%; 47 patients (23.6%) had an A_1c value <7.5% and 71 (36.4%) >9%. At transition time, 113 (57.9%) patients were treated with functional insulin therapy and 20 (10.3%) were on continuous subcutaneous insulin infusion (CSII). Insulin dose on last visit was 1.00 ± 0.25 UI/kg. During follow-up, 184 (94.3%) patients reached the mean final height of 167.50 ± 9.22 cm (SDS −0.47 ± 1.09). Of these, only 6 (3.3%) did not reach the target height. It was found a decrease in mean height SDS on last appointment when compared with the first visit, in both sexes – male: 0.04 ± 1.05 v. −0.54 ± 0.96; $P < 0.001$; female: 0.25 ± 1.07 vs −0.46 ± 1.22; $P < 0.001$.
Conclusion
The age of T1D diagnosis is coincident with the age group with the highest incidence reported in the literature. Overweight found in 30% of patients may reflect the global trend towards weight gain. The recommended target of A_1c was achieved by 23.6% of patients, despite 68.2% being on CSII and functional insulin therapy. Like other studies, the mean height SDS decreased during follow-up, suggesting an impaired growth, although there seems to be no impact on the final height.
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EP428

Waist circumference and diabetes risk in Colombian population
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Increased waist circumference is a cardiovascular risk factor, currently we have the cutoff value of International Diabetes Federation (IDF) or by Latin-American standards; in Colombia has not studies where showing the relationship between increased waist circumference and the risk of diabetes. This study aims to show the relationship between increased waist circumference by IDF criteria or Latin-American criteria and the risk of diabetes.
Methodology
Cross-sectional study where multivariate analysis was performed using two models: waist circumference increased by IDF criteria and waist circumference by Latin-American criteria and risk of diabetes; adjusted for age, sex, HDL cholesterol, and body mass index (relevant variables in univariate analysis).
Results
A total of 2200 patients were included: 30.45% (670 patients) with type 2 diabetes, of which 90.72% had increased waist circumference by IDF criteria; 76.65% by Latin-American criteria. In model 1 was found as independent factors associated with diabetes: Male gender OR = 1.30 (95%CI 1.05–1.6, $P = 0.014$) and increased waist circumference by IDF criteria OR = 1.44 (95%CI 1.02–2.04, $P = 0.038$); as a protective factor HDL cholesterol OR = 0.97 (95%CI 0.96–0.98, $P < 0.001$).
In model 2 were found: Male gender OR = 1.31 (95%CI 1.06–1.61, $P = 0.01$) and increased waist circumference by Latin-American criteria OR = 1.42 (95%CI 1.12–1.79; $P = 0.003$); as a protective factor HDL cholesterol OR = 0.97 (95%CI 0.96–0.98, $P < 0.001$).
Conclusion
Increased waist circunference by IDF or Latin-American criteria may be associated independently to the risk of diabetes in Colombian population.
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EP429

Oral fructose does not acutely affect circulating FGF21 in mice
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Impaired glucose tolerance and insulin sensitivity are established hallmarks of diabetes and it was speculated that also fructose tolerance could be impaired. However, investigation of fructose tolerance has been hampered by the lack of easy accessible pharmacodynamic markers. In humans, the hormone FGF21 has recently been demonstrated to be a sensitive pharmacodynamic marker responding to an oral fructose bolus and exhibiting a divergent secretion pattern in obese diabetic and healthy lean subjects. Here we investigated whether FGF21 excursion after an oral fructose challenge follows the same rules in mice.
Methods
Fasted male obese ob/ob mice received an oral fructose bolus (1 g/kg, $n = 10$). Lean ob/- mice were gavaged with water, only ($n = 10$/group). Another cohort of ob/ob mice was pre-treated with Sitagliptin (at $t = -30$ min, 40 μg/mouse, MSD Sharp and Dohme) before exposure to oral fructose ('ob/ob-S', $n = 10$). Blood was collected at timepoints −30, 0, 30, 60, 120 and 180 min after fructose or vehicle treatment for analysis of glucose, plasma insulin, GLP-1 and FGF21.
Results
ob/ob mice displayed higher plasma insulin when compared to lean mice ($P < 0.001$). Sitagliptin pre-treated ob/ob mice had significantly higher GLP-1 concentrations compared to ob/ob mice without pre-treatment ($P < 0.05$). Similar to humans, the oral fructose bolus did not significantly change blood glucose concentrations between 0–180 min (e.g. at $t = 30$ min; ob/-: 8.1 ± 0.2 mmol/l; ob/ob: 9.5 ± 1.4 mmol/l; ob/ob-S: 11.9 ± 2.0 mmol/l). Throughout the study, ob/ob mice (independent of pre-treatment) showed significantly higher FGF21 concentrations compared to ob/- mice (e.g. at $t = 30$ min; ob/-: 317 ± 108 pg/ml; ob/ob: 2268 ± 330 pg/ml; ob/ob-S: 2071 ± 298 pg/ml). However, plasma FGF21 concentrations were not significantly affected by oral fructose ingestion in lean and obese mice at all timepoints.
Conclusion
In mice, circulating FGF21 was not responsive to an oral fructose load, at least under the conditions studied. Thus, the oral fructose tolerance test with the pharmacodynamic readout FGF21 cannot be easily translated from humans to laboratory rodents.
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EP430

Changes in the expression level of transcription factor Foxp3 in rat's pancreatic lymph nodes under streptozotocin-induced diabetes and metformin administration

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Introduction
Type 1 diabetes mellitus is a T-cell mediated autoimmune disease characterized by the destruction of β-cells of the pancreas. Numerous studies have demonstrated the key role of FoxP3+ regulatory T-cells in the development of type 1 diabetes.
Aim
The aim of research: 1) to determine the expression patterns of transcription factor FoxP3 in the pancreatic lymph node cells in animal model of diabetes mellitus and 2) to assay an effect of metformin of these processes.
Methods
Researches are made on Wistar rats. For an induction of diabetes streptozotocin was used in doses 50 mg/kg. Structure of population of $FoxP3^+$ cells has been studied by the analysis of serial histological sections using the method of indirect immunofluorescense with monoclonal antibodies to FoxP3 of rat.
Results
Development of experimental streptozotocin-induced diabetes mellitus (3-week ESIDM) led to a change in representation of $FoxP3^+$-lymphocytes in paracortical zone and medullary cords of pancreatic lymph nodes (PLN), in which the total density decreased by 25% ($P<0.05$) and 28% ($P<0.05$) as compared to control group. Indicators in the group of rats with 5-week ESIDM decreased by 50% ($P<0.05$) only in medullary cords of PLN. After the administration of metformin in rats with 3-week ESIDM total density of FoxP3+-lymphocytes increased by 96% ($P<0.05$) in the paracortical area and by 93% ($P<0.05$) in medullary cords PLN rats with respect to 3-week ESIDM. The fluorescence intensity of $FoxP3^+$-cells appeared to be a significant increased in medullary cords PLN as at 3-week ESIDM and at 5-week ESIDM, namely $FoxP3^+$-medium and small lymphocytes. Administration of metformin resulted in a decrease in medullary cords PLN concentration FoxP3 in $FoxP3^+$-medium and small lymphocytes with respect to indicators of a group of animals with a 3-week ESIDM that did not take metformin.
Conclusions
Our results demonstrate the metformin is able to increase the Treg number in PLN, by the way these effects manifest on the third week of the diabetes mellitus and they reduce of the fifth week of the pathological process duration.

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EP431

Diabetic case treated by steroid

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Introduction
Isolated eosinophilic pancreatitis is very rare disease and usually occurs either as hyperoesinophylia syndrome or as part of eosinophilic gastroenteritis.
Case report
A 55-year-old man presented to his general practitioner (GP) with a 3 week history of flu-like symptoms, pruritis, weight loss and diarrhoea. Initial investigations showed eosinophilia (32.2×10^9/l) and a normal random glucose. He was seen in a general medical clinic 3 weeks after the initial referral from GP and at this point had polyuria and polydipsia. He was previously well and was on no medication. He denied illicit drug abuse. There had been no recent travel abroad. Physical examination was unremarkable.
Further investigations showed elevated random blood glucose (15.9 mmol/l), raised HbA1c (89 mmol/mol), raised creatinine (171 μmol/l). There were no ova, cysts and parasites in urine or stool. Plasma virology, parasitology and vasculitis screen were negative. A cytogenetic analysis test and F1P1L1-PDGFRA (to rule out eosinophilic leukaemia) was also negative. Computerised Tomography (CT) of chest and abdomen showed a bulky pancreas.
In the context of previous finding, the diagnosis of diabetes mellitus secondary to eosinophilic pancreatitis was established and he was commenced initially on insulin, then prednisolone (40 mg/day). After starting steroids, the eosinophil count fell and insulin requirements decreased. After 2 months, the eosinophilic count was normal and insulin was stopped. Steroids were weaned off over the next 8 weeks. The patient has been off all the treatment for the last 8 months with eosinophil counts just above the normal range and the latest HbA1c of 48 mmol/mol.
Conclusions
We presented a rare case of eosinophilic pancreatitis as part of hyper-eosinophilic syndrome with minimal involvement of other systems. This was a unique situation in which steroids, which usually cause hyperglycaemia, were effectively used to treat diabetes mellitus.

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EP432

Predictive value of risk factors for the progression from prediabetes to type 2 diabetes

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Background
Diabetes and prediabetes have become major public health problems in recent decades.
Objectives
The aim of the study was to evaluate the predictive value of risk factors on progression from prediabetes to type 2 diabetes.
Materials and methods
A total of 383 subjects (213 females, 170 males), mean age 51.93 ± 13.47 years and mean BMI 29.11 ± 5.3 kg/m^2, divided in three groups – 147 with normal glucose tolerance, 122 with impaired fasting glucose (IFG) and 114 with impaired glucose tolerance (IGT), were included in the study and were followed-up a year later. OGTT was performed in all participants; categories of glucose tolerance were defined according to 2006 WHO criteria. Anthropometric, laboratory parameters (HbA1c, lipids, hsCRP, insulin, proinsulin), blood pressure, body fat mass and FINDRISC were assessed.
Results
Progression rates from IFG and IGT to diabetes over 1 year were 12.08 and 19.91 per 100 person-years, respectively. Baseline determinants of progression from IFG to diabetes were age, HbA1c, systolic blood pressure, lack of daily fruit and vegetable intake, FINDRISC, hsCRP; and from IGT to diabetes – overweight and obesity (BMI), waist circumference, HbA1c, lack of daily fruit and vegetable intake. Baseline insulin resistance (HOMA-IR) appeared to be a predictor for the progression from both IFG and IGT to diabetes, while basal insulin secretion (HOMA-%B) - a predictor for the progression from IGT to diabetes. Baseline proinsulin level and proinsulin:insulin ratio were independent predictors for progression to diabetes in both IFG and IGT.
Conclusions
Individuals with IFG or IGT identified through high-risk strategies in Bulgarian population, have a rather high risk of developing diabetes within one year. Overweight and obesity, waist circumference, systolic blood pressure, lack of daily fruit and vegetable intake, insulin resistance appear to be significant determinants of progression to diabetes, which implies for adequate measures for their control aiming at prevention of the disease.

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EP433

Cause-of-death trends for diabetes mellitus over 20 years

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Background
Recently, diabetic mortality is lower than ever before, likely due to dramatic improvements in diabetes care. This study set to analyze changes in the cause of death in type 2 diabetes mellitus (T2DM) in the past 20 years.
Methods
All subjects were T2DM patients over the age of 30 whose death certificates were issued at six hospitals in the Busan metropolitan area from 2010 to 2014. The patients were excluded if they had been clinically diagnosed with significant tuberculosis, liver, thyroid, renal, connective tissue diseases and cancers, prior to T2DM diagnosis. We classified the cause of death into several groups. The results were compared with our published data on the period from 1990 to 1994 and 2000 to 2004.
Results
The study comprised 680 patients of which 61.7% were male. The average age of death was 66.5 years. The most common cause of death was malignancy (47.7%),

followed by renal disease (14.0%), infectious disease (10.6%), cardiovascular disease (8.5%). Compared with previous studies, cancer became the most common cause of death in T2DM patients, while cardiovascular disease and infectious disease significantly decreased in the rank.
Conclusion
Over the 20 years, death by cancer in T2DM patients was is rising steeply. Preventive strategies to promote primary prevention and early detection of malignancy are urgently needed to reduce this excess mortality.

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EP434

The part of taste in cephalic phase of insulin secretion

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Background
Secretion of insulin by beta-cells of the islets of Langerhans is a very complex dynamic process that includes basal and stimulated insulin secretion. Two phases, one early and one late, can be distinguished in insulin secretion. The early phase is characterised by the secretion of preformed insulin granules, lasts about 15 min and is formed by cephalic and gastrointestinal components. The cephalic phase of insulin secretion starts by stimulating visual, olfactory and taste receptors.
The aim of this study is to show to what extent the concentrations of insulin, C-peptide and cortisol are changed by a simple mouth rinsing with a sucrose or sweetener solution.
Methods
Fifteen non-obese voluntary male participants were included in this study. The experiment consisted of mouth rinsing with either a sucrose or aspartate solution or pure water as a placebo. Blood was taken in short intervals of 0, 5, 10 and 20 min. Blood glucose, C-peptide, insulin and cortisol were determined.
ANOVA was used for statistical analysis.
Results
C-peptide and glucose were unaffected, a short-term increase in insulin was observed after the sucrose, but not after the aspartate or placebo. The decline of cortisol level within 20 min was also observed after aspartate or placebo, it was probably caused by stress factors or anticipation.
In conclusion, we proved the contribution of taste to the cephalic phase of insulin secretion.

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EP435

Relation between uric acid and lipid profiles in patients with type 2 diabetes

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Aims
High level of uric acid is known to associate with stroke, coronary artery disease and metabolic syndrome. Some epidemiologic studies suggested that high uric acid level is connected with dyslipidemia. However, this relationship was not examined in type 2 diabetic patients. This study was conducted to investigate the association between serum uric acid level and lipid profiles in type 2 diabetic patients.
Methods
A total of 972 type 2 diabetes patients were included in the present study. We measured height, body weight and blood pressure. Biochemical parameters including low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG) and total cholesterol (TC) were checked.
Result
The mean age of total subjects was 56.90 ± 13.91 and men were 507 (52.2%). The mean body mass index (BMI) was 23.89 ± 3.88. In the univariate analysis, TG and uric acid level was significantly positively correlated ($r = 0.155$, $P < 0.001$). HDL was significantly negatively associated with serum uric acid ($r = -0.171$, $P < 0.001$). LDL and TC were not related with uric acid level. Multiple regression analyses were then performed by adjusting for age, sex and body mass index. The significantly positive association between TG and uric acid was retained (beta coefficient $= 0.131$, $P < 0.001$). The negative connection between HDL and uric acid was persisted (beta coefficient $= -0.111$, $P = 0.001$).
Conclusion
In the present study, we found that serum uric acid level is significantly positively associated with TG, whereas it is significantly inversely associated with HDL in type 2 diabetic patients. Management for hyperuricemia may help to control dyslipidemia in patients with type 2 diabetes.

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EP436

Thyroid dysfunction among Greek type 1 and type 2 diabetic patients attending an outpatient clinic

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Introduction
The aim of this study was to determine the prevalence of thyroid dysfunction in Greek patients with type 1 (T1DM) and type 2 (T2DM) diabetes as well as its possible relation to glycemic control and to diabetic complications.
Patients and methods
A total of 990 patients (60.7% men) with T1DM or T2DM, consecutively followed in the Outpatient Diabetes Clinic, participated in the study. In every patient anthropometric and biochemical measurements, occurrence of diabetes complications and classical comorbidities were assessed. Average HbA1c of the previous year was calculated. Moreover, the well-being of every patient was determined, using a scale from 1 to 10. All the above parameters were compared between subjects with or without thyroid disease.
Results
All 990 patients were euthyroid at the time of the study, either on thyroid medications or not. 13% of them had T1DM and 87% T2DM. Mean age of T1DM patients: 47.5 years and of T2DM patients: 67.6 years. Mean duration of diabetes: 23.6 years and 16.1 years respectively. The prevalence of hypothyroidism in T1DM patients was 43.8% vs 23.5% in T2DM patients ($P < 0.05$). The prevalence of nodular goiter in T1DM patients was 17.5% vs 32.1% ($P = 0.05$) in T2DM patients. Moreover, T2DM patients with hypothyroidism compared to matched patients without, had higher HbA1C: 7.41% vs 6.97% ($P < 0.01$), higher total cholesterol 181.4 mg/dl versus 164 mg/dl ($P < 0.001$) and higher HDL 51 mg/dl vs 46 mg/dl ($P < 0.005$). T2DM patients without hypothyroidism had a better wellness feeling compared to the patients with hypothyroidism: 7.5 vs 5.3 ($P < 0.001$).
Conclusions
Screening for thyroid disease among patients with type 2 diabetes should be routinely considered because of the high prevalence of thyroid dysfunction in these patients. It is another risk factor that if remains undiagnosed could aggravate the usual comorbidities of diabetes mellitus.

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EP437

Study on role of TNF-α and oxidative stress in pathogenesis of type 2 diabetes mellitus

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Aim
The work was initiated to study TNF-α gene polymorphism and parameters of oxidative stress in patients with type 2 diabetes mellitus
Materials and methods
We examined 41 healthy subjects and 20 patients with diabetes mellitus to study G308A (rs1800629) polymorphism in TNF-α gene by means of allele-specific

PCR method (AS-PCR). Rates of lipid peroxidation (LP) were determined by concentration of malon dialdehyde (MDA); catalase activity was assessed by antioxidant protection degree.
Results
Excessive production of TNF-α is known as a pathological link in diabetes mellitus onset and progression. In our study, frequency of GG, GA and DD in patients with diabetes mellitus was 85.0, 15 and 0.0, respectively. Frequency of GG, GA and AA genotypes in the control group was 90.2, 9.8 and 0.0%, respectively. Frequency of A-allele, the one associated with the increased production of TNF-α, in the diabetics and healthy volunteers was 7.5 and 4.9%, respectively. Our findings demonstrated significant LP intensification with accumulation of secondary products in the blood serum of all patients with diabetes mellitus (MDA concentrations increased by 2.5 times), and suppression of activity of catalase more than by two times in the diabetics as compared with the controls.
Conclusions
In patients with diabetes mellitus frequency of a mutant A-allele in TNF-α gene is higher than in healthy persons. Our findings indicate significant role of G308A polymorphism in TNF-α gene in pathogenesis of diabetes mellitus. In patients with type 2 diabetes mellitus we have managed to establish correlation between intensity of oxidative stress and TNF-α production.

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EP438

The change of adherence to a process quality-of-care-indicator after the initiation of clinical audit in Korea

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Background
Adherence to recommended guideline for monitoring of glucose control and screening of diabetic complications has been demonstrated to prevent the chronic complications of diabetes. In Korea, the clinical audit for quality of diabetes care has been started in 2011. The aim of this study is to investigate the change of adherence to a process quality-of-care-indicator in diabetes after the initiation of audit in Korea.
Methods
This retrospective study was performed using the national health insurance claims database from the Health Insurance Review & Assessment Service (HIRA) of Korea, from 2009 to 2014. Study patients were aged 30 years or older, had type 2 diabetes, had taking at least one hypoglycemic agent in only one attending clinic at 2009, and had no history of any diabetes-related chronic complications including cardiovascular diseases before December, 2010, cancer, or hospitalization for ≥ 90 days (n=280,698). Process indicators included measurement of HbA1c more than once a year, annual measurement of lipid, annual examination for retinopathy and nephropathy.
Results
The number of patients receiving HbA1c and lipid measurement at least once a year increased to 69.9 and 54.5% in 2014 from 52.7 and 32.5% in 2009. Although the annual screening of nephropathy and retinopathy is also increased gradually, it is still low at 16.5 and 24.5% in 2014. Despite a gradual increase in the proportion of patients who underwent annual measurement of HbA1c and lipid and annual screening for retinopathy and nephropathy, only 6.1% of the patients met all four criteria in 2014 (1.5% in 2009 and 3.9% in 2011).
Conclusion
Although there were improvements in adherence to each process quality-of-care indicator, the percentage of patients undergoing all four examinations annually remained still very low.

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EP439

The effect of processes measures of diabetes care and medication adherence on the developments of chronic diabetic complications

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Background
Regular monitoring of glucose control and screening of diabetic complication and adherence to treatment are cornerstones for prevention of chronic diabetic complications. The aim of this study is to investigate the association between quality of diabetes care and the development of chronic diabetes complications.
Methods
This retrospective study was performed using the national health insurance claims database from the Health Insurance Review & Assessment Service (HIRA) of Korea. Study patients were aged 30 years or older, had type 2 diabetes, had taking at least one hypoglycemic agent in only one attending clinic at 2009, and had no history of any diabetes-related chronic complications including cardiovascular diseases before December 2010, cancer, or hospitalization for ≥90 days (n=280 698). Patients who measured HbA1c and lipid profile at least once a year every year and had ≥80% of the possession rate of oral hypoglycemic medication every year from 2009 to 2014 were compared with those who did not.
Results
The number of patients receiving two quality-of-care measures at least once a year increased to 52.5% in 2014 from 30.3% in 2009. Those having ≥80% of the medication adherence also increased from 60.3 to 73.5%. However, the patients who meet both conditions every year during study period were only 13 625 (4.9%). In them, the cumulative incidence of microvascular complications (nephropathy and retinopathy) was 4.1%, and that of macrovascular complications (myocardial and cerebral infarction and peripheral arterial disease) was 0.8%, (4.8 and 1.5%, respectively in those who did not).
Conclusions
The proportion of patients who received two quality-of-care measures and had ≥80% of the medication possession rate every year are seriously low, but they experienced fewer diabetic macrovascular complications. This result provides support for the importance for enhancing the quality of diabetes care.

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EP440

The effect of vitamin D on rat pancreatic beta cells *in vitro*

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Introduction
Vitamin D is currently known for its effects on the bone and muscle systems as well as for its pleiotropic and antiproliferative effects. The relationship between vitamin D and diabetes mellitus is in the focus of scientific research. Vitamin D deficiency has been found to be associated with the development of diabetes mellitus type 1 as well as with poor glycemic control in diabetes mellitus type 2.
Aim
The aim was to study the effect of vitamin D on the proliferation of rat pancreatic beta cells *in vitro*.
Methods
The effect of $1,25(OH)_2D_3$ (Sigma–Aldrich) at an initial concentration of 100 nM on INS-1 rat pancreatic beta cells was studied *in vitro*. INS-1 rat pancreatic beta cells were incubated for 48 h at a temperature of 37°C in a humidified atmosphere of 5% CO_2 in the presence and absence of $1,25(OH)_2D_3$. INS-1 rat beta cells were incubated with progressively decreasing concentrations of $1,25(OH)_2D_3$, at an initial concentration of 100 nM (range 100–3.125 nM) to assess the proliferation of INS-1 rat beta cells. The proliferation of INS-1 rat beta cells was assessed using the XTT cell proliferation assay (AppliChem). In order to determine the number of viable cells the cell proliferation kit XTT employs 2,3-Bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide salt (XTT). Only in living cells

mitochondria are capable to reduce XTT to form an orange colored water soluble dye. Therefore, the concentration of the dye is proportional to the number of metabolically active cells.
Results
$1,25(OH)_2D_3$ was found to reduce the proliferation of INS-1 rat beta cells *in vitro*.
Conclusions
Vitamin D was found to modulate the proliferation of rat pancreatic beta cells *in vitro*. Similarly, Blauer *et al*. (Pancreatology 2015) have recently found that vitamin D in physiologically attainable and clinically relevant concentrations reduces the proliferation of pancreatic stellate cells *in vitro*.

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EP441

The effect of melatonin on rat pancreatic beta cells *in vitro*

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Introduction
Melatonin is a hormone mainly synthesized and secreted by the pineal gland. It is involved in the orchestration of circadian rhythms its levels being elevated during the hours of darkness in the human. Melatonin may have other pleiotropic functions in the human organism. In particular, it may be involved in the regulation of glucose metabolism and the pathogenesis of diabetes.
Aim
The aim was to study the effect of melatonin on rat islet cells *in vitro*.
Methods
Rat pancreatic beta cells INS-1 were incubated for 48 h at 37°C in a humified atmosphere 5% CO_2 in the presence and absence of melatonin (Sigma-Aldrich). Melatonin was used at decreasing concentrations, the initial concentration being 200 nM, range (200–6.25 nM). The proliferation of INS-1 rat beta cells was assessed using the XTT cell proliferation assay (AppliChem). In order to determine the number of viable cells the cell proliferation kit XTT employs 2,3-Bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide salt (XTT). Only in living cells mitochondria are capable to reduce XTT to form an orange colored water soluble dye. Therefore, the concentration of the dye is proportional to the number of metabolically active cells.
Results
Melatonin was not found to influence beta cells proliferation *in vitro*.
Conclusions
Melatonin, a pineal hormone involved in the regulation of circadian rhythms is now being investigated for its effects on glucose regulation. It has been found in human genome wide association studies that genetic variations in the melatonin receptor MT2 encoded by MTNR1B may coexist with diabetes. It was also suggested that genetic variations of MTNR1B may disorder b-cell function directly, via its effects on insulin secretion. In the present study melatonin was not found to affect islet cell mass *in vitro*. As it is speculated that melatonin and its receptors may be a new therapeutic avenue in diabetes further studies are needed to assess the effect of melatonin on insulin secretion.

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EP442

Implementation of guidelines in a large outpatient Diabetes Clinic

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Introduction
The aim of the study is to determine whether the guidelines on glycemic control and cardiovascular risk factors are being followed in everyday clinical practice and to describe the lifestyle habits and the wellbeing of patients with Type1 or Type 2 diabetes.
Patients and methods
A total of 990 patients with diabetes consecutively followed in the Outpatient Diabetes Clinic were studied (60.8% men). Clinical and laboratory parameters and living habits were evaluated. Wellbeing was assessed by a scale from 1 to 10.
Results
Of the 990 patients, 12.5% had Type1, while 87.5% had Type2 diabetes. Mean age: 47.5 and 67.6 years, mean duration of diabetes: 23.6 and 16.1 years respectively.

		Type 1		Type 2	
Parameters	Target	Mean	% on target	Mean	% on target
HbA1c (%)	<7	7.45	30.9	6.98	52.4
Systolic BP (mmHg)	<140	110	98.4	120	95.9
Diastolic BP (mmHg)	<80	62.5	99.2	70.0	96.4
BMI (kg/m^2)	<25	25.9	40.8	28.78	18.1
HDL (mg% ♂)	>40	50.0	88.4	43.0	64.5
HDL (mg% ♀)	>50	63.0	76.1	50.0	50.0
LDL (mg%; with CVD)	<70	73.0	75.0	89.3	20.0
LDL (mg%; without CVD)	<100	100.3	57.4	94.5	63.3
Tg (mg%)	<150	79.0	91.2	113	70.6
eGFR (ml/min per 1.73 m^2)	>90	108.8	68.1	81.8	39.9
Hypoglycemia	No		18.6		67.0
Exercise (150 min/week)	Yes		49.1		52.3
Smoking	No		72.6		83.6
Wellbeing	>5	7	89.4	7	90.7

Conclusions
Our study suggests that most of diabetic patients achieve the glycemic as well as CVD risk factors and lifestyle targets, but there is still considerable potential for improvement of the guidelines implementation.

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EP443

The content of adipocytokines (resistin, adiponectin) in type 1 diabetic patients associated with the amounts of fat component

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Background and aims
Adipocytokines produced by adipose tissue cells, and their action is often systemic in nature. Connection of some adipocytokines (resisttin) with the development of autoimmune diseases such as type 1 diabetes (T1DM) is a perspective view. Therefore, the aim of study was to assess the association between adipocytokines (resisttin, adiponectin) and content of fat mass in T1DM.
Materials and methods
Ninety-five patients with T1DM (60 women, 35 males) (mean age: 30.6 (24.9–37.5) years, duration of DM: 13 (7–20) years, age of manifestation: 17 (12–23) years, HbA1c: 8,2 (7.6–8.9)%) and 55 (31 women, 24 men) controls. The research involved anthropometry of patients, general clinic examination, DEXA using a program 'Body composition'. A fat mass index (FMI) was measured as total fat mass/height^2.
Results
There were no differences in the percentage of fat component in women with T1DM (34.5 (29.3–38.6) vs 32.6 (26.5–37.2); $U=820$; $P=0.425$) and men (21.3 (17.5–28.5)% vs 23.95 (15.8–26.6)%; $U=385$; $P=0.865$) compared with control groups. The trend was confirmed compare FMI- in women 7.36 (6.15–9.33) vs 6.68 (5.02–8.8) kg/m^2; $U=787$; $P=0.28$; FMI in men 5.03 (3.26–6.55) vs 5.8 (3.37–6.79) kg/m^2; $U=378$; $P=0.641$) in comparison to the control group. The patients with T1DM have significantly higher than the control levels of serum resistin – 0.46 (0.35–0.69) vs 0.37 (0.3–0.49) ng/ml; $U=581$; $P=0.034$. The contents of adiponectin in patients with T1DM comparable to healthy individuals (27.77 (27.1–28.42) vs 28.02 (27.38–28.4) ng/ml, $U=790.5$; $P=0.847$). There was medium negative correlation between serum levels of resistin and FMI ($\rho=-0.48$; $P=0.004$) in women with T1DM.
Conclusions
Elevated levels of resistin may be associated with the presence of an autoimmune process in the development of diabetes. Influence of the level of resistin on content of fat mass in patients with T1DM needs further study.

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EP444

Association of eating behaviors and demographic profiles of Filipino adults with type 2 diabetes mellitus seen in a Tertiary Hospital

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Background
Patients with type 2 diabetes face daily challenges in making dietary choices that are influenced by eating behaviors. Recognition of eating behaviors and associated demographic profiles could aid in individualizing dietary plans and direct nutrition programs in forming cost-effective measures.
Objective
The goal of this study is to identify differences in eating behaviors across demographic profiles of Filipinos with type 2 diabetes.
Methods
Demographic data and answers of 197 Filipinos with type 2 diabetes to the Filipino eating behavior questionnaire were obtained and tallied. Paired *t*-test and one-way ANOVA were used to compare eating behavior scores across categories of the demographic data.
Results
Patients with type 2 diabetes who scored higher in uncontrolled eating tend to have a higher level of education, positive family history of diabetes, and ate two meals with no snacks per day. Those who were considered restrained eaters were previous smokers, on insulin and oral hypoglycemic agents, and ate three meals and a snack. Emotional eaters were observed to eat two meals with no snacks per day while social eaters tend to be younger, employed, have higher level of education, and family history of diabetes. High scorers in proactive eating have a longer duration of diabetes and ate no snacks. Uncontrolled, emotional, social, and pro-active eating domains seem to have direct relationships, while restrained eating tends to show an inverse relationship with the other eating behaviors. The estimated prevalence's were 14, 14, 12, 13, and 11% for uncontrolled, restrained, emotional, social, and pro-active eating, respectively.
Conclusion
Among patients with type 2 diabetes, eating behaviors may vary and depend on their demographic profiles. Eating behaviors related to overeating seem to be directly related to each other and inversely related to restrained eating. Prevalence rate of behaviors related to overeating and restrained eating were both relatively low.

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EP445

Functional characterization of a large deletion in the *AVPR2* gene causing severe nephrogenic diabetes insipidus in a Turkish family

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Changes in *arginine vazopression type 2 receptor* (*AVPR2*) gene mostly lead to a rare hereditary polyuric disease, X-linked nephrogenic diabetes insipidus (NDI). The disease is characterized by the production of large amounts of urine and an inability to concentrate urine in response to the antidiuretic hormone vasopressin. In our previous study we have identified a novel 388 bp deletion in the *AVPR2* gene in a patient with NDI and in his family. For functional analyze studies, identified deletion was re-created by PCR based site-directed mutagenesis and restriction fragment replacement strategy based on DNA sequence and expressed in COS7 cells. We performed total and surface ELISA assay and cAMP assay for assessing the ability of transfected cells to produce cAMP in response to stimulation with DDAVP. Results of functional characterization of 388 bp deletion have revealed that mutant V2R did not show any expression on the cell surface compared to the wild type receptor while showed reduced cellular expression in total ($31.93 \pm 8.8\%$) compared to the wild type receptor. cAMP accumulation assay results are supported the ELISA results of the mutant receptor protein. In conclusion we believe that our study will contribute to shedding light on mechanisms of molecular pathology of *AVPR2* deletions.

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EP446

Microbiological profile in diabetic foot infections: identification and susceptibility profile of bacteria isolated in 5 years in a Portuguese tertiary care hospital

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Introduction
The diagnosis of infected ulcer is mainly clinical. The goals of the microbiological studies are identification of the pathogen and evaluation of susceptibility to antibiotics to minimize exposure to drugs and selection of resistant strains.
Methods
Retrospective cohort study; Data collection: 1 January 2010 to 31 December 2014. Were included wound samples of aspirate, nonsurgical/surgical exudate, pus from abscesses and bone fragments from diabetic foot consultation and ward at Endocrinology Department. Data were obtained through the clinical process and analysed in SPSS.
Results
On gender, our sample included 71.3% of male patients with age of 62.8 ± 14 years. Regarding the origin of the requested studies, 78% were from the endocrinology ward ($n = 174$) and 74% were samples of nonsurgical wound exudate ($n = 165$).
One hundred and eighty-one samples were obtained for microbiological study with identification of 223 different agents.
Of gram-positive agents, *Staphylococcus aureus* (SA) was the most isolated in 39.5% of the samples ($n = 88$) followed by *Enterococcus faecalis* (EF) in 8.97%. Of gram-negative agents, *Pseudomonas aeruginosa* (PA) was isolated in 29 (13%) and *Proteus mirabilis* (*PM*) in 23 (10.31%). Of the 42 samples with polymicrobial isolation, the combination of agents most commonly found corresponded to co-infection with PA and SA (14.3%) and SA and PM (17.1%). Regarding to antimicrobial susceptibility in SA strains, was found resistance in 35.2% to oxacillin, 39% for levofloxacin, 29% to clindamycin, 3% to gentamicin, 1% to trimethoprim/sulfamethoxazole and there were no vancomycin or linezolid resistance *in vitro*.
Conclusions
Microbiological study is essential in ulcerated lesions particularly in moderate and severe infections. The most gram-positive isolated agent was SA and gram-negative agent was PA. 35.2% of the SA strains were methicillin-resistant which may be related to chronicity, recent hospitalization and previous antibiotic therapy, factors that are frequently present in diabetic patients followed in a tertiary care hospital.

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EP447

The association between the FTO gene and gestational diabetes mellitus

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Introduction
Common polymorphisms of the fat mass and obesity associated gene (FTO) is known to associate with increased obesity and diabetes mellitus type 2. This was the first study to investigate the association between the rs9939609 FTO gene polymorphism and gestational diabetes mellitus (GDM) in Turkish women.
Patients and methods
The case-control study included 203 gestational diabetes and 191 non-diabetic pregnant controls. Anthropometric and biochemical measurements were performed. Genotyping of FTO rs9939609 was studied.
Results
GDM had significantly higher age, gestational weeks, body mass index, fasting blood glucose, fasting insulin, HOMA-IR, HbA1c, systolic and diastolic blood pressure; as compared to controls ($P < 0.05$). The percentage of genotype TT (wild, 39.9 vs 41.1%), genotype AT (40.9 vs 46.6%) and genotype AA (19.2 vs 12%) were similar between GDM and controls, respectively. Genotype AA significantly had higher insulin and HOMA-IR than AT and TT. The FTO gene polymorphisms was not associated with an increased risk of GDM ($P = 0.05$, OR = 1.73, 95% CI 0.99–3.03).

Conclusion
The FTO rs9939609 SNP was not associated with an increased risk of GDM in women with GDM. The further studies is needed to be conducted to examine whether these risk variants predict the development of GDM.

Table 1 Clinical and biochemical parameters according to FTO genotype

	TT	AT	AA	*P*
Age	28.72±5.14	27.90±5.54	28.53±5.03	0.37
Gestational age (wk)	26.38±1.53	25.95±1.55	26.51±1.48	0.01
Body mass index (kg/m^2)	28.67±5.77	27.16±4.42	29.63±5.40	0.002
Fasting glucose (mg/dl)	88.29±17.46	85.96±17.54	90.70±16.53	0.15
Fasting insulin (mIU/l)	9.77±4.68	9.86±3.15	12.22±4.90	0.001
HOMA-IR	2.25±1.37	2.17±1.01	2.81±1.45	0.002
HbA1c (%)	5.29±0.46	5.23±0.43	5.31±0.51	0.13
Systolic blood pressure (mmHg)	103.47±15.25	107.06±12.92	110.54±12.12	0.009
Diastolic blood pressure (mmHg)	67.85±8.71	69.07±7.19	69.67±6.35	0.30

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EP448

Clinical inertia in type 2 diabetes mellitus without insulin treatment

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Introduction
Clinical inertia applied to type2 Diabetes Mellitus (T2DM) treatment, is defined as a lack of treatment's intensification of patients who are not in HbA1c target. Clinical inertia leads to a postponement of new therapeutic introduction, with all complications associated with a poor metabolic control. In Portugal there are only studies that show good or poor metabolic control but do not mention clinician's attitude towards these values. Recently published international studies reveal partial clinical inertia in 52.5% of cases and full clinical inertia in 12.8%.
Objective
To evaluate clinical inertia of T2DM's treatment in an Endocrinology department.
Methods
Cross-sectional, retrospective study of a random sample of patients with non-insulin treated T2DM, with minimum 12 months follow-up, during 2014–2015. It was established individualized HbA1c target based on patients' characteristics: life expectancy,hypoglycemia, cardiovascular disease or other comorbidities. Total clinical inertia was defined as no treatment's intensification at every visit and partial clinical inertia in at least one visit.
Results
We analyzed 317 patients, 73.9% male, 69.4±9.8 years, T2DM diagnosed for 11.5±8.7 years. 4.7% of patients had T2DM without treatment, 34.7% were treated with one non-insulinic antidiabetic drug (ANI), 38.5% with two ANI, 19.6% with three ANI, 2.2% with four ANI. It was established target HbA1c of 6.5% in 13.9% of patients; 7% in 48.9%; 7.5% in 30.9%; 8% in 5.6%. One hundred and twelve patients (35.3%) had HbA1c above target in at least one visit. Of these, there was total clinical inertia in 2.7% and partial inertia in 38.3%. HbA1c value was 0.1–0.5% higher than target in 65.6%; 0.6–1.0% in 17%; >1% at 13.8%. In subsequent visit, 43.8% recovered their HbA1c target, 38.1% had therapeutic intensification and 28.1% remained with clinical inertia.
Conclusion
The value of clinical inertia in our service was lower than described in literature and was associated with HbA1c values close to established target.

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EP449

Stress hyperglycemia ratio as a marker of disease severity in hospitalized patients with acute pyelonephritis

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Introduction
Hyperglycemia (irrespective of the presence of diabetes) has been associated with worse outcomes in hospitalized patients with a variety of diseases, namely critical illness. It is been recently proposed that a relative hyperglycemia – Stress Hyperglycemia Ratio (SHR) – might be even better associated with disease outcomes. We studied how SHR correlated with various morbidity parameters in hospitalized patients due to acute pyelonephritis.
Methods
We conducted a retrospective study in a Portuguese hospital. We included every patient admitted to Medicine or Endocrinology wards with the main diagnosis of acute pyelonephritis (which had HbA1c measured during the stay) between 2012 and 2015. SHR was calculated as admission glycemia divided by estimated average glucose derived from HbA1c. We assessed the duration of the hospital stay, analytical markers and Systemic Inflamatory Response Syndrome (SIRS) criteria at admission.
Results
A total of 57 patients (71.9% female) were included, with a mean age of 76.7 years old. 77.2% had the diagnosis of Type 2 Diabetes and the remainder were non-diabetic. 45.6% had sepsis criteria and the mean duration of hospital stay was 12.4 days. SHR (but not absolute glycemia) correlated positively with the length of hospital stay ($P=0.041$) and negatively with estimated glomerular filtrate rate (CKD-EPI formula) ($P=0.018$) at admission, in a Pearson correlation test. After adjusting for age, sex and diabetes presence, SHR correlated positively with the number of SIRS criteria.
Conclusion
SHR, which takes into account background glycemia rather than absolute glycemia alone, might be a biomarker of disease severity in case of patients hospitalized with acute pyelonephritis irrespective of being diabetic or not. Given this was a retrospective study and sample size was rather small, further studies are needed to confirm this hypothesis and to assess SHR relation with clinical outcomes.

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EP450

Reactive hypoglycemia: effectiveness of dietary regimen in a Tunisian population

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Introduction
Reactive hypoglycemia (RH) is characterized by postprandial hypoglycemic disorder aggravated by the ingestion of high *glycaemic index* (GI) foods.
The aim of this study was to evaluate the effectiveness of dietary regimen recommended for patients with RH.
Methods
This interventional prospective study included 20 patients consulted with symptoms suggesting RH, duration of monitoring was one month. Data had been collected by a spontaneous dietary survey and a questionnaire containing four items (demographic conditions, eating habits and lifestyle; evaluation of the effectiveness of the regimen). The questionnaire data had been collected before and after the diet regimen. Data entry was made by the Excel and analyzed by SPSS statistical software 16 and 19 and the food BILNUT investigation software.
Results
The mean age of the patients was 45.4±14 years. Daily caloric intake has been decreased from mean 2910.6 to 2717.1 Kcal/day and even carbohydrate intake of 396.3 (±213.7) to 314.5 (±102.3) g/day.
Daily intakes of respective proportions before and after the diet as shown below: for the protein was 90 (±35.8) and 90.4 (±21.8) g/day for the fibbers was 20.8 and 30 g/day for lipids was 107.3 (±46.2) and 122 (±25.1) g/day. There was significant reduction in frequency and severity of hypoglycemia ($P=0.021$).
Discussion and conclusion
The recommended regimen was effective in reducing episodes and severity of RH. We need other long-term prospective studies to better explain factors involved in this effectiveness.

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EP451

Gut microbiota and diet in patients with various glucose tolerance

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Background
Type 2 diabetes (T2D) is a progressive disease. The gut microbiota has recently been identified as a new potential diabetes risk factor.
Design
To investigate the gut microbiota composition in association with the dietary patterns in patients with different glucose tolerance we analyzed 92 patients: with normal glucose tolerance ($n=48$), prediabetes ($n=24$) and T2D ($n=20$). Metagenomic analysis was performed using 16SrRNA sequencing. The diet has been studied by a frequency method with a quantitative evaluation of food intake using a computer program.
Results
Patients with different glucose tolerance did not differ among themselves in the amount of consumed proteins, fats, carbohydrates. Patients with various glucose metabolism disorders differed among themselves the level of fasting glucose and HbA1c (higher in T2D), as well as the energy value of the daily diet and the amount of consumed carbohydrates (less in T2D). Microbiota in the samples was predominantly represented by Firmicutes and in a less degree by Bacteroidetes. Blautia was a dominanting genus in all samples. The representation of Blautia, Serratia was lower in prediabetes than in T2D patients, and even lower in those with normal glucose tolerance. After the clustering of the samples into groups according to the percentage of protein, fat, carbohydrates in the diet, the representation of the Bacteroides turned to be lower and Prevotella abundance turned to be higher in carbohydrate cluster. There were more patients with T2D ($P=0.002$) in the fat-protein cluster. Using the Calinski-Harabasz index identified the samples with more similar diets. It was discovered that half of the patients with a high-fat diet had normal tolerance, the others had T2D. The regression analysis showed that these T2D patients also had a higher representation of Blautia ($P=0.0001$).
Conclusions
The high Blautia representation in combination with high-fat diet (138 ± 63 g/day) is correlated with T2D.

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EP452

Circulating adipokine levels and insulin resistance in type 2 diabetes mellitus and metabolic syndrome

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Objectives
The prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly with obesity being a major risk factor. Adipocytes, besides storing fat, release a number of adipokines. Our study explored the association of leptin and resistin released by adipocytes in the pathogenesis of T2DM in context of metabolic syndrome.
Methods
This was a cross sectional study in which we measured plasma levels of insulin, leptin and resistin in 50 healthy non-diabetic controls and 114 subjects with T2DM. Diagnostic variables for metabolic syndrome were measured, including: blood pressure, adiposity indices, lipid profile and fasting glucose. Homeostasis model assessment of insulin resistance (HOMA-IR) was used to measure insulin resistance with 75th percentile value taken as cutoff point.
Results
Leptin strongly correlated with adiposity indices especially abdominal volume index, $P<0.001$. Resistin, however, did not show such correlation. In both genders, there was significant difference in the levels of insulin, HOMA-IR and resistin between control group and T2DM ($P<0.01$) and between controls and T2DM with metabolic syndrome ($P<0.001$). This relationship was not seen with leptin. Insulin resistance in males and females, as according to HOMA-IR level, was ≥ 3.7 and ≥ 3.8, respectively, and was significantly greater ($P<0.01$) in diabetics.
Conclusion
Leptin levels strongly correlate with and may be used as a potential marker of obesity. Resistin does not directly correlate with insulin resistance and metabolic syndrome. However, its significant rise in T2DM and metabolic syndrome groups as compared to controls cannot be ignored and require further studies.
Keywords: metabolic syndrome, adipokines, HOMA-IR, type 2 diabetes mellitus, Insulin resistance

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EP453

Frequency of diabetes and thyroid autoantibodies in patients with type 1 diabetes and their siblings

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Background
We investigated the frequency of autoimmune thyroid and diabetes antibodies in patients with type 1 diabetes mellitus (T1DM), their siblings, and controls.
Methods
Glutamic acid decarboxylase antibodies (GADA), islet cell antibodies (ICA), insulin autoantibodies (IAA), and thyroid antibodies were identified in all subjects.
Results
The rates of positive GADA and IAA were significantly higher in probands compared to siblings ($P<0.001$) and controls ($P<0.001$). None of the pancreatic autoantibodies were different between siblings and healthy controls. Thyroid antiperoxidase antibody (TPOAb) and antithyroglobulin antibody (TGAb) were significantly different between probands and control subjects ($P=0.002$ and $P=0.018$, retrospectively). The positive rates of TPOAb and TGAb in siblings were higher than those of controls, but no differences were detected between the groups. Thyroid autoimmunity (TA) was significantly different among the groups ($P=0.004$). Siblings of TA-positive probands revealed a greater prevalence of thyroid autoantibodies than did the control subjects ($P=0.022$), whereas siblings of TA-negative probands did not show such an increase over controls.
Conclusion
The prevalence of pancreatic and thyroid antibody positivity in probands was statistically significant compared to siblings and controls. Siblings of TA-positive probands revealed a greater prevalence of thyroid autoantibodies than did the control subjects. So the screening for TA in siblings, particularly siblings of TA-positive probands, is as important as in probands.

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EP454

PAI-1 polymorphism in patients with diabetes

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Background
Plasminogen activator inhibitor-1 (PAI-1) refers to group of is a serine protein inhibitors. It inhibits fibrinolysis and contributes to angiogenesis and atherogenesis processes. 4G/5G polymorphism was found to be associated with increased risk for cardiovascular diseases. It was of special interest to study PAI-1 polymorphism in patients with diabetes.
Aim
Aim to study PAI-1 polymorphism in patients with type 2 diabetes (T2D) and concomitant coronary heart disease (CHD).
Materials and methods
48 patients were included: group 1–20 almost healthy person, group 2–13 patients with T2D, group 3–15 patients with T2D and CHD. Patients were under 60 years old, patients with T2D were compensated by HbA1c ($6.5+1.2\%$ in group 2 and $6.5+0.6\%$ in group three correspondingly). Polymorphic variant of PAI-1 was determined by polymerase chain reaction (PCR).
Results and discussion
4G/5G polymorphism was statistically significant more frequent in patients with T2D and concomitant CHD (ten of the 15, 66,7%) compared to patients with diabetes (three of the 13, 23.1%) ($P<0.05$) and almost healthy person (ten of the

20, 50%) ($P<0.05$). In group 2 4G/4G polymorphism was recorded in five patients (38.5%) that was more frequent compared to group 3 (two of 15, 13.3%) ($P<0.05$), and six of 20 in controls (30%). There was no difference in frequencies between groups in 5G/5G polymorphism (three patients (15%) in group 1, four patients (30.8%) in group 2 and three patients (20%) in group 4).
Conclusion
4G/5G polymorphism is associated with CHD in patients with type 2 diabetes. 4G/4G polymorphism is supposed to have protective role in relation to macrovascular complication in diabetic patients.

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EP455

Metabolic syndrome as independent risk factor of poor glycemic control in type 2 diabetic patients

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Type 2 diabetes is considered a disease of epidemic proportions, its control is important to prevent macro and microvascular complications.
This study aims to determine the factors associated with poor glycemic control, defined as HbA1c $>7\%$ in type 2 diabetic patients of cardiovascular risk program of the Central Hospital of National Police in Colombia
Methodology
This is a descriptive cross-sectional study, where it is performed univariate and multivariate analysis of factors associated with poor glycemic control in the type 2 diabetes patients.
Results
3417 patients of cardiovascular risk program of which 1058 are type 2 diabetic patients were included. As independent factors of poor glycemic control found an LDL cholesterol >100 mgdl OR $=1.47$ (95% CI 1.12–1.944, $P=0.006$); HDL <40 mg/dl in men and <50 mg/dl in women OR $=1.44$ (95% CI 1.043–1.99, $P=0.027$); Duration of diabetes OR $=1.066$ (95% CI 1.049–1.084, $P=0.001$); Microalbuminuria >30 mg/g creatinuria OR $=1.484$ (95% CI 1.11–1.978, $P=0.007$) and IDF criteria of metabolic syndrome OR $=2.30$ (95%CI 1.47–3.59, $P=0.001$); adjusting for age, smoking, BMI and triglycerides.
Conclusion
The metabolic syndrome is an independent factor of poor glycemic control in type 2 diabetic patients; highlighting the importance of therapeutic lifestyle changes; they have been included in the programs of prevention and control of cardiovascular risk patients, in order to reduce the presence of the constituent factors of metabolic Syndrome.

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EP456

Serum vitamin D levels in patients with gestational diabetes mellitus

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Background
Insulin resistance and diabetes mellitus are associated with decreased serum vitamin D level. Therefore, we evaluate the 25-OH-vitamin D in GDM. This study was performed to evaluate the serum vitamin D levels in GDM patients.
Methods
This study consisted of 38 patients with GDM who followed up in Haseki Training and Research Hospital's Endocrinology outpatient clinic. GDM was diagnosed with 50 g (if postprandial 1 h >130–199 mg/dl) and then 100 g oral glucose tolerance test (OGTT) in 24–28 gestational weeks. The cut off criteria for GDM were as following at least two of results as; fasting blood glucose: 95 mg/dl, postprandial 1 h: 180 mg/dl, 2 h: 155 mg/dl, 3 h: 140 mg/dl. Serum vitamin D level and biochemical parameters were analyzed. Patients were divided into two groups as Group A (vitamin D <20 ng/ml) and Group B (>20 ng/ml).
Results
Mean BMI was 28.37 ± 4.02 in Group A, 25.62 ± 5.60 in Group B, (P: 0.033). Mean peripartum HbA1c was $5.51\pm0.54\%$ in Group A and $5.04\pm0.48\%$ in Group B, (P: 0.006). There was no any statistical difference in other biochemical parameters. Vitamin D was found to be negatively correlated with BMI (r: -0.377, P: 0.03) and peripartum HbA1c (r: -0.424, P: 0.014).
Conclusion
Vitamin D has a close relationship with BMI and peripartum HbA1c value. Moreover, decreased serum vitamin D level was correlates with higher BMI and HbA1c. Serum vitamin D level should be analyzed and followed up in patients during pregnancy.

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EP457

Acute pancreatitis and diabetic ketoacidosis in non-diabetic psychotic patient

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Introduction
Simultaneous occurrence of acute pancreatitis and diabetic ketoacidosis represents a very rare complication of antipsychotic medications.
Herein we report the case of acute pancreatitis and diabetic ketoacidosis in a non-diabetic patient while on treatment with haloperidol, chlorpromazine and carbamazepine
Case report
Mr. Z A is a 50-year-old non-diabetic man who was diagnosed with psychotic disorder and treated with haloperidol, chlorpromazine and carbamazepine. There were no past or present history of alcohol use and no history of gallstones or trauma.
In September 2015, the patient presented with sudden onset weakness and vomiting. On examination, he had a body weight of 110 kg, a BMI of 40.4 kg/m^2 and he was tachycardic and tachypnoeic. Abdominal examination revealed tenderness in the epigastrium. Capillary glycemia was 3.56 g/l with glycosuria $=+++$ and acetonuria $=+++$. On laboratory tests, he had a glycemia of 24 mmol/l, a bicarbonate level <3 mmol/l and an acute inflammation. Lipase was elevated at 1024 U/l (nr $=7$–60). Calcemia, lipid and liver function tests were normal.
Abdominal CT-scan showed acute pancreatitis features.
Patient was managed with insulin and intravenous fluids with a good recovery.
Conclusion
In our patient, features supporting acute pancreatitis secondary to antipsychotic drugs include the absence of alcohol intake, trauma or gallstones and normal lipids and calcemia. The possibility of developing acute pancreatitis and diabetic ketoacidosis while treated with antipsychotic agents impose periodic metabolic screening.

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EP458

Identification of LADA in normal weight diabetic Albanian population

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Background
Latent autoimmune diabetes of adults (LADA) constitutes 5–10% of the population with diabetes. Early diagnosis of LADA prevents misdiagnostification of type 2 diabetes and helps in the optimal treatment of patients, while maintaining a residual B cell function and delaying the time of their destruction.
Aim
The aim of the study identifying groups with higher risk of LADA in an Albanian population.
Material and methods
We recruited 149 neo-diagnosed diabetic patients aged from 30 to 60 years old. Age, sex, BMI, Waist circumference (WC), family history (FH), C-peptide, insulinaemia and anti-GAD antibodies were measured. Based on BMI the

population was divided in three groups: (N) normal weight BMI <25 kg/m^2, (Ov) overweight (BMI 25–30 kg/m^2) and (Ob) obese BMI >30 kg/m^2. According to family history the population was divided in positive FH and negative FH. LADA prevalence was calculated in all the groups.
Results
The overall LADA prevalence was 18.7%. The Prevalence of LADA in the N group was 33.3%, in the Ov group 30.9% and in the Ob group 9.5%. LADA's prevalence in the positive FH group was 17.2% and in the negative FH group 34.7%. In the non obese group (N+Ov) with negative FH LADA's prevalence reached 35.9% and increases even more in the N with negative FH the reaching 46.2%.
Conclusion
The overall LADA prevalence was 18.7%. According to our data subjects with normal weigh and no family history of diabetes have a higher risk of LADA, this emphasis the importance to investigate the autoimmune pattern in order to have earlier diagnosis and optimal treatment.

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EP459

The risk of developing of obstructive sleep apnea syndrome in type 2 diabetes mellitus patients in Uzbek population

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Actuality
According to WHO, 36% of patients with type 2 diabetes mellitus (T2DM) suffer from obstructive sleep apnoe syndrome (OSAS), which is one of global problems of modern medicine. International classification of sleep disorders identified that 24% of men and 9% of women with T2DM observe symptoms of OSAS. Sleep apnea has a negative effect on the function of the beta cells of the pancreas and insulin sensitivity. Obstructive sleep apnea has a negative impact on the quality of life of patients with type 2 diabetes in the physical and psychological sphere, lowers the overall health and performance of physiological sleep.
Purpose
Study the risk of OSAS in T2DM patients in Uzbekistan.
Materials and methods
The study included 300 patients, 150 women and 150 men with T2DM in middle age (45–60 years). Disease duration from 5 to 15 years. Identification of OSAS was carried out by STOP-BANG questionnaire with measurement of neck circumference, body mass index. OSAS risk was determined by summing up the points(p): high risk 5-8p, average 3-4p, low 0-2p.
Results
46 (31%) women and 46 (31%) of men had high risk, 78 (52%) women and 69 (46%) men had medium risk, 26 (17%) women and 35 (23%) men had low risk of OSAS. OSAS prevailed in the group of middle-aged women with low quality of life in comparison with men.
Conclusion
Our data results showed no gender differences in the high risk of sleep apnea development among patients with type 2 diabetes mellitus in Uzbekistan. While middle risk groups included more women 78 (52%). Low risk group consisted of 35 (23%) men predominantly. Our results contradict international data and show that women are more prone to OSAS than men.

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EP460

Importance of determination of albuminuria in patients with newly diagnosed type 2 diabetes mellitus

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Introduction
Worldwide, patients with type 2 diabetes mellitus (T2DM) compose 90–95% of total number of diabetics. 10% of people aged under 60 years are affected with T2DM, also are 10–20% of people aged 60–69 years, and 15–20% over the age of 70 years. The risk of diabetes may reach 30–40% during lifetime due to other factors than age. T2DM is characterised by higher development of cardiovascular lesions, which even more worsens the condition of the patient and increases the burden on the health care system. And since albuminuria is considered as a risk factor for cardiovascular complications and mortality, its determination is very important in screening programs for diabetes even after adjustment of other risk factors.
The aim of the study
To determine the level of albuminuria in patients with actively diagnosed T2DM.
Materials and methods
The screening for albuminuria involved 200 people aged 45–65 years, 100 males and 100 females, who during the screening for T2DM, were found to have HbA1c level over 6.5%. Albuminuria was determined by quantitative and qualitative methods. Detection sensitivity test regarding protein is 10–15 mg/l. All patients also were measured, in sitting, state for blood pressure on the shoulder by a mercury manometer.
Results
Albuminuria was found in 20% of males and 30% of females of the study. Subjects with BP up to 160/90 mmHg were found to have albuminuria in 32%, and with BP over 160/90 mmHg – 68%. Albuminuria was found in 13% of examined patients with HbA1c level 6.5–7.0%, and in 27% of patients with HbA1c level over 7.1%.
Conclusions
i) Albuminuria was found in 20% of males and 30% of females with newly diagnosed T2DM.
ii) The number of patients with albuminuria increased with HbA1c level over 7.1%.
iii) Albuminuria was diagnosed among all patients with both T2DM and hypertension.

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EP461

Procrastination and glycemic control of gestational diabetes – preliminary report

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Introduction
Psychological dimensions of gestational diabetes mellitus (GDM) are not adequately studied and related research is limited. Procrastination as a personality trait is involved in many aspects of daily life; it has not been studied in relation to GDM.
Aim
To assess procrastination in insulin-treated women with GDM.
Patients-methods
A total of 15 women (mean age $+$S.D.: $33+4$ years) diagnosed with GDM between 24–28 weeks of gestation (with a 75 g OGTT and the HAPO study criteria) and treated with >1 insulin injection/day. Over the last 4–5 weeks of pregnancy the women replied to Lay's questionnaire (General Procrastination Scale; validated Greek version), consisting of 20 questions, with five answers each (from 'never' to 'always'). The minimum possible score on the questionnaire is 20 and the maximum score is 100. Glycemic control of GDM was assessed by SMBG diaries covering a 1–3 week period. Glycemia was regarded as satisfactory with fasting glucose values <92 mg/dl and postprandial values <130 mg/dl ($+1$ hour) or <120 mg/dl ($+2$ hours). Glycemic control was considered as being satisfactory when 75% of measurements were within targets. Data were analyzed by plotting a ROC plot.
Results
Less than half of the women ($n=7$) had satisfactory glycemic control. Women with low procrastination score (<50) had worse glycemic control compared to those with high procrastination score (>50) (area under the ROC curve $=0.82$).
Discussion
The diagnosis of GDM creates tension and anxiety in pregnancy – especially in women treated with insulin – leading to increased obsessive-compulsiveness and stress. Procrastination is a self-defeating behavior, characterized by short-term benefits but long-term problems. This study shows that procrastination can, however, play a favorable role in the glycemic control of GDM.

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EP462

Factors associated with increased irisin levels in type 1 diabetes mellitus

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Aims
We aimed to determine the irisin level in patients with type 1 diabetes mellitus (T1DM) and to examine the relation of irisin level with inflammation and autoimmunity.
Methods
This study included 35 cases diagnosed with T1DM and 36 healthy volunteers. Anti-glutamic acid decarboxylase (Anti-GAD), islet cell antibody (ICA), insulin autoantibody levels of the patients have been measured at the time they were included in the study and were recorded from the patient files. Serum irisin levels were measured by ELISA kit.
Results
The median irisin level was determined higher in T1DM group compared to the control group (6.8 ng/ml vs 4.8 ng/ml, $P=0.022$; respectively). Median irisin level was found higher in anti-GAD ($P=0.022$) and ICA ($P=0.044$) positive groups compared to negative groups. In T1DM group irisin level displayed a positive correlation with glycosylated hemoglobin (HbA1c) ($r=0.377$, $P<0.001$) and anti-GAD ($r=0.392$, $P=0.020$) and a negative correlation with creatinine ($r=-0390$, $P=0.021$). In multivariate regression model, HbA1c (B ± SE: 2.76 ± 17 683, $P<0.001$), and anti-GAD (B ± SE: 2.311 ± 0.610, $P=0.001$) were determined as independent predictors for predicting the irisin level.
Conclusion
In patients of T1DM, which chronic inflammation and autoimmunity take part in its etiopathogenesis, anti-GAD level was an independent risk factor for irisin. This suggests that factors such as inflammation and autoimmunity can be effective in the synthesis of irisin.
Keywords: anti-glutamic acid decarboxylase, fibronectin type III domain containing 5, HbA1c, hyperglycemia, PGC1-α
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EP463

Interleukin-6, interleukin-15 concentrations and insulin resistance in autoimmune diabetes

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Background
Interleukin-15 and -6 play a role in an inflammation, autoimmune, infectious and cancerous processes. Their increased concentrations were observed in psoriasis, asthma, multiple sclerosis and type 2 diabetes. However, the role of IL-15 and IL-6 in autoimmune diabetes (AD) pathogenesis is still unknown.
Aim
The aim of our study was to assay circulating IL-15 and IL-6 levels in newly diagnosed AD patients, their I° relatives and healthy controls in comparison to the presence of anti-islet antibodies and insulin resistance.
Material and methods
The group studied consisted of 54 patients with AD (28 with LADA and 26 with T1D), 70 I° relatives and 60 controls. IL-6, IL-15 and anti-islet antibodies concentrations were measured by ELISA method. HOMAIR and eGDR were calculated.
Results
The patients with AD had significantly higher IL-15, IL-6 and HOMAIR and lower eGDR than the controls ($P<0.001$) and I° relatives ($P<0.001$). Significantly higher IL-15 and IL-6 were shown in the relatives with positive Ab as compared to the relatives without antibodies ($P<0.001$) and the controls ($P<0.001$). IL-15 negatively correlated with eGDR ($r=-0.436$, $P=0.02$) in LADA and positively with HOMAIR in LADA and T1D ($r=0.5072$, $P<0.001$; $r=0.4209$, $P<0.001$).
Conclusions
Significantly higher IL-15, IL-6 concentrations, HOMAIR and markedly lower eGDR in newly diagnosed AD patients and I° relatives with positive anti-islet antibodies might suggest the role of these proinflammatory cytokines and insulin resistance in the pathogenesis of AD. IL-15 and IL-6 might be used as biomarkers of the risk of AD development, in particular IL-15 for LADA. Both type of method of IR measurement seem to be equally useful for calculate insulin resistance in AD.
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EP464

The importance of gender difference in evaluation of relationship between MPV and serum biochemical parameters in type 2 diabetic patients

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Introduction
Increased mean platelet volume (MPV) is an independent risk factor for thromboembolism, stroke and myocardial infarction. In this study we tried to emphasize the importance of gender difference in evaluation of relationship between MPV and serum biochemical parameters in type 2 diabetic patients.
Methods
A total of 509 patients with diabetes mellitus who hospitalized due to several causes were retrospectively evaluated. Age, gender, other comorbidities, HbA1c, and other biochemical parameters were recorded. All data were analyzed by using SPSS 22.0 statistical package for Windows.
Result
A total of 509 patients consisted of 269 women and 240 men were included in this study. There was no difference in regard to other comorbidities between genders ($P>0.05$). Mean ages of women and men were 65.43 ± 16.1 and 64.84 ± 14.98 years, respectively ($P=0.669$). The mean MPV values of women and men were 8.61 ± 1.40 and 8.52 ± 1.47 fL, respectively ($P=0.486$). Erythrocyte sedimentation rate (ESR) ($P=0.016$), HDL-cholesterol (Chol) ($P=0.024$), total-Chol ($P=0.01$), and platelet (PLT) ($P=0.035$) levels were significantly higher in women whereas urea ($P=0.08$), creatinine ($P=0.0001$), and triglyceride ($P=0.002$) levels were significantly higher in men. There were positive correlations between MPV and urea, creatinine, uric acid, and PDW values and there were negative correlations between MPV and total-chol, LDL-chol, and PLT in women. Also there were positive correlations between MPV and HbA1c, glucose, uric acid, and PDW values and there were negative correlations between MPV and ESR and PLT values in men.
Conclusion
We did not find any difference in MPV values between male and female patients with diabetes. But we have showed that the significance of correlation analysis between MPV and each biochemical parameter depended upon gender. Thus the importance of gender difference in studies evaluating MPV levels in diabetic patients should be considered.
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EP465

Descriptive observational study of a group of diabetic patients admitted to Hospital Punta De Europa from Gibraltar area health field during the year 2015

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Objectives
The prevalence of diabetic patients admitted in hospitals close to 20% in some series. Our goal is to determine the prevalence of diabetic patients assessed by interclinical calls from different medical and surgical specialties that have been entered during 2015 in our Hospital, in order to describe the characteristics that these diabetic patients.

Material and methods
We present 116 patients evaluated by interclinical consultation request form from different medical and surgical specialties. The patients were admitted in Algeciras Hospital (Gibraltar Health Area) during 12 months - period beginning from 1 January to 31 December 2015. We have determined the different quantitative and qualitative variables: source of income, sex, age, type of diabetes, time of evolution, place of origin, family history, hospital stay, treatment before and during admission, complications of their diabetes and other cardiovascular risk factors associated.
Summary of results
58.3% were women compared to 41.7% of men with diabetes. The type 2 diabetes was 83.3%, 12.5% with type 1 diabetes, and 4.2% Diabetes not known before admission. The mean age of patients admitted with type 2 diabetes was 59.3 +/− 19.14 ST, and average age of type 1 patients was 34.6 years. Mean hospital stay was 23.5 +/− 19.7 days, and a 31.7% of readmissions. The survival rate was 87.5% versus 12.5% EXITUS.
Conclusions
• The Endocrinology Unit of Punta Europa Hospital (Gibraltar Health Area) received an average of 9.7 interclinical calls per month in 2015, in order to assessment of hyperglycemia in diabetic patients, either secondary to diabetes known as metabolically decompensated or in patients with no known diabetes before to admission.
• Hyperglycemia is a common finding in hospitalized patients. It is associated with increased days of hospital stay, morbidity and mortality.

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EP466

Influence of hypercalcemia and elevated parathyroid hormone level in the development of type 2 diabetes

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Status of carbohydrate metabolism in patients with primary hyperparathyroidism (PGPT) has been studied extensively in recent years, but the results of studies on the impact of long-term elevated levels of parathyroid hormone and hypercalcemia on the risk of type 2 diabetes continues to be in the discussion.
Objective
To study is to examine the prevalence of type 2 diabetes in patients with manifested and asymptomatic PGPT.
Materials and methods
General clinical examination of 136 patients with PGPT (note the presence of type 2 diabetes, available at diagnosis PGPT and developed in the period from diagnosis to surgical treatment PGPT), investigated parathyroid hormone, vitamin D and calcium.
Results
The asymptomatic PGPT reported in 54 patients (a mean age was 51.5 ± 11.6 years), manifested PGPT - 82 patients (a mean age was 52 ± 10.4 years). Type 2 diabetes is detected in 2 (3.7%) patients with asymptomatic PGPT and 12 persons (14.3%) with the manifested PGPT.
Significant differences was detected in the prevalence of type 2 diabetes in both groups of patients with PGPT ($F = 0.81$, $P < 0.05$).
Conclusion
The results of the study show an increasing prevalence of type 2 diabetes in patients with manifested PGPT compared with asymptomatic PGPT. The results may indicate the influence of long-term hypercalcemia and elevated levels of parathyroid hormone in the frequency of manifestation of type 2 diabetes in patients with PGPT.

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EP467

Hypertension in type 2 diabetes mellitus: associated treatment and degree of control

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Objectives
To evaluate the prevalence of hypertension in patients with type 2 diabetes mellitus (T2DM) and to analyze the clinical characteristics, the degree of achieved control and the associated antihypertensive treatment.
Methods
Cross-sectional study which included patients with T2DM followed in a primary care setting. Data about age, sex, associated antihypertensive treatment, systolic blood pressure (SBP) and diastolic blood pressure (DBP) was collected.
Results
From 79 patients included, 78.5% had hypertension. Mean age was 72.5 years (standard deviation [S.D.] 10.1 years) and 62.9% were men. Mean SBP was 126.5 mmHg (S.D. 13.7) and mean DBP 72.9 mmHg (S.D. 8.6). 77.6% of patients achieved blood pressure levels $<140/90$ mmHg. All patients were on antihypertensive treatment: 35.5% with ACE inhibitors, 45.2% with ARBs, 61.3% with diuretics and 30.6% with calcium channel blockers. Average number of antihypertensives was 2.15 (29% monotherapy, dual therapy 30.6%, triple therapy 32.3%, four or more antihypertensives 8.1%).
Conclusions
The vast majority of patients with T2DM have high blood pressure, but it is usually well-controlled. At least two antihypertensive drugs were used is most patients to control blood pressure, being the most used drug class ARBs.

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EP468

Earlier development of diabetes mellitus type 2 as a consequence to psychological and physiological stress

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Diabetes mellitus type 2 (DM-2) is a disorder characterized by high blood glucose levels in the context of insulin resistance and relative insulin deficiency. DM-2 is typically an outcome of combinations of hereditary elements of impaired insulin release and insulin resistance, and natural variables like obesity, overeating, absence of activity, aging and stress. A number of hormones, such as cortisol and growth (GH), have insulin-antagonistic effects. Cortisol is a predominant biological marker of stress, whereas GH is released in response to stress. This study explored stress as a predisposing factor in causing DM-2 by determining psychological stress using depression, anxiety and stress scale, physiological stress by measuring plasma cortisol and GH through ECLIA and random blood sugar (RBS) levels by glucometer in 100 male and female DM-2 patients of 21–60 years and 100 age-matched controls. The level of psychological stress was moderate to severe in all age groups with significantly higher level in age groups of 21–30 and 31–40 years. The higher level of psychological stress corresponded well with higher level of physiological stress in terms of release of cortisol in patients of 21–30 and 31–40 years, although cortisol concentrations were higher in all groups compared to normal subjects. The higher level of psychological stress did not influence physiological stress much in terms of GH release, although GH concentrations were markedly but non-significantly higher in diabetic patients compared to control groups. The concentrations of cortisol and glucose were positively correlated in all age groups. The majority of patients was married, belonged to lower middle class, fell in normal BMI category, had diabetic mothers and exhibited higher RBS whether or not they exercised, followed diet plan or used oral medication. In conclusion, stress is one of the dominant factors resulting in development of type 2 diabetes mellitus in our local population.

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EP469

The differences in insulin doses and the risk of hypoglycemia in 2 distinct days in the Romania diabetes futsal team

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In type 1 diabetes athletes, the proper adjustments of insulin doses and carbs intake are essential in order to avoid a hypoglycemic event that could affect the sport performances.
The aim of the study was to assess the risk of hypoglycemia, the insulin and glycemic variability in 2 different days (with and without physical activity) in a group of nine players with type 1 diabetes, members of the Romania diabetes futsal team (twice European champion).
The evaluation was achieved by means of a self monitoring journal in which the players were asked to note at least 7 glycemic values (at least one during the night, at 0300 h) in 2 different days. The relative risk (RR) and the odds ratio (OR) were used to compare the risk of hypoglycemia between the 2 days and the Pearson coefficient (r) to establish the correlations between the insulin doses and, respectively the average glucose levels.
The average age was 27.77 ± 4.57, with a glycated hemoglobin of $7.6\% \pm 0.9\%$ and 11.22 ± 6.38 age of diabetes. There were strong correlations in the total ($r = 0.858$), basal ($r = 0.784$) and prandial ($r = 0.884$) insulin doses between the 2 days. Also, a weak positive correlation ($r = 0.473$) between the average glucose levels in the 2 days was observed. According to OR there is a 4.375 higher risk of developing a hypoglycemic event in the day with physical activity (RR = 75%).
Our study confirms that physical activity it is an important risk factor for hypoglycemia in type 1 diabetes athletes. Our study also suggests that individualized strategies (including higher insulin doses reductions and proper carbs intake) are needed to avoid hypoglycemia and increase the athlete's performances.

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EP470

Type 2 diabetes and obesity

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Introduction
Type 2 diabetes is one of the most common not transmised disease in the world. Obesity is the main risk factor for type 2 diabetes. Both conditions are responsible of a significant increase in morbidity and mortality.
The aim of our study was to determine the prevalence of diabetes and fasting hyperglycemia in the general population and to compare this prevalence in obese and non-obese subjects.
Methods
This is a descriptive and analytical cross-sectional study conducted among a sample of individuals aged between 18 and 64 years living in the province of Algiers. The diabetes is defined by blood glucose levels > 1.26 g/l in fasting blood twice or > 2 g/l whatever the time of day. The IFG is defined by a fasting glucose between 1.10 and 1.26 g/l.
Results
Our survey covered a sample of 2210 individuals (1583 men and 627 women).
- The average blood glucose is 1.023 g/l (0.24–1.8).
- A moderate fasting hyperglycemia is found in 15.52% of individuals.
- A history of known diabetes was found in 7.65% of individuals.
- A diabetes mellitus was detected in 11.45% of sample.

The multi-varied analysis of subjects with global obesity (BMI > 30 kg/m^2) showed that the known diabetics were not more obese than non-diabetics: OR 1.17 (95% CI 0.77–1.78) $P = 0.471$. The pre diabetics and diabetes screened during our survey are more obese than non-diabetics. Pre diabetes: OR = 1.4 (95% CI 1.04–1.87) $P < 0.02$. Diabetics screened: OR = 1.4 (95% CI 1.67–3.17) $P < 0.001$.
Concerning abdominal obesity (IDF criteria) the same observation was made for known diabetics with global obesity OR = 1.22 (95% CI 0.66–1.188) $P > 0.05$. Pre- diabetics screened have not more risk for abdominal obesity than non-diabetic OR = 1.25 (95% CI 0.91–1.72) $P > 0.05$ unlike screened diabetes OR = 1.62 (95% CI 1.68–2.42) $P = 0.018$.
Conclusion
Obesity plays a key role in the pathophysiology of type 2 diabetes, early treatment of obesity is essential in the prevention and treatment of type 2 diabetes.

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EP471

Prevalence of dyslipidemia screened by Accutrend GCT

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Introduction
Obesity and especially abdominal obesity is therefore often associated with atherogenic dyslipidemia which lead to cardiovascular complications.
The aim of our study was to analyze the distribution of cholesterol and triglycerids and to determine the prevalence of dyslipidemia in the Algerian adult population and their variation depending on the presence or absence of obesity.
Methodology
Capillary samples using a validated lipids player (Accutrend GCT) were performed in 2210 individuals randomly selected from the general population. High cholesterol is defined by a fasting cholesterol (fasting 12 h) > 2 g/l. The hypertriglyceridemia is defined by a triglyceride levels after 12 h of fasting > 1.5 g/l, or a person treated to dyslipidemia.
Results
The mean fasting total cholesterol in our sample was 1.70 g/l (1–2.4).
The Average fasting triglycerids is 1.15 g/l (0.39–2.69). A known history of dyslipidemia was rated at 7.06% of subjects. A Dyslipidemia was detected in 26.11% of the individuals in our population.
The Comparison of the obese group with the non-obese group found a clear predominance of the prevalence in known and screened dyslipidemia in the obese group (global obesity and android) especially in men.
In multi-analysis varied patients with known and screened dyslipidemia are more obese than the normolipidemic
OR1 known 2.4 (95% CI 1.59–3.63) $P < 0.001$.
OR2 screened 1.63 (95% CI 1.27–2.08) $P < 0.001$.
When we analyzed abdominal obesity (IDF) known and screened dyslipidemic subjects are also more obese than subjects with normal lipid profile.
Known OR1 2.27 (95% CI 1.24–4.15) $P < 0.001$.
OR2 screened1.8 (95% CI 1.38–2.62) $P < 0.001$.
Conclusion
Dyslipidemia is a frequent complication of obesity that must be screened to prevent installatation of cardiovascular complications that often have implications for high morbidity and mortality and a significant financial cost.

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EP472

Patients with type 2 diabetes mellitus have an elevated prevalence of cardiovascular disease

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Objectives
To evaluate the prevalence of cardiovascular disease (CVD) and associated risk factors in patients with type 2 diabetes mellitus (T2DM) attended in a rural primary care setting.
Methods
Cross-sectional study which included patients with T2DM followed in a rural primary care setting. Data about several cardiovascular risk factors was collected (age, sex, smoking, hypertension and dyslipidemia). Also, data about coronary heart disease (CHD) and cerebrovascular disease was gathered.
Results
Seventy-nine patients were included in this study, with a mean duration of T2DM of 5.9 years (s.d. 5), mean age 70.1 years (DE 11.8), 63.3% males, and mean BMI 30.8 kg/m^2 (DE 11.8). 17.7% of patients had CHD, and prevalence of cerebrovascular disease was 12.7%. Regarding cardiovascular risk factors, smoking was found in 11%, hypertension in 78.5% and dyslipidemia in 54.4% of patients.
Conclusions
Most patients with T2DM attended in a rural setting have an elevated prevalence of cardiovascular risk factors and CVD is frequent, especially coronary heart disease.

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EP473

Insulin secretion several years after type 1 diabetes diagnosis: case reports

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Introduction
Currently, type 1 diabetes (T1D) is defined by the autoimmune destruction of the pancreatic β cells that culminates in dependence on exogenous insulin, typically 1–3 years after diagnosis. This ability to maintain a residual function of pancreatic β cells is, however, heterogeneous, appearing to be worst if the disease is early diagnosed. Recently, it was demonstrated that many type 1 diabetic patients produce small amounts of insulin decades after diagnosis.
Clinical cases
Case 1: Male, 42-years-old, diagnosed with T1D 18 years before. Currently on an insulin pump, he has reasonable metabolic control and no known complications. He has controlled hypertension and dyslipidemia. He was submitted to elective laparoscopic cholecystectomy that complicated with choleperitonitis. During postoperative period, under glycosylated fluids but *nil per os*, he remained without exogenous insulin administration for 7 days, with controlled blood glucose levels and without ketonemia.
Case 2: Female, 32-years-old, diagnosed with diabetes at age 19. At 29-years-old, because of a chronic poor metabolic control under irregular treatment with oral antidiabetic agents, she was referred to Endocrinology consultation. The investigation showed positive anti-GAD antibodies and a history compatible with T1D. She began insulin therapy with slight improvement in metabolic control due to lack of adherence. However, in periods of good therapeutic adhesion, glycemic control was relatively easy and predictable. She was recently hospitalized with diabetic ketoacidosis (first known episode).
Conclusion
The residual insulin production, detectable by the assay of C-peptide and its functional and clinical significance have been recently discussed. According to recent evidence, these cases show us that insulin production in type 1 diabetic patients can be kept for many years after diagnosis and that the end of the 'honey-moon phase' does not necessarily lead to the absence of insulin production.

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EP474

Pregnancy diabetes in a patient with phenylketonuria: when the diet is complicated

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Precedents
Thirty-nine year old Woman. Classic phenylketonuria diagnosed for neonatal screening in Germany. Good adherence to the diet from the infancy, with good metabolic control. Not response to test with BH4.
Pregnancy in 2007 with good controls of phenylalanine (Phe). Son with congenital cardiopathy.
Evolution
In 2013 she planed new pregnancy, departing from very good controls (<4 mg/dl) and ingestion of 22–24 Phe's rations and supplements without Phe. She did Phe and tyrosine controls weekly (Tyr), analysis with plasmatic amino acids and dietary survey quarterly.
In 24 pregnancy week O'Sullivan test was pathological (164 mg/dl). Oral overload of glucose was not tolerated. She had fast glycemias between 99 and 121 mg/dl and postprandial glycemias up to 146–169 mg/dl.
Initially controlling the ingestion of carbohydrates improved the glycemic control. In the third quarter the low levels of Phe and Tyr did necessarily to increase up to duplicating Phe's rations. Since the patient could not take proteins of high biological value, she increased the ingestion of vegetables, potatoes and changed the cereals, pasta and rice without proteins into others of normal content into proteins. This implied a deterioration of the glycemic control that derived in the prescription of Insulin NPH in two doses, and rapid insulin for postprandial control with good later control. She needed supplementation with tyrosine.
The childbirth was without incidents, with a healthy newborn child. Later she returned to reduce Phe's rations of the diet, tyrosine supplement and insulin therapy was suspended.
Discussion
The syndrome of maternal phenylketonuria appears in children of mothers affected for seriously or moderated hiperphenylalaninemia with Phe's plasmatic high concentrations during the previous months and/or the gestation. It involves in the fetus mental delay, microcephaly, cardiac malformations, atresia of esophagus and dismorfias facial, between others. The Phe crosses the placenta and high concentrations of the same one are difficultly metabolizables due to the foetal immaturity. It is indispensable to contribute quantity of proteins and energy adapted and to evaluate the contribution of proteins of formula without Phe. We report a case in the one that is necessary to be increasing Phe's rations based on food and supplements rich in carbohydrates, which complicates the managing of the pregnancy diabetes and it us forces the insulinoterpy, since it is not possible to reduce the ingestion of carbohydrates because a minor caloric contribution in patients with phenylketonuria would worsen Phe's levels.

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EP475

'Metabolic endotoxemia' in the presence and absence of type 2 diabetes mellitus

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Background
Type 2 diabetes mellitus (T2DM) is a condition of multi-factorial origin, involving several molecular mechanisms related to the intestinal micro-biota for its development. The micro-biota able to favor systemic exposure to the lipopolysaccharides (LPS), large glycolipids derived from the outer membrane of Gram-negative bacteria. LPS can cause a condition of 'metabolic endotoxemia' characterized by low-grade inflammation, insulin resistance.
Design
We performed a study in 21 individuals (10 T2DM patients, 11 controls) mean age 56.12 ± 13.2 years and analyzed the relationship between LPS and body mass index (BMI), age, lipoproteins, serum fasting glucose, glycated hemoglobin (HbA1c), parameters of low-grade inflammation.
Results
These groups not differed significantly in terms of total serum cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), interleukin (IL)-6, C-reactive protein (CRP), BMI and age. Group 'without T2DM' and group 'with T2DM' significantly differed in terms of HbA1c level ($4.3 \pm 0.23\%$ vs $7.56 \pm 0.47\%$, $P=0.0005$). Plasma LPS levels in T2DM patients (0.46 ± 0.31 nmol/ml) were significantly different from those in controls (0.29 ± 0.12 nmol/ml), $P=0.034$.
Significant relationship between LPS and glucose ($r(s)=0.3$; $P=0.026$), LPS and HbA1c ($r(s)=0.64$; $P=0.0049$) in all patients were revealed. After separate in groups significant relationship between LPS and glucose ($r(s)=0.4$; $P=0.003$), HbA1c ($r(s)=0.72$; $P=0.034$) in T2DM patients were revealed. In controls significant relationship were not revealed.
Conclusions
T2DM patients show higher LPS level, which significant relationship with the levels of fasting glucose and HbA1c unlike control group. Due to the small number of patients in the group we did not find a relationship between LPS and low-grade inflammation, lipoproteins.

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EP476

Mast cell a new player in Type 2 diabetes

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Introduction
Mast cells are critical effectors in inflammatory diseases, including cardiovascular and metabolic diseases and their associated complications. These cells exert their physiological and pathological activities by releasing granules containing histamine, cytokines, chemokines, and proteases, including mast cell-specific chymases and tryptases.

Aim of the study
To detect the role of mast cell in diabetic obese and correlation to different diabetic complications.
Subject and method
Seventy Type 2 diabetic obese patients attending the Diabetes and Endocrinology clinic in Kasr El Ani hospital compared to 15 healthy control.
Full medical history, complete physical examination, Anthropometric measurements (BMI, waist circumference) Michigan neuropathy score, Echo heart, fundus examination, fasting glucose–HbA1C – serum cholesterol – triglycerides-LDL-HDL(assessed after 12 h fasting) A/C ratio and Typtase level.
Results
Statistical difference between patients and control regarding BMI, glucose, cholesterol, HDL, LDL, tryptase ($P<0.001$), triglycerides ($P=0.001$). Tryptase correlated with BMI, fasting glucose, HbA1C, triglycerides which is statistically significant ($P=0.014$, $r=0.031$)/($P=0.012$, $r=0.297$)/($P<0.001$, $r=0.862$), ($P=0.039$, $r=0.247$). Tryptase is higher in patients with complication mean value (39.32 ± 4.9) ng/ml. Four patients with retinopathy, six patients with peripheral neuropathy, three patients diabetic nephropathy, eight patients ischeamic heart disease , three patients with cerebro vascular disease.
Highest level in patients with diabetic nephropathy mean (38.2 ± 3.7) ng/ml.
Conclusion
Tryptase participate in the pathogenesis of diabetes mellitus and its complication targeting mast cells as novel therapy for diabetes requires further investigations.
Keywords: Diabetes, mast cells tryptase, complication.
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EP477

Knowledge, and behaviors of Albanian nurses in primary care toward diabetes mellitus type 2 risk factors reduction

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Introduction
The rising incidence of diabetes mellitus type 2 in Albania intensifies the need for effective health education for diabetes risk factors reduction among nurses and other health care practitioners.
Purpose
The purpose of this study was to develop a description of nurses' knowledge about, attitudes toward, practice behaviors related to Diabetes mellitus type 2 risk reduction.
Methods
We surveyed 50 primary care nurses in 10 health centers in northwestern Albania located in two cities in Lezhe and Shkoder). The data was collected over five weeks and was analyzed using descriptive analysis.
Results
The majority of the surveyed nurses could identify common risk factors for diabetes type 2 and had positive attitudes toward diabetes risk reduction.
However, <62% of the respondents could correctly answer questions about evidence-based recommendations for diabetes mellitus type 2 risk reduction. This sample of albanian nursing professionals lacked knowledge critical to providing guidance to individuals with or at risk for diabetes.
Conclusions
However this is a small scale study and further investigation need to be done.
More intensive and creative approaches to the education of nursing professionals regarding diabetes mellitus type 2 risk factors reduction are recommended.
Keywords: diabetes mellitus type 2, nurses, education, Albania.
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EP478

Evaluation of metabolic parameters of gestational diabetics in postpartum period

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Background
Gestational diabetes mellitus (GDM) is the high blood glucose levels in pregnant women. GDM have high risk for type 2 diabetes mellitus after pregnancy. Therefore, we evaluated postpartum DM frequency and metabolic parameters of the patients who had GDM in this study.
Methods
It was enrolled 40 patients, who had high glucose level during fasting or/and after meal and abnormal glucose level during OGTT in 24–28 weeks, in endocrinology outpatient between 2011–2014. We evaluated metabolic parameters of GDM in the sixth month of postpartum period.
Weight, height, BMI were evaluated. Blood tests were performed (fasting and after meal glucose level, insulin, lipid profile, hbA1c, urea, creatinine, spot urea protein/creatinine).
Results
Postpartum diabetes mellitus was developed in seven patients in follow up period (17.5%). The median age of the postnatal diabetics is 33.14 ± 6.4, the postnatal nondiabetics median age is 34.48 ± 5.7. Mean fasting glucose level and hbA1c values were statistically higher in postpartum diabetic patients, 125.14 ± 49.421, 6.243 ± 1.41, *P*:0.001, *P*:0.005, respectively. The mean BMI, waist circumference, triglyseride levels of the postpartum diabetic patients are 31.47 ± 8.91, 99 ± 16.381, 165.271 ± 127.499, of nondiabetics are 29.13 ± 4.4, 96.45 ± 13.44, 102.706 ± 68.525. There is no significant difference between BMI, waist circumference, triglyseride level of two groups. (*P*:0.521, *P*:0.607, *P*:0.240).
Conclusion
There was not a precise finding to forsee permanent diabetes mellitus after pregnancy in GDM patients according to our study. Moreover, GDM enhances risk of postpartum ongoing diabetes mellitus.

Table 1 Comparison of metabolic and laboratory parameters of study groups

	Group A - GDM with initial vitamin D ≤20 ng/ml (*n*: 17)	Group B - GDM with initial vitamin D >20 ng/ml (*n*: 21)	*P* value
Age	33.50±3.90	31.82±5.01	0.244
Weight in first trimester (kg)	70.61±7.91	66.47±13.22	0.241
Weight in peripartum (kg)	80.57±7.67	76.06±12.56	0.294
BMI (kg/m^2)	28.37±4.06	25.62±5.60	***0.033***
Fasting blood glucose (mg/dl)	96.17±13.51	89.93±10.63	0.341
HbA1c in peripartum (%)	5.51±0.54	5.04±0.48	***0.006***
Insulin (U/l)	9.21±3.12	12.44±4.95	0.027
HOMA-IR	1.92±0.93	2.82±1.34	0.297
50 gr OGTT – 1. hour (mg/dl)	165.19±20.32	176.15±16.02	0.856
100 gr OGTT – fasting glucose (mg/dl)	102.06±16.56	93.21±12.55	0.438
100 gr OGTT – 1. hour (mg/dl)	221.18±45.22	218.10±26.31	0.296
100 gr OGTT – 2. hour (mg/dl)	175.04±49.51	165.89±45.57	0.707
100 gr OGTT – 3. hour (mg/dl)	102.33±51.89	128.08±46.11	0.165
Free T4 hormone	0.72±0.25	0.75±0.24	0.641
Thyroid stimulant hormone	1.27±0.82	3.06±3.41	0.042
Anti thyroid peroxidase anticore	43.36±140.67	35.50±71.49	0.957
Anti thyroglobulin anticore	32.96±33.60	100.55±279.46	0.789
Parathormone	27.08±15.44	27.29±12.83	0.056
Calcium (mg/dl)	9.22±0.36	9.15±0.54	0.977
Phosphate (mg/dl)	3.90±0.63	3.68±0.92	0.486
Albumin (mg/dl)	3.74±0.21	3.61±0.42	0.241

Table 2 Spearman's correlation results between vitamin D and metabolic parameters

	BMI	HbA1c in Peripartum	Fasting Blood Glucose	HOMA-IR
Vitamin D				
R	***−0.377***	***−0.424***	−0.202	0.147
P	***0.030***	***0.014***	0.232	0.386
N	33	33	37	37

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EP479

How changed face of gestational diabetes mellitus within 12 years in Turkey

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Backgrounds and aims
We aimed to determine final status of carbohydrate (CHO) intolerance of women with GDM who were followed between 3 months and 10 years after delivery.
Materials and methods
Two hundred and fourty participants with GDM history were enrolled into study and divided into two groups. [Group I: 40 women (38.0±6.3 years) who had delivery before 11±2 years ago, Group II: 200 women (34.0±5.1 years) who had delivery within 3–6 months]. Final status of a participants was evaluated with 75 g OGTT and compared the features of groups according to possible risk factors indicating CHO intolerance.
Results

	Group I	Group II	*P**
n	40	200	
Age-at-gestation (yrs)	28.7±5.7	34.0±3.1	**0.001**
BMI (kg/m^2)	30.5±3.8	29.7±2.5	0.126
Family history of DM (n)	2.0±1.9	1.8±1.9	0.587
Multiparity	1.5±1.6	0.8±0.9	**0.004**
At diagnosis A1C (%)	5.0±1.0	5.5±0.5	0.093
At diagnosis OGTT glucose (mg/dl)			
Fasting	100.8±23.5	93.6±11.8	0.148
1.st h	212.6±44.4	198.6±26.9	**0.036**
2.nd h	194.0±50.0	165.4±38.3	**0.003**
3rd h	133±45.2	122.5±37.3	0.559
Gestational week at diagnosis	29.6±5.8	27.3±4.9	**0.022**
Weight gain (kg)	11.8±4.8	9.6±4.5	**0.006**
Delivery time	38.2±1.3	38.4±1.6	**0.018**
Fetus of birth			
Length (cm)/Weight (kg)	50.2±2.4/3355.0±547.5	47.5±3.2/3181.6±543.5	<**0.001/0.033**
Head circumference (cm)	36.0±5.9	34.7±5.6	0.250
Final HOMA-IR	2.8±1.7	1.4±1.1	<**0.001**
Final status of CHO tolerance *n*(%)			
Normal/IFG+IGT/DM	23 (57.5)/8 (20)/9(22.5)	177(88.5)/19(9.5)/4(2.0)	

Conclusions
In our country; as compared today, 12 years ago women used to became pregnant at younger ages but diagnosis was possible at later weeks of pregnancy, delivery time was early, maternal weight gain during gestation and fetal weight at birth were high. Postpartum follow-up of GDM after delivery is important. Although CHO intolerance normalizes soon after delivery in most women; it may sustain immediately after delivery and the frequency may be increased in the follow up years. Having multiparity and high BMI; obtaining high glucose levels at diagnosis, are crucial predictors of development of GDM but also we can conclude that the frequency of GDM increases as follow-up years after delivery increases.
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EP480

Does education effect the rates of prophylactic vaccination in elderly diabetics?
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Introduction
This study is performed for inspecting vaccination rates in geriatric patients, negatory effects leading to unvaccination and changes occuring in vaccination rates by patient education.
Methods
This study is planned in a combination of two formats: retrospectively for determining last 5 years' vaccination rates of patients and prospectively for determining the change in vaccination rates after patient education. Totally 579 diabetic patients, 206 patients of 65 years and over (group 1) and 373 patients under 65 years (group 2) were admitted to the study.
Results
Among preeducational reasons of avoiding vaccination, not to need vaccination was more frequently seen in group 2 when compared to group 1 (98.1% vs 91.7%, $P<0.001$). Pneumococ, influenzae and hepatitis vaccination rates all increased after education in the whole study population. (1.4% vs 12.4%, 12.1% vs 36.6%, 0.5% vs 3.8%, respectively; $P<0.001$).
Conclusions
It is seen that giving detailed information to geriatric patients about necessary vaccines and removing suspicions and anxiety about vaccination (about adverse events, for example) makes the vaccination rates raise. Primarily health professionals should be educated for this aim and they shouldn't withhold the effort to give sufficient education to patients on time.
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EP481

Influence of obesity and carbohydrate metabolism disorders in GLP-1 levels in women with history of gestational diabetes mellitus
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Introduction
There is a reduction of the incretin effect in patients with type 2 diabetes secondary to altered secretion of incretin hormones and/or failed of its action.
Objective
To study the GLP-1 secretion pattern after an oral glucose tolerance test (OGTT) in postpartum reassessment of women with previous GDM.
Materials and methods
Prospective epidemiological study of 48 women with a history of GDM. We evaluated age, history of GDM or macrosomia, family history of diabetes, insulin therapy use, birth weight and type of delivery; 13±1 months after childbirth, we reassessed clinical-analytical characteristics and performed a 75-g OGTT. We measured glucose, insulin and GLP-1 levels (basal-30-60-120′). Classification of patients was based on OGTT: normal vs prediabetic/diabetic and based on BMI: obese (IMC≥30 kg/m^2) vs non-obese. Differences between groups were analyzed using Mann–Whitney and χ^2 tests.
Results
Patients mean age 35±5 years, BMI 29±6 kg/m^2, A1c 5.5±0.3%, HOMA-IR 2.2±1.4. Women with pathological OGTT needed insulin therapy more often during pregnancy and had higher levels of insulin resistance, but they did not differ significantly from those with non-pathological OGTT in metabolic syndrome characteristics although they had higher cholesterol and triglycerides levels. There were no significant differences in GLP-1 basal levels and after the OGTT between groups. Obese women had significantly higher basal and postprandial insulin, HOMA-IR and HOMA-β with no differences in glucose levels, and lower levels of basal and postprandial GLP-1 than non-obese.
Conclusions
Women with a history of GDM and prediabetes/diabetes in postpartum reassessment do not differ in GLP-1 secretion after OGTT of healthy patients. However, obese patients have lower incretinic response after OGTT compared with non-obese.
The defect in incretinic secretion does not help to explain the pathogenesis of diabetes that occurs after GDM.
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EP482

Unstable expression of GPRC6A in human pancreatic β-cells
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Introduction
GPRC6A is a widely expressed seven-transmembrane G-protein coupled receptor mediating L-α-amino acids signaling (mainly, arginine, lysine, and ornithine), which has been proposed as receptor for osteocalcin. By interacting with GPRC6A, in β-cells, osteocalcin is thought to modulate the glucose-induced insulin secretion. However, GPRC6A functions have been studied only in rodents or in rodents-derived cells.

Aim of this study was to characterize the GPRC6A expression in different culture conditions in 1.1B4 cells, a human model of pancreatic β-cells.
Methods
1.1B4 cells were cultured in RPMI-1640 medium supplemented with 10% FBS. To evaluate GPRC6A expression cells were seeded at different densities, from 2000 to 40 000/cm^2 and harvested every day over 7 days.
At the end of the experiments total RNA was extracted, reverse transcribed to cDNA and amplified through PCR by means of GPRC6A specific primers. In parallel GPRC6A protein expression in cell lysates was evaluated by western blotting.
Results
Our results show that at low cell densities (2000–5000/cm^2) GPRC6A expression was kept very low over the culture period. Instead, at higher cell densities ($>$10 000/cm^2) the expression level is increased over time parallel to the cell growth, and it remained stable from day 4 up to day 7. Western blotting results, however, differed from gene expression data since from day 3 the protein level remained stable.
Conclusions
GPRC6A expression in 1.1B4 human pancreatic β-cells is very unstable and it is strikingly dependent on seeding cell density and days on cultures.

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EP483

Estimation risk model as a new method of insulin-induced lipohypertrophy diagnostics in diabetic patients

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Introduction
Lipohypertrophy (LH) is a chronic complication of diabetes mellitus that caused by frequent subcutaneous injections of insulin. Nowadays, LH were modified due to good quality modern insulin and expansion their concentration. As a result, some difficulties of diagnosis were appeared.
Design
The aim of this study has been to develop the estimation risk model of insulin induced LH in diabetic patients. This study was done on 140 diabetic patients (89 females and 51 males) who had been under the treatment with insulin a mean 8 years. Observation and palpation techniques, as well as ultrasonography of subcutaneous fat were used in assessing LH in these diabetics. All patients were divided into two groups. First group included 117 patients with LH, second – 23 diabetics without LH. Further, all LH risk factors were statistically processed using Spearman's, Kendall tau, Gamma rank correlation coefficients and binary logistic regression. Results were statistically significant when $P<0.05$.
Results
All risk factors were analyzed using rank correlation coefficients on first stage. Statistically insignificant parameters were eliminated ($P>0.05$). Ten factors from 23 were remained after first stage. Further, 10 parameters were subjected to ROC-analysis. Measure AUC was determined. All risk factors had high predictive value (AUC$>$0.5). So, they were used to development the estimation risk model. On the basis of binary logistic regression the estimation risk model was created. Predictive value of model was 86% taking into account threshold cut-off 0.3 and confidence interval 95%. Efficacy of estimation risk model were tested on 34 diabetic patients.
Conclusions
Nowadays, LH remains severe insulinotherapy complication. Primary prevention is necessary for diabetic patients with pathologic areas of subcutaneous fat. Therefore, we developed the estimation risk model with good quality and high predictive value (86%) for diabetic patients who are under the treatment with insulin.

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Diabetes complications

EP484

Association of the PPARG2 Pro12Ala, TNFα G(308)A and G(238)A, Lipc C(-514)T, Ace I/D, Slco1b1 Val174ala polymorphism with endothelial function and atorvastatin response in type 2 diabetic patients

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Aim
To assess the association of the endothelial dysfunction (ED) parameters and the lipid-lowering response to atorvastatin therapy in patients with T2D with genetic markers of inflammation.
Methods
We include 97 T2D patients with first prescribed atorvastatin 10–20 mg: M/F 26/71; mean age 57 years. After 12 month of statin therapy, patients had fasting lipid profiles and ED parameters repeated. For ED evaluation, we performed pulse wave analysis with reactive hyperemia by peripheral arterial tonometry. The genotypes were identified by PCR in real time with the TaqMan probes for a complex of polymorphic markers. Statistic analysis was evaluated using the Mann-Whitney, Wilcoxon tests, $P<0.05$.
Results
There was no difference in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) levels and ED parameters between the genotypes of studied genes in statin-untreated subjects. With statin therapy, PPARG2Pro/Pro had significantly TC, LDL-C lowering compared with PPARG2Pro/Ala, PPARG2 Ala/Ala patients (for TC: 20.74% vs 4.6% and 5.61%; $P=0.04$, respectively; for LDL-C: 26.00% vs 6.11% and 7.32%; $P=0.029$, respectively). The carries *GG of TNFα G(238)A* and *GA of TNFα G(308)A* had significantly greater in amplitude of postocclusive wave increase (Apw) compared with the carries *GA of TNFα G(238)A* and *GG of TNFα G(308)A* ($+8.16\%$ vs -0.93%, $P=0.04$; $+44\%$ vs -4.4%, $P=0.004$, respectively). The percentage of Apw and TC, LDL-C improvement did not depend on age, diabetes duration, basal lipids levels and HbA1c but it depend on genotypes distribution of *TNF-α G(238)A* and *G(308)A* and *PPARG2 Pro12Ala*, respectively. There was no statistically significant association between ED and atorvastatin response with other studied markers.
Conclusion
PPARG2 Pro12Ala polymorphism accounts for interindividual variability of response to statin therapy in patients with T2D. Significant association of *TNF-α* gene polymorphism with ED in T2D suggests an important role of inflammation in the genesis of MVD.

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EP485

Acupuncture treatment for diabetic gastroparesis

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Introduction
The aim of this study was to compare the effectiveness acupuncture for the treatment of diabetic gastroparesis (DG). Acupuncture may improve gastrointestinal symptoms in patients with various disorders, but its efficacy in diabetic gastroparesis is unclear.
Materials and methods
We have studied 23 subjects with type 2 DM with the duration of 14.2 ± 3.1 years, with longstanding and uncontrolled carbohydrate metabolism (mean value of HbA_1C was $8.6\pm1.3\%$) and symptoms of gastroparesis. All patients divided into two groups: diabetic with symptoms of gastroparesis (consisted of 11 participants (4 male/7 female), mean age was 46.8 ± 7.4 years, mean BMI was 25.2 ± 1.2 kg/m^2) received itopride hydrochloride (daily doses -50 mg) for 3 weeks and second group patients with confirmed diagnosis of DG (12 patients (5 male/7 female), mean age was 45.9 ± 6.5 years, mean BMI was 27.4 ± 4.6 kg/m^2) assigned to biweekly acupuncture treatments during 21 days. Gastric emptying rate, glucose and glycated haemoglobin (HbA_1C) levels were measured at start and end of each treatment period. The patients completed the Gastroparesis Cardinal Symptom Index (GCSI). No subjects studied have had the signs of other disorders of dysfunction in gastrointestinal motility.
Results
In the first group was no change in any of the outcome parameters after 3 weeks of the treatment with itopride hydrochloride. Acupuncture was associated with a decrease in scores for almost all cardinal symptoms of the GCSI and associated with significantly greater reductions in gastric retention with help of ^{13}C-octanoic breast test (^{13}C-OBT) ($-6.1\pm7.0\%$; 95% CI -13.3% to -6.1; $P<0.01$). There were no significant differences in fasting blood glucose levels between symptomatic therapy (itopride hydrochloride) and acupuncture treatments.
Conclusions
In patients with DG, 3 weeks of acupuncture reduces gastric retention and improves gastroparesis symptoms. It appears that this effect may be due to non-specific mechanisms.

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EP486

The dual burden of tuberculosis and diabetes in hospitalized Spanish patients

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Aims
The dual burden of tuberculosis (TBC) and diabetes (DM) has attracted much attention in the past decade. Patients with type 2 diabetes have a higher risk of developing pulmonary tuberculosis; moreover, DM co-morbidity in pulmonary TB is associated with poor treatment outcomes. Patients admitted to Internal Medicine (IM) Departments are an ideal setting to analyze the prognostic roll of DM on TBC clinical course.
Material and method
The Minimum Basic Data Set (MBDS) from all discharges of IM patients from public hospitals in Spain (2005–2011) was analyzed. All patients with a TBC diagnosis were selected (codes CIE 9-MC) comparing those with and without DM. The adjusted Charlson index was used as a measure of patient comorbidity. Univariate and bivariate statistical analysis was performed where a $P<0.005$ was considered significant.
Results
A total of 25 367 patients with TBC were identified; 9.2% had also a diagnosis of DM2. Patients with DM2 had higher mortality than non-DM patients (7.7% vs 4.8%; $P<0.01$). Hypoglycaemia was registered in 150 cases, also with higher mortality.
Conclusions
In our study TBC patients admitted to Spanish hospitals in the presence of DM2 and also those with hypoglycaemia showed an increased mortality. The extra-pulmonary and spread forms are also relatively frequent ($>30\%$) in subjects with DM2.
Early screening of DM2 and/or treatment with tight glycemic control in individuals hospitalized for TBC might be able to decrease the mortality associated in patients with both diagnoses on admission. Patients with diabetes with a poor treatment adherence and a HbA1C $>6\%$ could be a risk group for developing TBC, probably due to the long term immunosuppressive state thus generated. Recent studies indicate that the coexistence of DM and TB alters the distribution of the cell populations in the immune system, although large cross-sectional trials are required.

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EP487

Improvement of finger amputation technique in the treatment of diabetic foot

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Introduction
Diabetic foot is one of the leading disabling chronic complications of diabetes. From 40 to 60% (and in some regions up to 90%) of all non-traumatic amputations are performed in patients with diabetes. According to international epidemiological studies, the incidence of amputations reaches 206 cases per 100 thousand. In Ukraine in 2015, up to 2656 lower limb amputations were performed in patients with diabetes, which is 0.62 persons per 10 000 of population.
Methods
Amputations were performed in 31 diabetics with neuropathic and neuroischemic diabetic foot forms, including 11 males of 60.50 ± 1.50 years old and 20 females of 70.95 ± 1.45 years old. A control group composed 30 patients. The peculiarity of the proposed method was the application of silica sorbent on the wound after finger amputation, without suturing the wound. The next day, when the dressing was removed, the wound was debrided using ultrasonic cavitation system with continuous observation of the wound and application of vacuum therapy. The next step was plastic closure of the wound.
Results
The average length of stay of the research patients at the hospital before a plastic closure of wound was 15.50 ± 1.12 days, while the duration of the control group was averaged 24.42 ± 0.13 days.
Conclusions
1) Implementation of the proposed method of surgery eliminates the need for high amputations in patients with diabetic foot.
2) The proposed method of surgical treatment using the vacuum dressings in patients with diabetic foot eliminates the need for additional surgical procedures.
3) Combined surgical treatment of purulent complications of the foot using vacuum therapy helps to twice speed up cleaning of the wound and reduces surgical treatment duration in 1.6 times.
4) Improved technique of the surgical treatment of the foot with the preservation of its bearing capacity is recommended for implementation in treatment of purulent-necrotic complications of diabetic foot.

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EP488

Does type 2 diabetes mellitus affect bone mineral density?

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Introduction
The effects of diabetes mellitus (DM) on bone mineralization and osteoporosis is not well established. While reduction in bone mineral density in patients with type 1 diabetes is almost confirmed, effects of type 2 diabetes on bone health is still unclear. However in some studies bone mineral density (BMD) was suggested to be normal or elevated, epidemiological reports have shown an increased risk of fracture among patients with type 2 diabetes. This paper tries to report interim results of the study which was designed to evaluate the probable association between type 2 diabetes and osteoporosis.
Method
In this study, 1000 subject were selected randomly from patients undergoing bone densitometry in Gorgan, Iran. Their demographic data, history of concomitant disease and history of pharmacologic treatment were extracted. Bone mineral density was assessed by Norland machine at the lumbar and femoral neck. Data of patients with type 2 diabetes were separated. All data were analyzed by SPSS software version 16, using *T*-test.
Results
From the 1000 studied patients, 367 (36.7%) were diabetic. The mean age of diabetic patients was 56.23 years. 325 (88.55%) of these patients were female. In diabetic patients, mean *T*-Score at lumbar spine and femoral neck were -0.60 ± 7.11 and -1.48 ± 6.80 respectively. Mean BMD value at lumbar spine and femoral neck were also 0.90 ± 0.23 and 0.75 ± 0.13 respectively. The prevalence of osteoporosis at lumbar spine and femoral neck of diabetic patients were 31.06 and 38.96%, respectively. The association between DM with BMD and *T*-score in the femoral and lumbar areas was not statistically significant (*P*-value >0.05).
Conclusion
According to our results, it seems that type 2 diabetes mellitus does not affect bone density and the causes of increased risk of fracture in dieses patients can be other complications of DM (such as sensory neuropathy or visual impairment) however further studies are recommended.

Keywords: Bone mineral density, type 2 diabetes mellitus, osteoporosis
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Risk factors for mortality in elderly diabetic patients with pneumonia

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Introduction
In this study we aimed to examine the risk factors associated with mortality of pneumonia among diabetic seniors in Turkish general population.
Material and methods
After excluding individuals from other minorities, elderly diabetic patients who had been hospitalized due to pneumonia in recent three years consisted of study population. A total of 610 subjects aged 65 years or older were retrospectively analyzed and 196 patients who had no missing information on variables for the analysis were included. Patients' age, gender, hospital length of stay (LoS), mortality, presenting symptoms, other comorbid illnesses, chest X-ray findings, chest computed tomography (CT) findings, coagulation, complete blood count (CBC), and chemistry results were recorded and statistically analyzed.

Results
Female/male ratio was 0.83:1 (45.4% female, 54.6% male). Mean age was 79.03±7.25 years, median LoS was 9 days (range: 1–206 days), and mortality rate was 18.9%. Gender and age did not have an impact on mortality. In regard to presenting symptoms only impaired consciousness ($P=0.0001$) and impaired general condition ($P=0.05$) were associated with increased mortality. Similarly, concomitant acute kidney injury (0.026), pretibial edema (0.0001), hypertension (0.05), chronic heart failure (0.012), atelectasis on chest CT (0.0001), abnormal levels of gamma-glutamyl transferase (GGT) (0.033), urea (0.037), creatinine (0.010) and potassium (0.028) were associated with increased mortality. But fever, anemia, concomitant coronary artery disease, chronic renal failure, cerebrovascular disease, Alzheimer disease, all chest X-ray and CT findings (except atelectasis on chest CT) (e.g. right/left effusion, right/left infiltration, cardiomegaly), abnormal levels of all CBC parameters, AST, ALT, LDH, HbA1c, uric acid, total protein, albumin, sodium, and calcium were not associated with increased mortality.
Conclusion
Although diabetes is an independent risk factor for developing pneumonia, our proposed risk factors should be evaluated in those patients in order to predict increased mortality.

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EP490

Mauriac syndrome – a rare type 1 diabetes mellitus complication and an opportunity for intervention

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Introduction
Mauriac Syndrome is characterized by the presence of hepatomegaly, growth retardation, delayed puberty and cushingoid features. This entity is traditionally diagnosed during the work-up of hepatic enzymes alterations in children/young adults with type 1 diabetes mellitus (T1DM) with poor glycaemic control. However, the impact of metabolic control in the normalization of hepatic analytic profile is not clarified.
Methods and design
Retrospective study of five patients with T1DM with hepatic histopathology indicative of Mauriac Syndrome.
Results
The mean age of the patients at the diagnosis was 21.2±5.07 years-old, but 4 of them (80%) already had hepatic enzymes alterations on blood tests performed 1 year before. All the patients had long diagnosed diabetes (16.4±5.60 years), a poor glycaemic control (HbA1c 12.8±1.99%) and the presence of diabetes-related microvascular disease. Patients were referred to biopsy due to significant alterations on the enzymes of hepatic cytolysis: AST 339±368 U/L (reference value-RV: 10–37) and ALT 243±194 U/L (RV: 10–37). Enzymes of hepatic cholestasis were discreetly elevated and bilirubins were normal. All patients had hepatomegaly (21.6±2.97 cm in the midclavicular line) without splenomegaly. The most frequent histopathological features were cytoplasmatic clarification and ballooning and nuclear glycogenization. One patient had short stature criteria (below 3rd percentile on the WHO growth curves) and three others had a stature that was inferior to the 10th percentile for their age. Two of the patients had cushingoid features. After the diagnosis insulin therapy was intensified and therapy education was reinforced. One year after the diagnosis and the application of these measures patients presented with a mean HbA1C reduction of 2.72±2.40% and the hepatic blood parameters normalized in all five patients.
Conclusions
Mauriac Syndrome is rare and not readily diagnosed by most clinicians. The improvement of metabolic control seems to lead to hepatic enzymes normalization in these patients, reinforcing the importance of early intervention.

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EP491

The incidence of sleep apnea in patients with type 1 diabetes

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It is determined that sleep apnea itself can affect the level of HbA1c, thereby affecting the compensation of carbohydrate metabolism in type 2 diabetes.
Objective
To determine the quantity and type of sleep apnea in diabetes type 1, depending on the level of HbA1c.
Materials and methods
The study involved 50 people with type 1 diabetes without the presence of diabetic autonomic neuropathy or diseases of the pulmonary system and ENT with HbA1c levels of 6.2% vs 9.2%. Patients performed polysomnographic monitoring-'SOMNOlab2 (PSG) Polysomnography(R&K)', daily monitoring of blood glucose-'CGMSGold' by 'MedtronikMINIMED' (USA).
Results of the study

Indicator	**Group 1** ($n=20$) mean (min–max)	**Group 2** ($n=30$) mean (min–max)
HbA1c (%)	6.2 (5.0–7.5)*	9.2 (7.5–13.8)
The average value of glucose (AG) before going to bed (mmol/l)	8.1 (6.5–9.4)*	9.2 (3.2–16.6)
The minimum value of blood glucose during sleep (MGS) (mmol/l)	4.9 (2.3–9.8)	5.5 (2.0–11.5)
Obstructive sleep apnea (OA), total sleep time (TST) (number/h)	3.6 (0.16–12.0)*	1.6 (0.0–6.0)
The maximum duration of OA (s)	81.8 (14.0–118.0)*	31.03 (0.0–111.0)
Central sleep apnea (CA) TST (number/h)	0.5 (0.0–4.7)*	2.7 (1.0–45.0)
The maximum duration of the CA (s)	19.7 (0.0–52.0)	12.6 (0.0–73.0)
Average SpO_2 (%)	96.9 (94.7–98.0)	96.4 (94.1–98.2)
AHI TST	3.0 (0.2–17.4)*	1.37 (0.0–13.4)
AHI NREM	4.46 (0.0–17.4)*	1.38 (0.0–13.4)

*$P<0.05$.

Conclusions
OA and CA at type 1 diabetes are found mainly in the REM phase, S1 and S2 stages of sleep. Compensated type 1 diabetes occurs in OA 2.25 times more likely to have a longer duration and which requires further analysis. It was determined that the CA occurs for decompensated patients 5.4 times more often than in the comparison group. This describes the violation of a central mechanism for the regulation of respiration. Sleep apnea for examined patients was not accompanied by a decrease in oxygen saturation, but the increase in AG bedtime and MGS reduce blood oxygen saturation.

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EP492

Usefulness of plasma glucose concentration to HbA1c ratio in predicting clinical outcome during acute illness with extremely hyperglycemia

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Background
Stress induced hyperglycemia is common during acute illness and is related to poorer clinical outcome.
Objective
To evaluate the correlation between plasma glucose elevation from baseline and clinical outcome during acute illness.
Design
Retrospective, observational cohort of patients presenting to emergency department with plasma glucose concentration >500 mg/dl.
Participants
661 patients visiting the emergency department (ED) of Taipei veterans general hospital between July 1, 2008 and September 30, 2010 with plasma glucose >500 ml/dl were enrolled.
Measurements
Systolic blood pressure, heart rate, plasma glucose, white blood cell, neutrophil count, hematocrit, blood urea nitrogen, serum creatinine, liver function test, plasma glucose concentration were collected at initial presentation to emergency department. HbA1c data within 6 months was reviewed from our hospital database. GAR derives from plasma glucose divided by HbA1c.

Results
GAR of the deceased is substantially higher than survived (81.0±25.9 vs 67.6±25.0, $P<0.001$). There is a trend toward increased 90-day mortality in groups with higher GAR (Log-Rank test for trend $P<0.0001$). In multivariable Cox regression analysis, GAR is significantly related to 90-day mortality (Hazard ratio [HR] per 1-S.D. increase: 1.41, 95% CI: 1.22–1.63, $P<0.001$), but not plasma glucose (HR per 1- S.D. increase: 0.89, 95% CI: 0.70–1.13, $P=0.328$). Rate of intensive care unit (ICU) admission and mechanical ventilator use also elevated in higher GAR groups in a graded manner (Linear trend $P<0.001$ for ICU admission, linear trend $P=0.026$ for mechanical ventilator use).
Limitation
Randomization study design is not feasible.
Conclusion
GAR independently predicts 90-day mortality, intensive care unit admission, and frequency of mechanical ventilator requirement. It is a better predictor for patient outcome compared to plasma glucose in subjects with extremely high glucose.

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EP493

The influence of glycemic control on bone mineral density and bone metabolism in patients with Type 2 Diabetes Mellitus

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Introduction
Although patients with type 2 diabetes mellitus (T2DM) have normal or higher bone mineral density (BMD) comparing to healthy subjects, they appear to be at high risk of osteoporotic fractures. Factors that contribute to bone fragility in T2DM are not clearly understood. The aim of this study was to evaluate the influence of glycemic control on bones in T2DM.
Methods/design
We studied 40 patients with T2DM (mean age: 54.3+3.2 years, M/F: 24/16) at baseline and after 1-year follow-up (FU). We measured HbA1c, lumbar spine (LS) and femoral neck (FN) BMD by dual energy X-ray absorptiometry (DXA). Bone resorption was assessed by β-crosslaps and bone formation was assessed by serum levels of type 1 procollagen total N-terminal propeptide (TP1NP). Patients who were on thiazolidinediones and insulin treatment were excluded from the study and these with renal or chronic disease, as well. Based on the current literature BMD changes at LS more than 3% and at FN more than 6% are considered to be significant.
Results
Mean duration of DM was 6.1+1.9 years. At FU, there were no significant changes at BMI (kg/m^2) (27.8+3.4 vs 27.1+3.2, $P=0.09$) but significant changes were observed in mean HbA1c (7.7+0.6% vs 6.8+0.3%, $P=0.034$). BMD (g/cm^2) at LS and FN was similar at baseline and at FU (LS: 1.074±0.104 vs 1.071±0.113. $P=0.067$) (FN: 0.897±0.121 vs 0.893±0.111, $P=0.072$). At FU, TP1NP and β-crosslaps had a significant decrease in parallel with HbA1c levels (TP1NP: 46.6+5.3 vs 41.1+2.3 $P=0.045$ and β-crosslaps: 371.9+10.8 vs 364+6.8 $P=0.047$).
Conclusion
Effective management with improvement of hyperglycemia in patients with T2DM appears to have a positive contribution on bone turnover. More patients though are needed to be studied to confirm this result.

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EP494

Relation of mean platelet volume with serum paraoxonase-1 activity and brachial artery diameter and intima media thickness in diabetic patients with respect to obesity and diabetic complications

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Objective
To evaluate the relation of mean platelet volume (MPV) levels with serum paraoxonase-1 activity and brachial artery diameter and intima media thickness in diabetic patients with respect to obesity and diabetic complications.
Methods
A total of 201 diabetic patients grouped with respect to obesity (obese ($n=89$) and non-obese ($n=112$) and diabetic complications (with ($n=50$) or without ($n=150$) microvascular complications and with ($n=91$) or without ($n=108$) macrovascular complications) groups were included. Data on demographic and lifestyle characteristics of patients, anthropometric measurements, diabetes related microvascular and macrovascular complications, serum levels for MPV, brachial artery diameter and intima media thickness (IMT) and serum paraoxonase and arylesterase activities were recorded. Correlation of MPV values to paraoxonase and arylesterase activities as well as to brachial artery diameter and IMT was evaluated in study groups.
Results
Mean (S.D.) paraoxonase and arylesterase values were 119.8 (37.5) U/l and 149.0 (39.9) U/l, respectively in the overall population, with no significant difference with respect to obesity and macrovascular diabetic complications, whereas significantly lower values for paraoxonase (107.5 (30.7) vs 123.9 (38.8) U/l, $P=0.007$) and arylesterase (132.1 (30.2) vs 154.7 (41.2) U/l, $P=0.001$) were noted in patients with than without diabetic microvascular complications.
Mean (S.D.) MPV values were 9.10 (0.87) fl in the overall population, with no significant difference with respect to obesity and diabetic complications. No significant correlation of MPV values to paraoxonase and arylesterase activities and to brachial artery diameter and IMT was noted in the overall study population as well as in study groups.
Conclusion
In conclusion, our findings revealed a significant decrease I PON-1 activity in diabetic patients with microvascular rather than macrovascular complications, whereas regardless of obesity and diabetic complications, no increase in thrombogenic activity and no relation of thrombogenic activity with PON-1 activity and brachial artery diameter and IMK.

Keywords: Mean platelet volume, paraoxonase, arylesterase, diabetes mellitus, obesity, microvascular complications, macrovascular complications, brachial artery, intima media thickness, atherosclerosis
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EP495

Antibiotic susceptibilities of Gram-negative bacteria as infectious agents isolated from community-acquired urinary tract infections in diabetic and non-diabetic patients

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Introduction
Diabetes mellitus is a metabolic disease which causes acute and chronic complications including insulin deficiency and ineffectiveness or both its incidence is increasing every day. Urinary tract infections are more frequently seen and can lead a more aggressive course in diabetic patients when compared with the population in general. The aim of this study is to determine antibacterial susceptibilities of Gram-negative bacteria isolated from diabetic and non-diabetic patients as infectious agents of community-acquired urinary tract infections and to compare their rates of resistance to the antibiotics frequently used in empirical treatment.
Material and methods
Ninety-six diabetic and 68 non-diabetic patients whose urine cultures demonstrated Gram-negative bacteria were included in the study. For microbiological examination urine samples were seeded on culture media containing 5% sheep blood agar and eosin-methylene blue agar and incubated at 37°C for 24 h. Gram-negative bacteria grown at a concentration of $>10^5$ cfu/ml were identified using Vitek 2 automated system. Antibiotic susceptibilities of the isolated bacteria were again determined using Vitek 2 automated system and the results were evaluated as sensitive and resistant.
Results
Urinary system infections were more frequently seen in women. In both diabetic and non-diabetic patient groups, most frequently *Escherichia coli* (88.5% in diabetic and 85.3% in non-diabetic groups) were isolated. According to antibacterial susceptibilities of isolated microorganisms, the most effective antibiotics in both groups were carbapenems, nitrofurantoin, amikacin and

piperacillin-tazobactam. In the diabetic group, microorganisms mostly demonstrated the highest rates of resistance against ampicillin, cephalosporins, ciprofloxacin, amoxicillin-clavulanic acid and in the non-diabetic group ampicillin, amoxicillin-clavulanic acid, cefuroxime and trimethoprim-sulfamethoxazole.
Conclusion
Resistance to ciprofloxacin which is used frequently in the empirical treatment of community-acquired urinary system infections was at a significantly higher rate in the diabetic group. In diabetic patients, it will be more appropriate to give antibiotherapy in urinary system infections based on the antibacterial susceptibility test results.
Keywords: Diabetes mellitus, urinary tract infection, antibiotic, susceptibility
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EP496

Diabetes and cognitive impairment
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Introduction
Diabetic patients have an increased risk of developing dementia and cognitive impairments. DM related factors such as macrovascular and microvascular complications, glucose toxicity, hyperinsulinemia have been suggested to be involved cognitive impairment even in prediabetic stage. Our aim is to establish the relationship between insulin resistance and cognitive impairment and the effect of poorly controlled diabetes on cognitive impairment.
Research design and methods
Twenty prediabetic patients who were evaluated using a standard OGTT, 40 patients with T2DM and twenty non-diabetic healthy controls aged between 40 and 65 were included in this study. Forty patient with T2DM divided into two groups; well- controlled (A1c <7.5) and poorly controlled (A1c $>$ 7.5) based on their HbA1c. All factors that might affect cognitive function excluded from the study. We assesed neuropsychological profile of these groups and compared with twenty non-diabetic, healthy controls. All patients and healthy controls matched for sex ratio and level of education. Attention & working memory, psychomotor speed, verbal memory, visuospatial memory and executive function were tested.
Results
Statistically significant differences between the patients with poorly controlled diabetes mellitus in Verbal Memory Process Test (P value $<$ 0.05). In Trail Making Test part B diabetic patients showed significantly lower performances than prediabetics and controls. And in Wisconsin Card Sorting Test perseveration all three patients groups performed significantly worse (P value $<$ 0.05) than controls.
Conclusion
T2DM causes early brain ageing and declines cognitive functions even in prediabetic stage. Chronic hyperglycemia and vascular complications in poorly controlled T2DM worsen cognitive impairments.
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EP497

Cystatin C and renal function in patients with type 2 diabetes mellitus
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Background
Diabetic nephropathy (DN) is a serious complication of diabetes associated with increased risk of mortality, cardiovascular and renal outcomes. Diagnostic markers to detect DN at early stage are important as early intervention can slow loss of kidney function and improve patient outcomes. The aim of our study was to evaluate the role of serum cystatin C (CysC) for early detection of kidney damages in patients with type 2 diabetes mellitus (DT2).
Materials and methods
The renal function of the diabetic patients was evaluated using the albumin-creatinine ratio (ACR) and Kidney Disease Outcome Quality Initiative-Kidney Disease Improving Global Outcomes (K/DOQI-KDIGO) classification. Serum CysC and HbA1c were also measured in 84 diabetic and 36 healthy subjects.
Results
Serum CysC was significantly higher (1.3 ± 0.9 mg/l) in diabetic patients with eGFR <60 ml/min than control subjects (0.8 ± 0.2 mg/l), $P<0.05$. A significant correlation between CysC and eGFR ($r=-0.26$, $P<0.05$) was observed. CysC levels significantly increased with increasing CKD stage 1 to 3 and from normo- to microalbuminuria and showed a positive correlation with ACR ($r=0.32$, $P=0.004$). In a comparison of renal function markers in type 2 diabetic patients according to serum CysC level, all markers including ACR, serum creatinine, and eGFR showed significant differences between patients with CysC level <1.1 mg/l and those with CysC ≥ 1.1 mg/l.
Conclusion
According to our results, serum CysC is a useful marker for screening of DN in patients with DT2 because it reflects both a decrease in GFR and elevated ACR.
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EP498

Markers of endothelial and autonomic dysfunction in early stages of glucose intolerance and in metabolic syndrome
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Aim
The aim of the study was to evaluate sE-selectin and Endothelin-1 as markers of endothelial function and autonomic tone at early stages of impaired glucose tolerance and in metabolic syndrome (MetS).
Material and methods
A total of 87 subjects - 48 females and 39 males (mean age 45.7 ± 11.6 years, mean BMI 31.4 ± 6.6 kg/m^2), divided into three groups according to glucose tolerance: 35 with normal glucose tolerance (NGT), 35 with prediabetes and 17 with newly-diagnosed type 2 diabetes (NDT2D), and into two groups according to the presence of MetS: 66 with MetS and 21 without MetS, were enrolled. Glucose tolerance was studied during OGTT. Anthropometric indices, blood pressure, HbA1c and serum lipids were measured. Serum sE-selectin and Endothelin-1 were estimated using ELISA tests. Autonomic function was assessed by ANX-3.0 using frequency-domain analysis at rest and during deep breathing, Valsalva, standing.
Results
The prevalence of cardiovascular autonomic dysfunction was 5.7% in NGT, 8.6% in prediabetes, 23.5% in NDT2D. No significant difference was observed in sE-selectin and Endothelin-1 between the groups according to glucose tolerance and in endothelial markers and autonomic parameters according to MetS. Our results showed significantly diminished parasympathetic activity at rest ($P=0.005$, $P=0.016$, respectively) and during deep breathing ($P=0.043$, $P=0.046$, respectively) in NDT2D as compared to prediabetes and NGT; and elevated heart rate at rest in NDT2D in comparison to NGT ($P=0.024$). sE-selectin correlated with fasting plasma glucose ($r=0.211$, $P=0.050$) and heart rate at rest ($r=0.214$, $P=0.047$). There was negative correlation between both sympathetic and parasympathetic power and age, HbA1c, waist, BMI, total and LDL-cholesterol.
Conclusion
Our results demonstrate that slight increase in plasma glucose and the presence of MetS do not influence sE-selectin and Endothelin-1 concentrations. Autonomic tone is affected at early stages of impaired glucose homeostasis, the main determinants being age, long-term glycemic control, obesity, total and LDL-cholesterol.
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EP499

Androgenic state in patients with diabetes mellitus type 1 and diabetic nephropathy

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Objective
To analyze correlation between the duration of diabetes mellitus (DM), renal function and androgenic state indicators in patients with DM type 1.
One hundred and sixty three males with DM 1 type in the age of 18–55 years (39.75 ± 9.69) with the duration of disease more than 1 year were examined. The control group included 25 almost healthy males in the age 21–41 years (34.60 ± 7.80). The compensation of DM was estimated by the level of glycosylated hemoglobin (HbA1c). Also, the indicators of lipid profile (total cholesterol, triglycerides), glomerular filtration rate (GFR) MDRD, total testosterone, luteinizing hormone/follicle-stimulating hormone (LH/FSH), prolactin, sex hormone-binding globulin, homocysteine. The statistical analysis was conducted with the use of SPSS 17.0.
It was defined that there was the decrease of GFR according to the formula MDRD in the terms of the increase of diabetes duration: in the group with GFR < 60 ml/min per 1.73 m^2 the duration of the diabetes was 23.72 years (±8.04), in the group with GFR >60 ml/min per 1.73 m^2 it was 12.15 years (±8.37) ($P<0.05$). In the terms of the decrease of GFR the increase of correlation FSH/LH was defined: in the group with GFR <60 ml/min per 1.73 m^2 the correlation LH/FSH was 1.82 (±0.63), in the group with GFR >60 ml/min per 1.73 m^2 it was 1.37 (±1.26) (<0.005); the decrease of the total testosterone: in the group with GFR <60 ml/min per 1.73 m^2 the total testosterone was 9.90 nmol/l (±3.10), in the group with GFR >60 ml/min per 1.73 m^2 it was 10.61 nmol/l (±8.76) ($P<0.05$); the decrease of the homocysteine level was noticed: 11.42 ± 2.70 mcmol/l comparing with the 10.32 ± 4.92 mcmol/l in the group with GFR >60 ml/min per 1.73 m^2 ($P=0.006$). We have not revealed any differences in the level of prolactin, sex hormone-binding globulin. The revealed changes are important risk factors for development and progression of vascular complications and require appropriate arrangements.

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EP500

Audit of management of cystic fibrosis related diabetes mellitus in Nottingham University Hospital

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Introduction
Patients with Cystic fibrosis are now living longer due to advances in nutritional and medical care. As a consequence a larger number are developing related co-morbidities such as cystic fibrosis related diabetes (CFRD). CFRD is the most common co-morbidity in CF, with the prevalence being up to 50% by the age of 30.
Aims
To assess current practice in relation to the UK CF Trust guidelines 2004 – Screening for CFRD should begin at age 12 using OGTT. Patients should be treated with insulin and reviewed quarterly by MDT specialising in CFRD. HbA1C should be measured quarterly to guide further therapy. Annual screening for complications should occur in all patients older than 12 years.
Methods
Retrospective case notes and hospital database review of adults with CFRD at Nottingham University Hospital between the years 1998 and 2014. Also data was collected about changes to weight and lung functions following 1–2 years of insulin therapy.
Results
Seventy two patients were identified (40 males, 32 females). Mean age: 30 (range 18–62). In 83.3% of patients CFRD was diagnosed with OGTT and patients were treated with various insulin regimens. 61% of patients were seen quarterly. HbA1C was measured quarterly in 41.7%. Blood pressure, retinopathy, Foot, ACR, CVS events and lipid profile were screened annually in 47.2, 40, 25, 4.2 and 45.8% respectively. Weight after 1–2 years on insulin was static in 9.5%, increased in 44.4%, decreased in 46%, whereas, lung function was stable in 3.2%, increased in 38%, decreased in 58.7%.
Conclusion
Overall, most of our patients were diagnosed with OGTT and treated with insulin. However, our performance is average in terms of follow up, monitoring and screening for complications. These discrepancies could partially be explained by the fact that data was collected from 1998, but the guidelines were only issued in 2004. Also paediatric databases and notes were not used. Another issue with monitoring is the large number of DNAs. Nonetheless, there is likely room for improvement in these areas.

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EP501

Observational and retrospective study to analyze the changes in lipid and glycemic profiles in patients with metabolic syndrome after treatment with statins: ESMET study

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The diabetogenic risk associated with statin therapy is higher in patients with pre-existing risk factors, such as metabolic syndrome (MS).
Objective
To assess changes in lipid and glycemic profile in dyslipidemic subjects with MS after statin therapy.
Methods
Observational, retrospective, multi-center study, conducted in 40 endocrinology Spanish hospitals. Each endocrinologist included the first 10 patients >18 years with MS, HDL-C <40 mg/dl in men and <50 mg/dl in women and two or more MS risk factors according to NCEP-ATP III criteria, treated with statins for at least 12 weeks before their inclusion, and had signed informed consent. Demographic variables, medical history, diabetic complications, anthropometric data and analytical and therapeutic profiles were collected before and after starting statin therapy. ADA objectives for lipid and glycemic control, student *t* test for paired data or the Wilcoxon sign tests for quantitative variables, and McNemar test or Fisher's exact test for qualitative variables were used. A $P<0.05$ was significant.
Results
A total of 388 patients were enrolled, of them 345 were evaluated; 53.9% were men, age was 60.9 ± 9.3 years, 89.9% had abdominal obesity, 88.7% hypertension, 88.4% fasting glucose (FG) ≥110 mg/dl, 77.7% triglycerides(TGs) ≥150 mg/dl and 100% HDL-C <40 mg/dl in men and <50 mg/dl in women. After statin therapy, there was a decrease in total cholesterol, TGs, LDL-C, HbA1C and FG, and an increase in HDL-C and in the percentage of patients achieving the ADA objectives ($P<0.001$ for all). Multivariate analysis showed a greater increase of HDL-C with pitavastatin 18.4% (vs atorvastatin 7.4%; $P=0.0094$, and vs simvastatin 9.6%; $P<0.0001$), and univariate analysis a reduction on the percentage of change on FG (4.8 ± 20.5%; $P<0.0161$) after treatment with pitavastatin
Conclusion
In the MS patients studied, glucidic and lipid parameters and the percentage of patients achieving the ADA objectives improved after statin therapy. Pitavastatin could have better cardiovascular benefit due to the greater increase in HDL-C.

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EP502

Assessment of dermatological conditions in diabetic patients, associations with demographic values and metabolic compensation

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Introduction
Diabetes mellitus (DM) is a group of metabolic diseases where prolonged hyperglycemia provoke damaging impact on internal organs and the skin as well. Comprehension of dermatological changes in DM, association with demographic values, metabolic compensation level (HbA1C) could help to define groups where skin complications may develop more often. That could be a useful criteria to diagnose DM earlier.
Aim
To determine prevalence of skin pathological conditions in DM, to find out their association with demographic values, compensation level.

Material and methods
A retrospective cohort study was performed. Participants were included from Internal Medicine Clinic of Riga Eastern Clinical University Hospital. Patient interviewing, observation and retrospective analysis of case files were performed.
Results
A total of 151 patients were included - 70 (46%) men and 81 (54%) women; the mean age was 59.9 years (S.D. 15.9 years). Patients were divided into 3 age groups – group I ($\leq$45 years) 19%, group II (46–59 years) 25%, group III ($\geq$60 years) 56%; into groups by DM duration, type and therapy – (0–5 years) 27%, (6–10 years) 23%, (11–20 years) 34%, (>20 years) 16%; Type 1DM 19%, Type 2DM 75%, other (secondary) 6%;with insulin therapy (60%), with peroral therapy, diet (40%). 4 most frequent skin conditions were identified - atrophy (75%), dryness (70%), onychomycosis (59%), necrobiosis lipoidica diabeticorum (42%). Prevalences of skin conditions were found statistically significant: atrophy in III age group 86% ($P=0.001$); dryness with disease duration 80% ($P=0.043$), in women 78% ($P=0.02$); onychomycosis in III age group 74% ($P=0.001$), in patients with Type 2DM 67% ($P=0.004$); necrobiosis in patients with insulin therapy 49% ($P=0.03$), in II–III age groups 48% ($P=0.012$).
Conclusion
Most common dermatological conditions in DM patients are atrophy, dryness, onychomycosis, necrobiosis lipoidica, hypohidrosis. Associations with age, gender, treatment, disease duration, type were defined. There was no statistical significance found with compensation level.

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EP503

Investigational study of the impact of diabetes on cognitive function

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Introduction
Modern research studies reveal a negative impact of diabetes on cognitive function. Nonetheless, little is known about the risk factors that are involved in this disturbance. The present study aimed to examine the associations among cognitive/emotional functions and a number of metabolic factors associated with diabetes, in order to identify a possible link between cognitive decline and diabetes.
Materials and methods
One hundred thirty five people ($n=135$) from the region of Thessaloniki participated in the study. The sample consisted of patients from the outpatient diabetes clinic (First department of internal medicine AHEPA Hospital) and the local center of Alzheimer and Dementia. Two groups (diabetics and control) were investigated in this cross-sectional study. Only subjects with mild cognitive impairment or mild dementia were recruited in this study with those suffering from heavy dementia being excluded. A wide range of metabolic factors were investigated as well as cognitive function assessment using cognitive screening tests.
Results
In the group of diabetic patients a significant greater cognitive impairment, assessed with MOCA test, was revealed. Cognitive function was not associated with the duration of diabetes and metabolic deregulation, as assessed by HbA1c. A significant mild positive correlation between total cholesterol and triglycerides with cognitive function was found in the group of diabetic patients. A similar correlation between HDL and ADCS-ADL was present in the group of non diabetic patients. A mild positive correlation between waist circumference and cognitive function (ADCS-ADL test) was found in the group of diabetic patients. Peripheral neuropathy showed strong negative correlation with cognitive function.
Conclusion
It seems that metabolic abnormalities that accompany diabetes mellitus may provide a great amount of risk factors responsible for mild cognitive impairment and dementia.

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EP504

Abstract withdrawn.

EP505

Left ventricular hypertrophy and diabetic nephropathy; factors that influencing this relationship

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Introduction
The prevalence of left ventricular hypertrophy (LVH) is high among patients with chronic kidney disease (CKD) and associated with a lower cardiac functional status, particularly in patients with diabetes mellitus (DM). The aim of the study was to estimate prevalence of LVH and to define factors influencing to development of LVH in patients with diabetic nephropathy (DN).
Methods
patients with type 2 DM were studied - 22 males, 43 females, mean age 53.717.4.21 patients had normal renal function with mean hemoglobin (Hb) 13.72.0 g/dl, 44 patients had chronic renal failure (CRF) with decreased mean GFR 46.723.7 ml/min/1.73 m^2/ and Hb 11.82.4 g/dl ($P<0.05$). Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault formula. Anemia was defined as hemoglobin (Hb) $<$ 13 g/dl in men and $<$ 12 g/dl for women by the definition of WHO. 62 patients had arterial hypertension. Patients on dialysis were not included.
Results
LVH (left ventricular mass index (LVMI) $>$ 134 g/m^2 for men and $>$ 110 g/m^2 for women) was found in 50 DN patients (77.6%). At GFR $<$ 30 ml/min/1.73 m^2 the prevalence of LVH was 100%. Concentric hypertrophy of left ventricular (LV) was found in 51% patients, eccentric LV hypertrophy in 26.5% patients, 14.3% patients had concentric remodeling of LV, 8.2% - were with normal geometry of LV. The LVMI is significantly associated with older age ($R=0.43$, $P<0.01$), Hb ($R=-0.44$, $P<0.05$), GFR ($R=-0.29$, $P<0.05$). Independent factors affecting on development of LVH in patients with DN by multiple logistic regression analysis were Hb level and value of systolic blood pressure ($P=0.0003$).
Conclusions
We conclude that prevalence of LVH was higher in patients with type 2 diabetes, with impaired renal function. Anemia and systolic blood pressure were independent factors influencing on development of LVH in patients with DN.

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EP506

Estimation of the frequency of nighttime hypoglycemic reaction cases in diabetes maelicus of the Type 1

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Objective
To estimate the frequency of night time hypoglycemic reaction cases in daily monitoring of the glucose in interstitial fluid under the conditions of DM 1.
Materials and methods
The study of daily glucose dynamics was conducted with the use of the continuous glucose monitoring system made by the company Medtronik Minimed, USA. The study included 113 patients with DM 1. Patients ware divided into 2 groups: group 1 with hypoglycemic reaction cases ($n=50$), and group 2 without hypoglycemic reaction cases ($n=63$).
Results
The age of the patients in the group 1 was 29.49 (24.05; 36.18) years, in the group 2 it was 27.83 (21.13; 34.94) years ($P>0.05$). The period of the DM 1 in the group 1 was 9.07 (4.23;13.53), in the group 2 it was 7.18 (2.78; 13.62) years ($P>0.05$). The level of HbA1c in the group 1 was 8.20 (7.30; 9.40) %, in the group 2 it was 9.70 (8.40; 11.20] %, ($P<0.001$). BMI in the group 1 was 23.66 (21.97;

25.82) kg/m^2, in the group 2 it was 23.42 (21.45; 27.34) kg/m^2 ($P>0.05$). The daily dose of insulin in the group 1 was 0.72 (0.60; 0.87) IU/kg, in the group 2 it was 0.72 (0.56; 0.98) IU/kg ($P>0.05$). The frequency of night hypoglycemic reaction cases in the group 1 was 15% in males and 28% in females ($P>0.05$). Between 23:00 and 03:00 the level of glucose in interstitial fluid in the group 1 was 7.80 (5.50; 10.60) mmol/l, it was 10.50 (8.80; 13.40) mmol/l, ($P<0.001$) in the group 2. Between 03:00 and 06:00 the level of glucose in interstitial fluid in group 1 was 8.20 (6.10; 11.10) mmol/l, it was 10.80 (8.70; 13.30) mmol/l ($P<0.001$) in the group 2.

Conclusion

1. The frequency of nighttime hypoglycemic reaction cases doesn't depend on sex, age, period of DM 1, daily dose of injected insulin.
2. The risk of night hypoglycemic reactions is higher in patients with the lower risk index of hypoglycemia that coincides with the minimum value of glycaemia at night and glycosylated hemoglobin.

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EP507

The diabetic hand: a forgotten complication

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Background and aims

The diabetic hand infection is less reported in the literature. Therefore, it is easily ignored and underestimated resulting in increased morbidity among the diabetic population. The aim is to determine the clinical and therapeutic characteristics in our hospitalized patients.

Materials and methods

All hand infection patients admitted to the Department of Diabetes and Endocrinology at Oran University Hospital center during 10 years were reviewed retrospectively. A hand infection was defined as any Infection of the upper extremity in hospitalized diabetic patients. Thirty three patients with hand infection were found. Their etiology identified from clinical history and examination, number of operations and management, hospital stay and out-come-like amputation were recorded. Data collected were entered into a computer database using IBM SPSS Statistics 20 and analyzed using the same application.

Results

The mean age of the patients was 54 ± 2.44 years (range 23–76 years). 21 patients (64%) were male and 12 (36%) were female. Male to female ratio was 1, 75:1 (dominantly males). All male patients were manual workers (Carpenter, Farmers and Blacksmith), female were also having active life (Housewives). The mean duration of diabetes before presentation was 10.6 ± 7.2 years; three of the patients were newly diagnosed at presentation. The lesions consisted of cellulitis, phlegmon or ulceration of the finger, hand, and arm. During the course of treatment, seven patients (21.2%) required amputation of one or more digits of the dominant hand. But no patient required amputation of forearm, arm or hand.

Conclusion

Diabetic hand involves persons in active life period relatively in younger age group. Undiagnosed or uncontrolled diabetes is major contributory factor. Health Education, early diagnosis & prompt treatment in specialized units may be helpful.

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EP508

Improvement of specialised help to patient with diabetic foot syndrome in Uzbekistan

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Goal

Decrease a number of lower limb amputations in PDM in Uzbekistan by improvement of specialised help given to patients with DFS.

Materials and methods

Prior to 2010 there were only 2 'Diabetic foot' rooms in Tashkent, Uzbekistan. In 2010–2012, 'UMID' association jointly with Uzbekistan Ministry of Health and Research Centre for Endocrinology implemented a project 'Prevention of lower limb amputations in people with diabetes mellitus in Uzbekistan' granted by the World Diabetes Fund (WDF).

Results

Within the framework of the project for the first time in Uzbekistan, 288 'Diabetic foot' rooms were set up under 14 endocrinological dispensaries and in 274 rural district clinics which were also equipped with a medical armchair for feet examination, a tuning fork, monofilament, percussion hammer, kit of dressing materials. To work in these rooms, 615 podiatrists were trained who render a qualified medical help to PDM and teach them rules of foot care. Annually over 28 800 PDM undertake feet examination and training in these rooms. A 2-fold decrease in a number of amputations and increased awareness of PDM in foot care proves improvement of specialised help to people with DFS. Within the framework of the project, 288 multidisciplinary teams (surgeon + endocrinol-ogist + podiatrist) were trained throughout the country and now they render a specialised help to patients with DFS.

Conclusions

Implementation of the project 'Prevention of lower limb amputations in people with diabetes mellitus in Uzbekistan' improved a specialised help to people with DFS due to launching a network of 'Diabetic foot' rooms and an effective work of podiatrists and multidisciplinary teams trained on sites and that lowered a number of amputations in PDM by 2 times; increased awareness of people with diabetes on prevention of DFS.

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EP509

Risk factors for fetal macrosomia in gestational diabetes

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Background

A fetal macrosomia is the most frequent complication of gestational diabetes mellitus (GDM) in Lithuania. The aim of our study was to assess the predicting factors of fetal macrosomia in GDM.

Methods

Retrospective data analysis of 3 547 women who delivered in Vilnius University Hospital Santariskiu Klinikos in 2015 was performed. Documented GDM risk factors were obtained from medical records and electronic database. Newborns over 4000 g birth weight were defined as macrosomic cases. Comparisons were made between women who delivered healthy (group I) and macrosomic (group II) newborns. Multiple regression analysis was used to calculate the odds ratio (OR) and their 95% confidence intervals (CI).

Results

Two hundred and thirteen women (6%) out of 3547 had GDM. Fifty of them (24.39%) delivered macrosomic newborns. There were no age difference between the groups (31.7 vs 32.1 kg), but women had higher pre-pregnancy body weight (78.3 vs 67.0 kg, $P<0002$) and BMI (29.1 vs 25.7, $P<0.004$) and GDM was diagnosed later (31.0 vs 29.7 week, $P<0.048$) in group I compared to group II. Factors associated with increased risk of fetal macrosomia were maternal pre-pregnancy BMI (OR1.11 [1.0–1.2], $P<0.05$), previous fetal macrosomia (OR 8.04 [3.5 − 18.4], $P<0.05$), previous polyhydramnion (OR 4.04 [1.3–12.7], $P<0.05$), time of GDM diagnosis (OR 1.11 [1.0–1.2], $P<0.05$), and gestational age (OR 1.35 [1.0–1.8], $P<0.05$). In a multiple regression pre-pregnancy body weight and previous fetal macrosomia remained the only predictors for increased risk of neonatal macrosomia.

Conclusions

Neonatal macrosomia prevention remains a challenge. According to our study pre-pregnancy body weight and previous fetal macrosomia are associated with increased risk of fetal macrosomia of current pregnancy. This finding provides insights for the prevention of macrosomia development in women with GDM.

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EP510

Stroke recurrence (but not mortality) is higher among diabetic and prediabetic patients

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Introduction
Diabetes Mellitus (DM) and prediabetic states (pre-DM) are well known risk factors for stroke. Admission blood glucose level and its control during hospital stay, help predicting arterial recanalization after thrombolysis and middle and long term prognosis. We analysed recurrence, mortality and nosocomial infectious complications in DM, pre-DM and patients without previous or newly diagnosed DM or pre-DM.
Methods
Descriptive analysis in consecutive patients with a diagnosis of stroke or transient ischemic attack (TIA) in our centre from 15th November 2013 to 14th may 2014. Descriptive and bivariate analysis were made.
Results
One hundred and sixty one patients were included - 66 DM (41%), 32 pre-DM (19.9%) and 63 normoglycemic (NG) patients (39.1%). Stroke etiology was cardioembolic in 42 (26.09%) patients (NG 30.16%, DM + pre-DM 23.47%; ns) and lacunar in 31 (19.25%) (11.11% normoglucémicos, 24.45% DM + preDM). During the following year, 17 patients (11.49% of those alive at discharge) suffered a recurrent stroke, affecting 15.38% patients with DM or pre-DM (14.75% DM; 16.67% pre-DM) and 5.45% normoglycemic patients ($P<0.05$). One-year mortality (14.91%) was higher among normoglycemics (19.05% vs 12.24%), as well as in hospital mortality (7.94% vs 6.12%) and infectious comorbidities during hospital stay (20.63% vs 14.29%), but none of them reached statistical significance.
Conclusions
As most studies in stroke recurrence, our series demonstrates a higher recurrence rate not only in diabetics but also in prediabetic patients. On the other hand, in-hospital and on-year mortality, and in hospital infections were more frequent among non-diabetic patients. The fact that DM is over represented in lacunar strokes as compared with cardioembolic strokes may have influenced these results, as mortality and severity are much higher in those with a known embolic source.

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EP511

Clinical factors and severity of diabetic foot infection according to the PEDIS classification

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Introduction
The complications related to ulcerated foot lesions are a common cause of hospitalization among diabetics. Diabetic foot infection is associated with high morbidity and is the most common precipitating factor to precede amputations of the lower limbs.
Methods
Retrospective, cohort study; were included 200 patients from the Diabetic Foot consultation of the Endocrinology Department between 1 January and 31 August 2015. Ulcerated lesions were classified according to the infection part of the PEDIS classification of the IWGDF.
Results
Our sample consists in 84.5% of patients with type 2 diabetes mellitus, mean age 62.5 ± 13 years and mean duration of disease of 17.7 ± 13 years. Regarding the classification of foot, 57.5% were classified as neuroischemic diabetic foot. Of the 200 patients, 51% had active ulcers classified in 31.5% of the patients as grade 1 ($n=63$).
Concerning the therapeutic, 77.5% of the patients were under insulin therapy. Despite the trend towards higher number of patients on insulin therapy in higher categories of infection, this did not reach statistical significance ($P=0.105$).
The presence of diabetic retinopathy ($P=0.022$), previous history of ulcers ($P=0.000$) and osteomyelitis ($P=0.000$) and higher values of HbA1c ($P=0.002$) were associated with a significant increase in the severity of infection.
The existence of previous microbiological studies were associated with clinically more severe infections probably related to the bias of higher patient risk profile whom studies are requested ($P=0.000$).
Patients with no personal history of revascularization surgery ($P=0.019$) and no history of smoking ($P=0.048$) were associated with lower ulcerated lesion classification categories.
Conclusion
Diabetic foot ulcers are highly prevalent and are associated with high morbidity and mortality. The presence of diabetic retinopathy, previous history of ulcers and osteomyelitis and higher HbA1c values have an impact with statistical significance in the direction of worsening infection category.

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EP512

Sympathetic dysfunction in patients with diabetes revealed by task force monitor

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Introduction
It is common that patients with diabetes have a dominant parasympathetic dysfunction.
Aim
Assessing the function of the autonomic nervous system in diabetic subjects.
Methodology
Task force monitor was used for testing at rest and passive orthostasis evaluating baroreceptor sensitivity (BRS), spectrum variability of RR-interval of high frequencies HF RRI which is linked to the parasympathetic, low frequency variability of diastolic blood pressure interval LF-DBP, partly linked to effects of sympathicus, LF HF RRI sympathovagal balance of RR interval. In the first group were 20 subjects with type 1 diabetes, age X 37 years, of which 12 men and eight women. The second group contained 25 subjects with type 2 diabetes, age X 62 years of which 18 men and seven women.
Results
In groups with type 1 diabetes LF HF at rest X 1.745 s.d. 0.91; LF HF orthostasis X 3.08 s.d. 2.65; LF DBP at rest X 44.79 s.d. 16:52; LF DBP orthostasis X 51.91 s.d. 11:41; HF RRI at rest X 36.01 s.d. 14.65; HF RRI orthostasis X 25.98 s.d. 8.2; BRS at rest X 10.1 s.d. 6.18. In the group with type 2 diabetes LF HF at rest X 4.01 s.d. 7.02; LF HF orthostasis X 4.7 s.d. 8.9; LF DBP at rest X 37.17 s.d. 14.85; LF DBP orthostasis X 37.32 s.d. 10.89; HF RRI at rest X 43.51; s.d. 17:48; HF RRI orthostasis X 43.51 s.d. 23:30; BRS at rest X 9.78 s.d. 6.50. Correlation between the groups showed highly significant difference for LF DBP in orthostasis ($P<0.00067$).
Conclusion
Significantly lower values of LF DBP were registered in the group with type 2 diabetes, which represents the 'failure' of sympathetic in orthostasis. Analyses revealed sympathetic dysfunction in patients with type 2 diabetes but not in subjects with type 1 diabetes.

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EP513

Bad eating habits among type II diabetic patients at tertiary hospital: a case-control study

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Background
There is a strong association between type II diabetes mellitus (DM) and gaining weight. Lifestyle modification is an important factor for weight management to overcome the obesity as well as DM epidemics.

Aim of study
To find the differences of eating habits and Rosenberg Self-Esteem between DM patients and control and to find the strongest contributor of risk factors by study groups.
Methods
A hospital-based matched case-control study design was carried out on (250) patients with DM and control seen at Diabetic and Endocrine Centre and other outpatient clinics in Tertiary Teaching Hospital.
Results
There were direct weak significant correlations of Bad Eating Habits and Rosenberg Self-Esteem Scales by DM patients ($r=0.286$, $P=0.001$*) and control ($r=0.314$, $P<0.001$*). DM patients were 0.91 and 0.86 less likely to report bad eating habits and high Rosenberg Self-Esteem than control, respectively. DM patients were 19, 18 and 3 times more likely to have brothers and parent with DM than control as well as to have high HBA1c, respectively.
Conclusion
Assessing eating behaviors of diabetic patients as a routine nutritional assessment is an important implication in patient's health. Therefore, considering the complex association between diabetes and its health related consequences, there is a considerable need for educating diabetic patients.
Keywords: Bad Eating Habits, Type II Diabetes Mellitus, Rosenberg Self-Esteem Scale, HBA1c, waist circumference
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EP514

Assessment of neutrophil gelatinase-associated lipocalin in diabetic patients

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Background
Diabetic nephropathy (DN) is a major cause of morbidity and mortality in type 1 diabetes (T1D) patients and associated with increased cardiovascular risk in type 2 diabetes (T2D) patients. Early detection of DN using neutrophil gelatinase-associated lipocalin (NGAL) assessment can help to reveal predisposed patients to its progression and to prevent progression of DN. Especially important it is in patients with normoalbuminuria.
Aim
To determine NGAL concentrations in T1D and T2D patients and its correlation with HbA1c level and age.
Materials and methods
We included 57 patients with T1D aged 38.79 ± 10.35 (group 1) and 22 patients with T2D aged 53.15 ± 4.88 (group 2) ($P<0.001$). GFR was calculated by Cockcroft-Gault equation (ml/min per 1.73 m^2). Microalbuminuria was determined in 24-h collection urine by immunoturbidimetric method. Concentration of NGAL was determined in serum using immunofluorescence assay (ng/ml).
Results and discussion
There were no significant difference in GFR between groups: 96.33 ± 32.79 ml/min per 1.73 m^2 in group 1 and 85.83 ± 20.8379 ml/min per 1.73 m^2 in group 2 ($P<0,1$). Patients were normoalbuminuric. NGAL concentrations were higher in T2D patients (5.37 ± 2.00 ng/ml) vs T1D (1.57 ± 1.87 ng/ml) ($P<0.001$). It is suggested that such factors as age and HbA1c level (8.60 ± 1.51% in group 1 and 12.17 ± 1.82% in group 2, $P<0.001$) can affect of NGAL level. The positive correlation between NGAL concentrations and HbA1c levels($r=0.45$, $P<0.05$) was revealed. Positive correlation between age and NGAL level ($r=0.38$, $P<0.05$) was determined. Thus age may present impact factor on NGAL levels.
Conclusions
T2D is associated with higher level of NGAL compared to T1D. Increase in NGAL levels in patients with diabetes may be associated with advanced and long-lasting hyperglycemia as well as with higher age.
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EP515

Hydroxyvitamin D status and it is relation to some cardiovascular risk factors in Egyptian female patients with type 2 diabetes

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Introduction
Recent observational evidence suggests strong links between low vitamin D levels and a range of cardiovascular risk factors, including hypertension, diabetes, obesity and hyperlipidemia. In addition increased rate of all-cause and cardiovascular mortality.
Objectives
To determine 25-hydroxyvitamine D (25(OH) D) levels as well as its relationship with some cardiovascular risk factors among Egyptian Female patients with type 2 diabetes.
Study design and methodology
This study was conducted on 50 middle age premenopausal type 2 diabetic patients, compared to 50 age matched apparently healthy women. After complete clinical examination including body mass index (BMI), waist circumference (WC), and blood pressure measurements, blood samples were withdrawn to determine fasting, and postprandial blood glucose levels, HbA1c, lipid profile, fasting serum insulin and 25(OH) D. HOMA-IR was calculated. Of imaging techniques, Echocardiography and carotid intima media thickness (CIMT) were done.
Results
Diabetic patients had significantly lower 25(OH) D levels (54%) 'deficient' compared to control group (4%).
25(OH) D was negatively correlated with body weight, BMI, WC, systolic and diastolic blood pressure, FPG, HbA1c, fasting serum insulin, HOMA-IR, total cholesterol, triglycerides, left ventricular mass (LVM), left ventricular mass index (LVMI), and left atrial diameter (LAD).
Conclusion
25(OH) D levels are significantly lower in middle aged Egyptian type 2 diabetic women compared with controls. Vitamin D concentrations are linked to glucose homeostasis and insulin resistance. It is associated with cardiovascular risk factors such as hypertension, obesity and dyslipidemia. Low vitamin D is negatively correlated with LVM, LVMI, and LVD.
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EP516

Assessment of quality of life in anemic and non-anemic patients with early stages of diabetic nephropathy

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Aims
Anemia occurs early and predicts high risk of cardiovascular events and death in patients with diabetic nephropathy. The aim of this study was to assess the influence of anemia on the quality of life of patients with early diabetic nephropathy.
Methods
We investigated 95 anemic and 32 non-anemic patients with type 2 diabetes mellitus and early diabetic nephropathy (CKD stages 1–3). Anemia was defined according to WHO criteria. Anemic patients were divided into groups 1–3 according to the stage of CKD. Patients' quality of life was assessed with SF-36 health survey. Student's *t*-test was used for statistical analysis.
Results
As compared to patients without anemia subjects from groups 1–3 had lower scores of physical role functioning (49.8 ± 4.2 vs 25.0 ± 7.2, 34.8 ± 3.0 and 12.5 ± 9.6, respectively, $P<0.05$) and emotional role functioning (57.9 ± 5.2 vs 33.6 ± 5.9, 39.8 ± 3.5 and 33.5 ± 6.2, respectively, $P<0.05$). Groups 1 and 2 had no significant differences in other SF-36 sections with the non-anemic group. Patients in group 3 had lower scores of general health perceptions, physical functioning, bodily pain, vitality and mental health than patients in the non-anemic group: 27.4 ± 4.1 vs 43.3 ± 3.2, 25.0 ± 4.2 vs 65.9 ± 6.9, 43.7 ± 3.3 vs 60.3 ± 3.9, 32.5 ± 5.8 vs 49.6 ± 4.2 and 38.8 ± 3.5 vs 57.8 ± 2.8, respectively ($P<0.05$). Social role functioning was similar in all four groups.

Conclusion
The results of the study suggest that anemia has a substantial influence on patients' quality of life in settings of early diabetic nephropathy. Physical role functioning and emotional role functioning are affected by anemia irrespective of the CKD stage.

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EP517

Macular pigment optical density in type 2 diabetes and normal controls: correlation with vitamin D levels

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Aim
To compare macular pigment optical density (MPOD) in diabetic and non-diabetic patients by using heterochromatic flicker photometry and to investigate the correlation of MPOD with glycosylated hemoglobin (HbA1C), serum lipid levels and vitamin D levels.
Methods
Sixty-seven patients with 10/0 visual acuity were divided into group 1 (controls, *n*: 35) and group 2 (diabetics without retinopathy, *n*: 32). MPOD was measured with a heterochromatic flicker method and compared between groups. Diabetes duration, smoking status, HbA1c and serum lipid levels and body mass index were recorded for each patient. The correlation of HbA1C, serum lipid (HDL, LDL, total cholesterol, and triglycerides) and vitamin D levels with MPOD were analyzed in both groups.
Results
The mean ($\pm$S.D.) age in group 1 (48.74 ± 1.568) and group 2 (51.59 ± 1.527) were statistically similar ($P > 0.05$). Mean MPOD was not significantly different between group 1 (0.5589 ± 0.02183) and group 2 (0.5716 ± 0.023) ($P > 0.05$). No significant correlations were found between MPOD and HbA1C, serum lipid levels or vitamin D levels in both groups ($P > 0.05$).
Conclusions
Type 2 diabetic patients without retinopathy had not reduced MPOD when compared with non-diabetic patients. No correlation was found between MPOD, HbA1C, serum lipid levels and vitamin D levels.

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EP518

Vitamin D deficiency association with microvascular complications in type 1 diabetic patients

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Introduction
Low levels of vitamin D are commonly found in people with type 1 diabetes and recently studies found that vitamin D deficiency (VDD) contributes to the risk of developing diabetic microvascular complications. The aim was to determine the relationship between microvascular complications of diabetes and 25-hydroxyvitamin D (25(OH)D) levels in type 1 diabetic patients.
Methods
A total of 143 adults (60 male and 83 female) with type 1 diabetes were enrolled in the study. 25(OH)D level (VD) was measured from October untill April. Patients with GFR < 30 ml/min and with end stage renal disease were excluded from the study.
Results
Thirty-six (25.2%) type 1 diabetic patients had VDD – VD concentration was < 25 pmol/l and 107 (74.8%) – had no VD deficiency (NVDD) – VD was > 25 pmol/l. Age, sex,duration of diabetes, HbA1c, BMI, lipid profile, eGFR, use of alcohol, diabetic retinopathy – were no different ($P > 0.05$) comparing between groups of VDD (the mean of VD 19.9 ± 3.64 pmol/l) and NVDD (the mean of VD 42.3 ± 13.73 pmol/l). There were more current smokers (38.9–19.0%, $P = 0.05$), patients with GFR 30–59 ml/min (13.9–1.9%, $P = 0.016$) and macroalbuminuria > 300 mg/24 h (19.8–2.8%, $P = 0.05$) in VDD group. VDD was more frequent in patients with multiple microvascular complications (VDD 80%, NVDD 41.9%) than in those without any complications (VDD 20%, NVDD 58.1%) ($P = 0.005$) and in those with diabetic polyneuropathy (VDD 86.1%, NVDD 68.3%), that in patients without complications (VDD 13.9%, NVDD 31.7%) ($P = 0.038$). Diabetic nephropathy was associated with VDD (VDD 47.2%, NVDD 22.4%) compared to patients with no renal complications (VDD 52.8%; NVDD 77.6%) ($P = 0.004$). Binary logistic regression analysis revealed that the odds ratio (OR) for diabetic nephropathy independently increases linearly with VDD (OR = 3.43; 95% CI 1.47–7.96, $P = 0.004$).
Conclusion
Vitamin D deficiency was more common in type 1 diabetic patients with multiple microvascular complications and especially in those with diabetic nephropathy.

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EP519

Diabetes mellitus type-II related hypertension and cardiovascular diseases: involvement of impaired regulatory renin-angiotensin-aldosterone system

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Diabetes mellitus type-II (DM-2) is a metabolic disorder characterized by high blood glucose levels due to insulin resistance and relative insulin deficiency. DM-2 often leads to hypertension, a prolonged condition of elevated blood pressure (BP). Both hypertension and diabetes have a pathological role in causing cardiovascular diseases (CVDs). While renin-angiotensin-aldosterone system (RAAS) regulates arterial BP, any pathology in RAAS system may lead to hypertension and related CVDs. This study investigated the involvement of RAAS in causing DM-2-related hypertension and CVDs. Hundred male and female DM-2 hypertensive CVDs patients between ages 21 and 60 years and hundred healthy age-matched controls were examined. Using structured questionnaire, height, weight, BMI, BP, random glucose levels, blood samples, history, qualification, and socioeconomic status were gathered from both groups. Plasma aldosterone concentrations were determined by employing ELISA. Eighty-one patients were treated with either RAAS inhibitors (RAASi), non-RAASi or a combination of RAASi and non-RAASi, while 19 patients remained untreated. Of 20 patients treated with RAASi, 17 responded with aldosterone concentrations dropping to normal range, whereas 3 remained resistant to RAASi. Among 21 patients treated with non-RAASi, aldosterone concentrations fell to normal range in 13, while remained higher in 8 patients. Of 40 patients treated with both RAASi and non-RAASi, 31 responded with aldosterone concentrations falling within normal range, while 9 patients did not respond. Nine of 19 untreated patients had their aldosterone concentrations within normal range, whereas 10 patients exhibited significantly higher aldosterone concentrations. The majority of patients was married, fell in categories of overweight and obese, regularly exercised and followed diet plan, was illiterate or had primary level education, belonged to low and lower middle class socioeconomic status. In conclusion, the present study demonstrates that the over activity of RAAS may contribute in causing DM-2-related hypertension and consequent cardiovascular diseases in our population.

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EP520

Frequency of occurrence and factors of diabetic retinopathy advancement in people with DM type 2 in Uzbekistan

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Goal
To study a frequency of occurrence and factors of progressive diabetic retinopathy (DR) in people with DM type 2 in Uzbekistan.
Materials and study methods
Within the framework of WDF project 'Prevention of blindness in people with diabetes mellitus in Uzbekistan' granted to 'UMID' association in 2008, we carried out DR screening in people with DM type 2 in three pilot regions of Ferghana, Bukhara areas and the Republic of Karakalpakstan.
In three regions we examined 1587 people with DM type 2 aged 40–67 (prescription of disease 5–15 years). Levels of glycemia, HbA1c, cholesterol, LDL, HDL were measured. Examination of fundus of eye, visual acuity determination and intraocular pressure measurement were also carried out.
Results and discussion
Results of examination showed that a frequency of DR occurrence in people with DM type 2 made 56.9%, of them DR of grade I was found in 32.8%, DR grade II – 18.6%, DR grade II – 5.5% and in 43% of cases no DR was found; 52% of patients with prescription of the disease 10–15 years undertook ophthalmological examination for the first time.
DR prevalence in patients with prescription of disease of 10 years made 45%, and that of 15 years and over – 68%. In 80% of patients at the stage of decompensation (HbA1c > 9.5%) prevalence of DR grades I–III made 36.9, 15.8 and 8.8% respectively which is a major factor of advanced development of DR.
Mean rates of TC, LDL and HDL made 5.5 ± 0.2 mmol/l; 4.14 ± 0.22 mmol/l and 0.94 ± 0.03 mmol/l respectively, in that a mean value of LDL in PDM was reliably higher than in patients without DR (3.65 ± 0.07 mmol/l).
Conclusions
According to screening data, a frequency of DR in PDM type 2 in Uzbekistan makes 56.9%. Advancement of DR in PDM type 2 depends on prescription of disease, degree of compensation of carbohydrate metabolism, hypercholesterinemia and dislipidemy.

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EP521

Determinants of diabetic retinopathy in Moroccan type 2 diabetic patients: which glycosylated haemoglobin threshold?

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Background
Diabetic retinopathy represents a major cause of the blindness worldwide. A variety of risk factors has been identified in several population, but to date, comprehensive data concerning our particular risk factors are lacking. The aim of the study was to determine the risk factors of diabetic retinopathy in Moroccan type 2 diabetic patients and to determine the threshold of HbA1c predicting retinopathy.
Materials and methods
All patients 18 years or older diagnosed as type 2 diabetes and who were able to complete the laboratory data and retinal examination were invited to participate in the study. The diabetic retinopathy was classified by the ETDRS severity scale. Data were collected about duration of diabetes, smoking status, medications, evidence of macrovascular disease, blood pressure, nephropathy or neuropathy and actual therapeutics. Laboratory parameters included: HbA1c, lipid panel and microalbuminuria. Statistical analysis was performed using SPSS 16.0. The association between DR and each of the risk factors was assessed by bivariate analysis. A multivariate logistic regression analysis was performed to check the effect of independent variables on DR. the predictors on the binary logistic regression model were disease duration, HbA1c, systolic blood pressure, nephropathy, neuropathy and evidence of macrovascular disease.
Results
A total of 231 patients were included. The bivariate analysis has identified as risk factor for diabetic retinopathy: microvascular and macrovascular diabetic complications, presence of hypertension, duration of disease, glycemic control and insulin use. The multivariate regression analysis retrieved as independent risk factors: glycosylated hemoglobin >7% (OR: 2.71 95% CI 1.06–7.43), microalbuminuria (OR: 2.6 95% CI 1.2–5.4), diabetes duration(per 10 years) (OR: 2.6 95% CI 1.2–5.4) and blood pressure (per 10 mmgh) (OR: 1.27 95% CI 1–1.70).
Conclusion
Our study found similar factors to those described for other populations. We emphasize on the important role of early medical intervention and adequate therapeutic education especially concerning the glycemic and blood pressure control.

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EP522

Waist circumference is a predictive factor for cardiovascular disease in diabetic patients

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Introduction
Obesity worsens the prognosis of diabetic patients by increasing the cardiovascular risk and chronic complications. Waist circumference, as a brief indicator of visceral obesity, is associated with multi-metabolic disorders and cardiovascular diseases. The aim of the study was to report the prevalence of WC in individuals with diabetes and find out their association with other cardiovascular risk factors.
Material and Methods
We performed a transversal study, in which 100 patients with essential hypertension, and type 2 diabetes, were evaluated in comparison with 100 patients with only hypertension. We evaluate these patients for: BMI, waist circumference (cut offs as 90 cm in men and 80 cm in women); IMT; microalbuminuria; fundus oculi, LVMI. Serum PCR and lipid concentrations were measured.
Results
A total of 200 hypertensive patients were enrolled in the study (138 female and 62 male, respectively 69 and 31%). Mean age for HTA group was 58.2 (± 11.9) years and for the other group 60.7 (± 9.3) years. The diabetic hypertensive subjects significantly had higher BMI ($P = 0.01$) and WC statistically significant (103.6 cm vs 98.3 cm; $P = 0.005$). There was a significant positive association between WC and microalbuminuria ($P = 0.009$); WC and IMT ($P = 0.028$); Was seen a relation of waist circumference and diabetic retinopathy; 84% of patients with abdominal obesity have changes of diabetic retinopathy independently of stage of changes.
Conclusions
Prevalence of obesity in diabetic hypertensive patients was high. There was a positive relation of waist circumference and microalbuminuria, IMT, and diabetic retinopathy. So, abdominal obesity is not only reflects sub-clinical atherosclerosis in early stage, but also predicts the progression of atherosclerosis and development of microalbuminuria. This underlines the importance of measuring waist circumference when assessing cardiovascular risk factors in diabetic patients.

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EP523

Risk factors of diabetic cardiac autonomic neuropathy in patients with insulin dependent diabetes mellitus: a meta analysis

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Objectives
We aimed to stratify the possible risk factors for diabetic cardiac autonomic neuropathy (CAN).
Methods
We did a metaanalysis of risk factors of CAN. We did a web based search for literature in MEDLINE/PubMed, SCOPUS database, and CENTRAL database up to August 2015. We included clinical trials or cohort studies that provide data about relationship between CAN and variables of interest. Our risk factors of interest were age, sex, duration of diabetes, BMI, systolic (sBP) and diastolic blood pressure [dBP], HbA1c, HDL, LDL, triglycerides, retinopathy and

nephropathy. We generated Forest plots, chi squared test and (I2) as tests for heterogeneity, risk ratio (RR), mean difference (MD), confidence intervals, and *P* values by Revman5.3 software.
Results
We found a total of 882 related item. We excluded 873 studies from the title and abstract and four studies after review of full reports. Four studies were included. Our meta-analysis showed significant association between CAN and age (MD = 4.94 [3.46, 6.42]), duration of diabetes (MD = 4.51 [2.51, 6.52]), HbA1c (MD = 0.48 [0.28, 0.67]), BMI (MD = 0.55 [0.08, 1.01]), serum triglycerides (MD = 0.09 [0.01, 0.17]), proliferative retinopathy (RR = 3.69 [1.20, 11.34]), microalbuminuria (RR = 2.47 [1.43, 4.29]), hypertension (RR = 4.18 [2.52, 6.91]), and sBP (MD = 4.10 [2.20, 6.00]). We discovered absence of significant association between development of CAN and male sex (RR = 1.57 [0.45, 5.39]), dBP (MD = 0.89 [−0.36, 2.14]), cholesterol level (MD = 1.19 [−0.99, 3.36]), LDL (MD = 0.12 [−0.15,0.39]), nor HDL level (MD = −0.28 [−0.58,0.03]).
Conclusion
Age, duration of diabetes, HbA1c, BMI, serum triglycerides, proliferative retinopathy, microalbuminuria, hypertension, and systolic blood pressure are directly related to the risk of development of diabetic CAN.

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EP524

Is there a tendency for thrombosis in gestational diabetes mellitus?

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Aims
Impact of gestational diabetes mellitus on the coagulation system, dynamics involved at a pathophysiological level and the exact mechanism remain unclear. To evaluate association between diabetes-related parameters and haemostatic factors in order to search for a tendency of thrombosis in gestational diabetes mellitus.
Methods and Material
Nineteen pregnant women who had gestational diabetes mellitus, 16 healthy pregnant and 13 healthy non-pregnant controls admitted to the Endocrinology outpatient clinics were enrolled in the study. Fasting and postprandial glucose, haemoglobin A1c and insulin levels, and insulin resistance; fructosamine, thrombin activatable fibrinolysis inhibitor, tissue factor pathway inhibitor, plasminogen activator inhibitor type-1, tissue type plasminogen activator, fibrinogen, plasminogen and haemoglobin levels, platelet counts, prothrombin time, activated partial thromboplastin time were studied. One-Way analysis of variance, Kruskal Wallis and post hoc Tukey HSD or Conover's non-parametric multiple comparison tests for comparison of the study groups.
Results
Prothrombin time and activated partial thromboplastin time were significantly lower in gestational diabetes mellitus patients compared to controls ($P < 0.05$), while fibrinogen and plasminogen levels were significantly higher in this group compared to both non-pregnant and healthy pregnant controls ($P < 0.05$ for each). Thrombin activatable fibrinolysis inhibitor, tissue factor pathway inhibitor, plasminogen activator inhibitor type-1 and tissue type plasminogen activator levels were not significantly different among groups.
Conclusions
Our findings indicate tendency to develop thrombosis in gestational diabetes mellitus similar to diabetes mellitus; but more comprehensive studies with larger sample size are needed to determine the relationship between gestational diabetes mellitus and haemostasis. Levels of coagulation factors may vary in different stages of pregnancy and postpartum period with diverse etiopathogenesis. Similar to previously reported studies, our study suggests that GDM may play a role in the pathogenesis leading to a thrombotic tendency similar to diabetes mellitus.

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EP525

Analysis of disability in population due to diabetic ophthalmopathy

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Introduction
Among the complications of diabetes ophthalmic are among the most severe. Uzbekistan's population is over 30 million people; according to statistics the number of diabetes patients is 130 000 people, but the real number is at least six times bigger - more than 800 000 (WHO). Our study aimed to investigate the disability features due to ocular complications of diabetes in Tashkent within 10 years.
Methods
Data of examinations in specialized ophthalmic medical–social expert commissions in Tashkent of diabetic patients for the 2003–2012 years was studied. The total number of disabled people was 307; patients with Type 1 - 13%, 2 - 87%; men - 59% women - 41%; the mean age was 55 years.
Results
The level of total disability due to ocular complications of diabetes is not high: in 2003–2006 - 0.23 per 10 000 adults, decreasing to 0.17 in 2007; in 2008 - 0.14; in 2009 - 0.09; in 2010 - 0.11; in 2011 - 0.13; in 2012 - 0.11. On average, it was equal to 0.16 on 10 000 of the adult population. The share of new disability cases - 35.9% is significantly less than the number of repeatedly recognized disabled - 64.1%. From the new cases of disability group I disabled - 49.6%, group II - 47.2% and group III - 3.2%. Among repeatedly recognized, group I - 69.5%, group II - 24.7% and group III - 5.8%. Analysis of the structure by age of disability shows that in both primary (52.7%) and repeated disability (46.5%) a significant proportion is working-age population.
Conclusion
Prevention of ophthalmic complications of diabetes will not only reduce the state budget expenses, but will also improve the quality of patients life.

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EP526

Diabetic muscle infarction in a 54-year-old female: a case report

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Introduction
Diabetic muscle infarction is a very uncommon complication of diabetes and predominately occurs in type 1 diabetes (70% of cases) or long standing poorly controlled type 2 diabetic patients, often misdiagnosed as cellulitis. It is defined as spontaneous ischemic necrosis of skeletal muscle that is unrelated to atheroembolism or occlusion of major arteries.
Case presentation
We report a case of 54-years-old women non-smoker with an 8 years history of type 2 diabetes mellitus. Glycemic control had been unsatisfactory during the last years, HbA1c over 12%. The patient presented with a 2 days history not being able to walk. Her symptoms started about 2 weeks ago. One morning she was awoken with a sudden onset of right thigh pain and swelling. The pain increased during exercise. No preceding trauma, fever, animal bites or infection. On physical exam, she had a localized, tender area with swelling and indurations of the surrounding tissue, no skin erythema. She was apyrexial. Her white cell count was 10.700/l in normal range, erythrocyte sedimentation rate (ESR) was normal 20 mm/h. HbA1c was 13.9% range from 4.8–6.1, blood glucose 25.5 mmol/l. She had normal creatinine kinase (62 UI/l). Additional diabetic workup failed to reveal any signs of retinopathy or neuropathy. Deep venous thrombosis was excluded by Doppler ultrasound on both legs. Magnetic resonance imaging (MRI) in both coronal and axial planes demonstrating on T2-weighted images a high-intensity signal in the intra- and perimuscular tissues of the left vastus medialis muscle secondary to edema and necrosis. She did not required surgery or biopsies. Glycemic control was established with intensive insulin therapy, pain was controlled with analgesic medication, bed rest and corticosteroids for edema. The patient gradually recovered over the period of ∼4 weeks.
Conclusion
Diabetic muscle infarction is a rare complication of diabetes, which should be suspected in any diabetic subject with uncontrolled and longstanding diabetes who presents with a painful swollen limb. The diagnosis can be made when the characteristic clinical presentation is combined with a typical MR imaging results.

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EP527

Detection of hypoglycemia in type 2 diabetic patients

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Introduction
Hypoglycemia consists a significant problem in insulin treated type 2 diabetic patients. The present study compared the incidence of hypoglycemic episodes in type 2 diabetics between continuous glucose monitoring/CGM vs self monitoring of blood glucose/SMBG.
Methods
Seventeen patients with type 2 diabetes underwent a 24 h CGM for a period of 3–5 consecutive days. At the same period they recorded their glucose values using SMBG from four daily measurements. The main end points were: i) potential differences in detection of hypoglycemic episodes depending on the recording method (CGM vs SMBG) and ii) assessment of the recorded hypoglycemic episodes pattern (nocturnal vs no nocturnal hypoglycemia).
Results
According to CGM, ten type 2 diabetic patients experienced at least one hypoglycemic episode, while four patients experienced at least one hypoglycemic episode as illustrated by SMBG (58.8% vs 23.5%, $P=0.07$). i) 23 hypoglycemic episodes were recorded by CGM vs eight episodes which were recorded using SMBG (mean 1.35 vs 0.48, $P=0.008$) ii) four patients (23.5% of type 2 diabetic subjects) were detected by CGM suffering from nocturnal hypoglycemia. In contrast, no nocturnal hypoglycemic episodes detected and none recorded by SMBG, since no patient performed glucose measurements during the night. In addition to, six patients recorded hypoglycemia while they were alert, four of whom (23.5%) were asymptomatic.
Conclusions
In type 2 diabetic patients more hypoglycemic episodes are detected using CGM than SMBG (24 vs 8, $P=0.008$). Furthermore, 23.5% of type 2 diabetics experience nocturnal hypoglycemia and an equal percentage experience unawareness of hypoglycemia undetected by SMBG. In conclusion, CGM seems to be a useful tool for the detection and assessment of hypoglycemia in type 2 diabetic patients.

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EP528

Diabetes mellitus, pre-dialysis, extreme anxiety, and sarcoidosis

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Diabetic nephropathy is the leading cause of chronic kidney disease and is responsible for 30–40% of all end stage renal disease (1). Where there is rapid decline in eGFR, we should also consider other aetiologies.
This is the case of a 65-year-old Caucasian gentleman with complex presentation and novel management strategy with type 2 diabetes mellitus since 1999 which was effectively managed, evident by reasonable control of HBA1c; Pharmacotherapy regimen was modulated sensitive to patient tolerability and outcome. On subsequent follow up his creatinine was 389 umol/l from baseline of around 160 umol/l. When patient was informed of possibility of dialysis over coming year, it caused him severe anxiety. During history taking, it was revealed that the patient had an episode of anterior uveitis. Thorough physical examination led to the discovery of an erythematous lesion on his left shin, and meticulous review of laboratory findings revealed intermittent hypercalcemia. This triad of observations led to discover shadowing, suspicious of hilar lymphadenopathy on chest X-ray: Hence moderate-dose prednisolone therapy was initiated for presumptive sarcoidosis; Biopsy was precluded due to body habitus. Corticosteroids provided a rapid return of creatinine to baseline, however, necessitated introduction of insulin due to induction of hyperglycaemia. On subsequent commencement of azathioprine, prednisolone dosages were rapidly reduced, and insulin requirement were significantly reduced.
Conclusion
Encourage physicians to consider alternative aetiologies to diabetic nephropathy for rather swift deterioration of renal function in patient with diabetes, such as renal sarcoidosis. Secondly, rapid withdrawal of moderate-dose corticosteroids and substitution with a steroid-sparing agent as a novel therapeutic modality for treatment of renal sarcoidosis in the setting of diabetes mellitus was superior to the established protocol (2, 3). This sequential pharmacotherapy has preserved quality of life, as renal failure requiring long-term haemodialysis was imminent, and corticosteroid withdrawal allowed for continuing better glycaemic control.

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EP529

Good renal and vital prognosis of metformin induced Lactic acidosis

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Metformin Associated Lactic Acidosis (MALA) is defined by a Ph <7.35 and lactate levels greater than 5 mM. It must be distinguished from other lactic acidosis usually secondary to septic shock. Renal functional prognosis and mortality are not clearly separated in publications and many make the amalgam between the two entities with an estimated mortality of 30 to 50% and poor renal prognosis.
We did a retrospective, observational, cohort study of patients who were admitted consecutively in intensive care unit for MALA between January 2010 and July 2015 in a tertiary hospital.
Seventeen patients, nine men; mean age 60 years were included. The presumed cause of MALA was renal insufficiency by dehydration in seven, sepsis in seven, and voluntary intoxication in three.
The mean initial Ph was 7.05 (extreme 6.58 to 7.35), lactacidemia: 10.33 mM (extreme 5.12 to 15.2), creatinine was 551 µM (extreme 56 to 1338), blood glucose: 1.62 g/L (extreme 0.29 to 4.5). The ICU stay was of 10.2 days (extreme 1 to 26). Only two patients deceased because of septic shock. Fifteen had abnormal creatinine clearance <60 ml/min, 14 recovered of their renal insufficiency.
Eleven out of seventeen patients had dialysis to prevent the ionized calcium decrease, volume overload, hyperosmolality and remove metformin.
Thus at the opposite of Lactic Acidosis due to others causes, MALA represents a situation with good prognosis and rapid renal improvement by dialysis.

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EP530

A rare case of acute renal failure: rhabdomyolysis due to hyperosmolar hyperglycemic state

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Introduction
Rhabdomyolysis is usually attributed to trauma. However, there is an association of rhabdomyolysis with hyperosmolar states. It is also important to realize that hyperosmolar coma can be the presenting complaint of a diabetic seeking medical attention for the first time. In this case-report we aimed to present a patient with acute kidney injury due to rhabdomyolysis and hyperosmolar state.
Case report
Forty nine-year-old black male patient was brought to emergency room because of new onset confusion during an international flight. His past medical history was remarkable for only asthma. Bibasilar decreased breath sounds and 2+ bilateral pretibial edema were detected on physical examination. His laboratory studies were as follows: blood glucose 1505 mg/dl, urea 163 mg/dl, creatinine 9.8 mg/dl, creatine-kinase (CK) 45,750 U/l, sodium (Na) 146 mmol/l, potassium (K+) 4.67 mmol/l, blood pH 7.3, osmolarity 368 mosm/l. His urinary ultrasonography was normal. The patient was brought to intensive care unit and received continuous arteriovenous hemofiltration. His consciousness level gradually improved, his urinary output increased and creatinine level decreased to normal value. The patient was discharged after his blood glucose levels were controlled.
Result
The exact mechanism of rhabdomyolysis in a hyperosmolar state remains unclear. Singhal *et al.* concluded that serum sodium, osmolality and glucose levels are the major determinants for the occurrence of rhabdomyolysis in the diabetic state. Pharmaceutical agents, alcohol, illicit drugs, hypokalemia, hypophosphatemia, hypothermia and hyperosmolar situations are significant causes of rhabdomyolysis. To our knowledge, there are around a dozen cases reported in the literature.

Although it is rarely clinically important, it has been suggested that over 50% of patients presenting with hyperosmolar state may develop rhabdomyolysis to greater or lesser degree.

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EP531

Clinical profile of type 2 diabetic patients suffering of erectile dysfunction

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Introduction
The number of patients with diabetes has been increasing at an alarming pace for the last decade. Sexuality is frequently affected in diabetic patients.
The aim of this study was to describe the clinical profile of a group of type 2 diabetic patients suffering of erectile dysfunction (ED).
Methodology
This was a cross-sectional study involving a population of 70 type 2 diabetic patients recruited from the day hospital during May and June 2015.
All men were invited to complete a sexual activity questionnaire (the abridged five-item version of the International Index of Erectile Function-IIEF-5) as a diagnostic tool for ED.
Results
Of the 70 patients studied, 61 suffer of erectile dysfunction. The erectile dysfunction is mild, moderate and severe in respectively 47.1, 19 and 33.9% of cases. 81.9% of the subjects are smokers. 65.5% are overweight and 32.7% have dyslipidemia. The average HbA1c is 10.62%. Men with *ED were significantly older than* subjects without *ED*. On our study, the onset of ED is directly correlated to diabetes' duration. Cardiovascular risk factors as well as degenerative complications are associated with an increased risk of ED.

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EP532

Diabetic papillopathy with macular edema treated with intravitreal ranibizumab

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Introduction
We report a case of diabetic papillopathy that demonstrated a resolution of optic disk swelling and rapid visual recovery when intravitreal ranibizumab was administered.
Case report
A 51-year-old male presented with acute painless visual loss in his right eye. His vision was 20/320 in the right eye and 20/50 in the left eye. Fundus examination of the right eye showed nonproliferative diabetic retinopathy with macular edema and a swollen optic disk. Fluorescein angiography showed dye leakage from the right optic disk. Optical coherent tomography revealed a significant increase in retinal nerve fiber-layer thickness. Magnetic resonance imaging of the brain was normal. The patient received a single intravitreal ranibizumab (0.5 mg) injection. Two weeks following injection, there was marked regression of the disk swelling and improvement of macular edema, with vision improving to 20/100. Three months following injection, there was complete resolution of the optic disk swelling. No further treatment was required.
Conclusions
A rapid improvement in vision was noted in our patient shortly after intravitreal injection of ranibizumab. Therefore, it may be that the intravitreal ranibizumab played a positive role in stabilizing and improving the patient's optic nerve edema. However, the efficacy and safety of this management of diabetic papillopathy needs to be proven through further larger clinical studies.

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EP533

Diabetes and rhino-orbito-cerebral mucormycosis

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Introduction
Rhino-orbito-cerebral mucormycosis is a rare invasive fungal infection more common in diabetic and elderly patients. The presentation is acute, severe and rapidly progressive to disseminated infection. The diagnosis is done by the identification of risk factors, clinical and radiologic signs and tissue biopsy consistent with mucormycosis. The mortality rate is high, so timely diagnosis and intervention lead to better outcomes.
Clinical case
Male patient, 85-years-old, with a past medical history of diabetes type 2 medicated with Vildagliptin/Metformin 50/850 mg twice a day, hypertension, glaucoma and prostatic adenocarcinoma. With good metabolic control, as described in previous medical records. The patient was admitted to the emergency department because of right eye inflammation, epistaxis and nasal congestion over a period of 24 h. At physical examination he showed exophthalmia and right periorbitary edema. The plasmatic glycemia was 480 mg/dl and bioinflammatory parameters were elevated. The CT scan revealed: 'Right ethmoidal-maxillary sinusitis and ipsilateral periorbitary cellulitis with post septal component'. The patient was admitted to ENT department and underwent nasal endoscopy and a biopsy was performed to remove tissue from the sites of infection for examination. Initially treated with antibiotic, later on switched to amphotericine B due to fungal disease confirmation. The histological examination was consistent with mucormycosis. During hospitalization the patient's glucose levels improved. On the 5th day the clinical state aggravated and on the 16th day of hospitalization the patient died due to multi-organ dysfunction.
Discussion
This clinical case is relevant due to the gravity of the disease in the context of hyperglycemia. Owing to the increased number of newly diagnosed cases of mucormycosis worldwide resulting from uncontrolled metabolic conditions this is a disease to have in mind. Therefore any diabetic patient with sinonasal disease, regardless of metabolic control, should prompt evaluation to rule out mucormycosis.

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EP534

Lipemic diabetic ketoacidosis as a presentation of type 1 diabetes mellitus

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Introduction
Diabetic ketoacidosis (DKA) is a complication of insulin deficiency and can rarely be associated with diabetic lipemia, which is a life threatening condition.
Case report
We report a 20-year-old male, who visited emergency department with a short history of abdominal pain and vomiting. Clinically he was alert, had kussmaul's breathing, and was found to be hyperglycaemic, with metabolic acidosis and ketonemia (RBS 18, Ph 7.18 HCO3 8.4). His venous blood appeared grossly lipemic (Triglyceride 35 mmol/l). Amylase was normal. His DKA was treated in accordance with the British Joint society of Diabetes guidelines. The initial management dilemma we faced were laboratory interference due to hyperlipidaemia that lead to a delay in resolution of DKA. His diabetes autoantibodies were detected, however, Lipoprotein lipase genetic testing was not done as it is not available in our region. His lipids normalised on follow up.
Discussion
In DKA, insulin deficiency activates lipolysis in the adipose tissue releasing free fatty acids, which accelerates formation of VLDL, together with reduced lipoprotein lipase activity results in hypertriglyceridemia. Evaluation of electrolytes are pivotal in the management of DKA due to the rapid infusion of insulin and fluids. As seen in our case, lipemic samples cause analytical errors and pose challenges to fluid management and electrolyte replacement in the management of DKA, due to the difficulties in analysis, especially those without ultracentrifuges. In such circumstances, emphasis should be placed on clinical evaluation followed by hydration and insulin administration which assists in the resolution of DKA and eventually lipemia. If available, the use of high speed micro centrifuges showed effectivity in reducing lipid levels provided a suitable alternative to ultra-centrifuges.
Conclusion
Severe hyperlipidaemia causing lipemic serum in patients with DKA is rare phenomenon, and clinicians should consider devastating consequences such as acute pancreatitis or lipemic retinalis, thus prompt insulin administration is pivotal.

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EP535

Diplopia as a presenting symptom of diabetes mellitus

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Introduction
The neuropathies are one of the most common complications seen in diabetes, affecting up to 50% of diabetic patients. Isolated or combined paralysis of 3rd, 4th and 6th cranial nerve can be seen.
Case presentation
Sixty-six-year-old male patient was admitted to the neurology department with the complaints of diplopia persisting for 15 days. Cranial images revealed no abnormal findings. Patient was directed to internal medicine clinic due to the complaints of weight loss, thirst and polyuria in detailed interrogation. Due to detecting fasting blood glucose level of 317 mg/dl and postprandial blood glucose level of 535 mg/dl in laboratory tests, he was admitted to the internal medicine service. HbA1c was measured as 12%. Insulin therapy was initiated. When the patient was consulted to clinic of *ophthalmology*, the 6th cranial nerve palsy was identified and recommended a clinic of *ophthalmology* control every 6 months. He was discharged with advice to go to the clinic control.
Discussion
Cranial mononeuropathy is one of more frequent vascular and neuropathic complications in the presence of advanced age and long standing, poorly controlled DM. It should be kept in mind that DM can be diagnosed with non-specific and rare symptoms of eyes such as diplopia.

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EP536

The presence of risk factors for type 2 diabetes and glucose tolerance in pregnant women

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Background
Pregnancy is a state of insulin resistance that can predict diabetes development in some women, and is associated with increased risk for neonate and for mother. Frequency of glucose intolerance may be increased in the follow-up years.
Aim
The aim of this study is to determine the presence of risk factors for type 2 diabetes and degree of glucose tolerance in population of pregnant women.
Materials and methods
The study included 77 healthy pregnant women in third trimester registered in centre for endocrinology CC Kragujevac that were tested, according to conducted 3 h OGTT with 100 g glucose (ADA criteria).
Results
Patients were average 30.8 ± 4.7(19–41) years old. The frequency of risk factors were: obesity (3.9%), hypertension (5.2%), previous gestational diabetes mellitus (23.5%), smoking (23.4%), previous maternity body weight >4 kg (8.8%), positive family history for diabetes (27.3%). Prepregnancy BMI of participants was 22.0 ± 2.6 kg/m^2, weight gain during pregnancy was obtained as 12.7 ± 1.5 kg. It was shown that there was impact the number of risk factors on degree of glucose tolerance disorder ($P = 0.034$), while most of patients had no risk factor (48%). Between 77 patients, the nine was with gestational diabetes mellitus and nine was with minimal disorder of glicoregulation. Including parameters of adverse outcome, it was shown that number of risk factors significantly impact on pregnancy outcome ($P < 0.005$).
Conclusion
This research showed presence some of risk factors for type 2 diabetes in more than half of pregnant women. Women with glucose intolerance have higher risk for diabetes development.

Keywords: risk factor, diabetes, pregnancy
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EP537

Calculator for myocardial infarction risk in patients with type 2 diabetes mellitus

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Study was initiated to perform integral assessment of myocardial infarction (MI) risk in patients with type 2 diabetes mellitus with genetic markers taken into account as well as to develop a method for its prediction in this category of patients. As to relative risk of factors causing MI in Uzbek patients with type 2 diabetes mellitus, myocardial infarction in family medical history comes the first followed by left ventricular hypertrophy, age, ACE gene DD genotype, arterial hypertension, diabetes duration, diabetic nephropathy, alcohol abuse, HbA1c ≤ 7%, obesity (BMI > 25 kg/m^2), stroke in family medical history, dislipidemia, TCF7L2 gene TT genotype, smoking and hypercoagulation. This type of rating is essential in a physician's practice to categorize MI risk contingent among patients with type 2 diabetes mellitus. Possible ranges of risk for all factors above were determined after calculation of MI risk relative risk parameters. It is expedient to divide the whole risk range into subranges which allow categorizing patients by various risk probability for the risk factors known. Thus, there are three MI risk subranges for patients with type 2 diabetes mellitus: the lowest MI risk subrange is for patients with favorable prognosis and minimum MI risk, intermediate MI risk subrange is for patients who have higher probability of MI and require focusing of physicians' attention and the highest MI risk subrange is for patients with unfavorable prognosis maximally affected by MI risk factors. Contrary to existing analogues, genetic risk factors, such as ACE gene DD genotype and TCF7L2 gene TT genotype, typical of Uzbek population are taken into account for MI prediction in patients with type 2 diabetes mellitus, as well. Prediction of MI risk degree in patients with type 2 diabetes mellitus facilitates timely interventions corresponding to MI risk degree. That will help delay or prevent MI, or smooth its course with minimal or no complications. Integral assessment of MI risk factors is a comprehensive strategy for myocardial infarction prevention in patients with type 2 diabetes mellitus. It makes possible for practical healthcare to combine a patient's social and clinical characteristics for the purposes of assessment of MI risk and prediction of MI progression, and thereby using the latest achievements in endocrinology and cardiology to perform appropriate interventions on early stages of the disease.

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EP537B

Renal function reserve state in patients with diabetic kidney disease

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Kidneys reserve mechanisms are of great scientific and practical interest.
In 56 patients with diabetes mellitus two types and diabetic kidney disease (DKD), 24 men (42.9%) and 32 women (57.1%) aged from 38 to 81 years (61.3 ± 2.65) had been estimated the renal functional reserve (RFR) with water-salt load of 0.5% NaCl in the amount of 0.5% body mass to determine the reduction of nephron's amount using the level of glomerular filtration rate (GFR) before loading (with formula of GFR – EPI) and after loading (with clearance of creatinine).
In patients with DKD 1 and 2 stage after water–salt load of 435 ± 37.1 and 465 ± 49.9 ml, urine output was 249 ± 55.5 ml and 220 ± 102 ml with albumin excretion of 7.96 ± 4.87 and 6.54 ± 2.54 mg/mmol. The GFR level increased from 95.1 ± 1.88 to 226 ± 60.2 ml/min and from 72.4 ± 4.47 to 173 ± 47.7 ml/min, the renal function reserve averaged 226 ± 60.2 and 137 ± 61.3 ml/min, accordingly. In patients with CKD 3a and 3b stage after loading of 432 ± 58.8 ml, the urine output was 179 ± 48.4 ml with albumin excretion of 16.63 ± 9.98 mg/mmol. GFR level increased from 55.7 ± 2.49 to 176 ± 36.3 ml/min and renal function reserve averaged 216 ± 59.3 ml/min.
In the renal function study were found that in 92.8% of patients with DKD 1 stage, in 50% of patients with DKD 2 stage and in 46.4% patients with DKD 3 stage despite markers of kidney damage like albuminuria or GFR bellow 60 ml/min, kidneys were able to increase the glomerular filtration rate to the level of standards and there was no reduction of the amount of functioning nephrons.

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Diabetes therapy

EP538

Liraglutide as additional treatment to insulin in patient with latent autoimmune diabetes in adults (LADA): a case report

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Introduction
LADA exhibits characteristics of both type 1 diabetes mellitus (DM) and type 2 DM. Patients with LADA usually have some components of metabolic syndrome. GLP-1 agonists have been widely used in type 2 DM. GLP-1 agonist therapies have shown some promising glucose lowering effect in T1DM. Almost no information is available on glucagon and incretin secretion in patients with LADA as well as effects on glucose and C-peptide levels.
Case report
A 40-year-old man with BMI 29.4 kg/m^2, diagnosed with LADA-diabetes (duration 6 months) had GADA and ICA – positive autoantibodies, fasting plasma C-peptide 1.8 ng/ml (1.1–4.4). The patient received insulin treatment. Mixed meal tolerance test (MMTT) was performed before and after treatment with liraglutide 1.8 mg in addition to insulin during next 6 months. Plasma glucose (PG), glucagon and C-peptide were measured at 0 min, 30 and 120 min during MMTT. HbA1c was measured before and after treatment. Informed consent was obtained from the participant. After the treatment HbA1c decreased from 10.5% to 7.4%. Dose of long-acting insulin was reduced and fast-acting insulin was abolished. BMI reduced from 29.4 kg/m^2 to 26.3 kg/m^2. Plasma glucose decreased from 10.3 mmol/l to 6.2 mmol/l on 30 min and from 9.6 to 8.1 mmol/l on 120 min. Liraglutide reduced glucagon levels from 153.2–179.3-226.7 pg/ml (on 0, 30, 120 min respectively) to 150-164-138 pg/ml. Plasma fasting C-peptide level has become 2.3 ng/ml after 6 months.
Conclusion
Addition of liraglutide to insulin in patient with LADA leads to improvement in glycemic control, HbA1c and reduction in insulin dose and body weight. It reduces glucagon levels and serves to increase C-peptide.

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EP539

Patients' understanding of hypoglycaemia in tertiary referral centers

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Objective
Hypoglycemia is a common adverse event and one of the main obstacles to achieving good glycemic control to minimize the risk of diabetic complications in patients with diabetes. Therefore, most physicians try to reduce hypoglycemia events through education about hypoglycaemia, such as diabetes self-management education. In this study, we surveyed the actual insight about hypoglycemia, behavior of diabetic patients to avoid hypoglycemia and the fear of hypoglycemia.
Methods
We conducted the survey for patients with diabetes who visited seven tertiary referral centers in Korea from June 2014 to June 2015. The questions sought information about personal history, symptom, education experience, self-management and fear about hypoglycemia.
Results
In 758 participants enrolled, 471 patients (62.13%) have experienced hypoglycemia and 274 patients (36.14%) had recently experience of hypoglycaemia at least once in a month. Eighty-five (27.9%) patients have experience a lecture about hypoglycemia at least once (average 2.2 times). But only 19.4% of patients knew exactly the definition of hypoglycemia. Among the 12 correct hypoglycemic symptoms in questionnaire, most participants chose dizziness (55.01%), sweating (53.82%), and hunger (33.24%). To recover from hypoglycemia, 40% of patients ate something first and they mostly ate candy (62.13%), chocolate (37.73%) and juice (36.80%); 51% of participants did not tell about hypoglycemic events before their doctor asked.
Participants who had experienced hypoglycemia had higher hemoglobin A1c, longer duration of diabetes and more use of insulin. Mean score of behavior to avoid hypoglycemia is 21.2 ± 10.71 and worry about hypoglycemia is 23.38 ± 13.19. These scores are higher than participants who had Hb A1c$>$ 8% and insulin users.
Conclusion
Doctors should pay more attention to how anxious patients are about hypoglycaemia. We must educate patients about what to do when they feel hypoglycemic symptoms, especially for patients who have the higher chance to experience hypoglycemia.

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EP540

Impact of obesity on management of type 2 diabetes

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Management of type-2 diabetes (T2D) should be individualised given recent increase in treatment options. There is a spectrum of phenotype of T2D from thinner patients who may be more insulin deficient to those who are overweight/obese and insulin resistant. We hypothesized that, if we are personalising treatment, thinner patients would be more likely to be treated with insulin secretagogues. To compare the management between these phenotypes, we reviewed 1007 patients with T2D consecutively attending for annual review. Patients were divided into quartiles by body mass index and those in the lowest ($n=252$, age 63 ± 13 years) and highest ($n=252$, age 60 ± 12) quartiles were compared (data are mean $\pm$ S.D. $P=0.001$ for comparison of age). Phenotypic and biochemical data were compared using t tests and proportions on different treatments were compared using χ^2 test. Systolic blood pressure, total and LDL cholesterol and eGFR, calculated using the MDRD equation, were not different between the groups. The mean BMI in the lowest quartile was 25.1 ± 2 kg/m^2 compared to 40.2 ± 5 kg/m^2 in the highest quartile, $P<0.001$). Mean HbA1c was 54 ± 15 mmol/mol in the lowest quartile compared to 59 ± 19 mmol/mol in the highest, $P=0.001$. In the lowest quartile, 14% of patients were on insulin, 28% on sulfonylureas and 71% on metformin, compared to 25, 37 and 81% in the highest quartile, respectively, $P<0.05$ in each case. More patients in the highest quartile were on GLP-1 agonists (13% vs 2% in the lowest quartile) but DPP4 inhibitors use was similar. In summary, thinner patients were slightly older and had slightly better glycemic control, despite less aggressive glycemia management. We believe that this reflects a different underlying pathophysiology of diabetes between these phenotypes and highlights the need for a personalised approach to T2D management.

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EP541

PPARG2 Pro12Ala, TNFα G(308)A and G(238)A, LIPC C(-514)T, ACE I/D, SLCO1B1 Val174Ala polymorphism as predictors of lipid-lowering response to statin therapy in patients with T2DM

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Aim
To evaluate the effect of *PPARG2 Pro12Ala, TNFα G(308)A and G(238)A*, *LIPC C(-514)T*, *ACE I/D*, *SLCO1B1 Val174Ala* polymorphism on the response to statins therapy in patients with type 2 diabetes mellitus (T2DM).
Methods
We consecutively recruited patients with type 2 DM requiring lipid-lowering therapy according to current guidelines. Patients were started on either atorvastatin 10 or 20 mg. After 12 month of statin therapy, patients had fasting lipid profiles repeated. The alleles and genotypes were performed by PCR in real time with the TaqMan probes. Statistic analysis was evaluated using the Mann–Whitney/Kruskal–Wallis and Wilcoxon tests, $P<0.05$.
Results
Ninety-seven patients were studied. There was no difference in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels between the genotypes of studied genes in statin-untreated subjects. With statin therapy, *PPARG2Pro/Pro* patients had significantly TC and LDL-C lowering compared with *PPARG2Pro/Ala and PPARG2 Ala/Ala* patients (for TC: 20.74% vs. 4.6% and 5.61%; $P=0.04$, respectively; for LDL-C: 26.00% vs. 6.11% and 7.32%; $P=0.029$, respectively). There was no gender difference in baseline lipid parameters or response to statin therapy.

Conclusions
PPARG2 Pro12Ala polymorphism accounts for interindividual variability of response to statin therapy in patients with T2DM.

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EP542

Add on exenatide treatment in obese type 2 diabetic patients under intensive insulin regiments

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Introduction
Intensive insulin treatment in obese patients with type 2 diabetes (T2DM) is often difficult. Insulin dosages are much higher, which further increase weight gain and the risk of hypoglycemia. Glucagon like peptide 1 receptor agonists (GLP-1RAs) are the promising treatment modalities causing weight loss and reducing the risk of hypoglycemia. There is no published data about the effect of adding on GLP1RAs to obese T2DM patients with un-controlled glucose levels under intensive insulin regiments.
Methods
This retrospective case series report the clinical outcomes of 23 obese patients with uncontrolled T2DM (female = 18, age = 59 ± 10.44 years, BMI 41.12 ± 6.77 years, HbA1c 9.92 ± 1.52), under intensive insulin regiments. Patients were treated with 10 micrograms exenatide twice daily for a mean follow-up period of 11.22 ± 7.01 (3–30) months. Intensive insulin regiments were continued in 7 patients while the other 16 patients were switched to basal insulin during the exenatide treatment. Metformin was the only anti-diabetic medicine taken by all the patients, other than exenatide and insulin.
Results
During the follow-up period, the mean HbA1c levels of the patients were significantly improved ($P = 0.019$) along with the significant decrease in BMI and the reduction in the total insulin dosages ($P < 0.001$ for both). The demographical and clinical characteristics of the patients in the intensive and basal insulin group were similar, other than the baseline insulin dosages before the exenatide treatment, which was significantly higher in the intensive regiment group ($P = 0.013$). When the clinical improvements of the two groups were compared, no significant difference was present between the alterations of HbA1c, BMI and the reduction in total insulin dosages ($P = 0.098$, $P = 0.617$, $P = 0.3$ respectively).
Conclusion
According to the results of this retrospective case series, add on exenatide appears to be an essential treatment alternative in obese T2DM patients without glycemic regulation under intensive insulin regiments.

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EP543

The impact of insulin sensitisation with metformin on lung function in patients with type 2 diabetes mellitus and chronic obstructive pulmonary disease

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Introduction
Pathophysiologic mechanisms that connect type 2 diabetes mellitus (T2DM) and chronic obstructive pulmonary disease (COPD) are complex and still unknown as are any respiratory effects of antidiabetic agents. COPD increases insulin resistance by chronic inflammation, hypoxia and corticosteroid treatment while, on the other hand, insulin as an anabolic hormone stimulates post-prandial protein synthesis and oxidative phosphorylation in skeletal muscle so that insulin resistance seems to be an important factor in the development of skeletal muscle weakness. We aimed to assess the influence of metformin treatment on lung function and its potential clinical benefit considering the fact that, as oral insulin-sensiting agent, increases respiratory muscle strenght.
Methodology
Retrospective study included patients with both T2DM and COPD who were hospitalized for acute exacerbation of COPD defined following Anthonisen criteria. COPD exacerbation was treated according to American Thoracic and European Respiratory Society quidelines, T2DM with pre-existing antidiabetic therapy. Spirometric parametres and lenght of hospital stay were compared according to presence or absence of metformin. Unpaired *t*-test was used for statistical analysis.
Results
Thirty-four patients were enrolled of whom 23 (67.6%) treated with metformin (mean age 67.3 ± 10.0 years; 52.2% males) and 11 (32.4%) with sulfonylureas and/or insulin (mean age 68 ± 7.7 years; 63.6% males). Patients in metformin group had significantly better FEV1 ($P = 0.007$) and Tiffneau index ($P = 0.017$) while the difference in FVC showed a considerable trend toward significance ($P = 0.063$). Among these patients, single dose of metformin 500 mg turned out to be sufficient for the beneficial effect on FEV1; further improvement in FEV1 with increased dosage was insignificant ($P > 0.05$). However, there was no significant difference concerning length of stay among them: median 10.8 days in metformin group vs 13.5 in non-metformin group ($P = 0.129$).
Conclusion
Treatment with metformin was associated with improvements in spirometric examinations in patients with both T2DM and COPD.

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EP544

Potential glycemic overtreatment in diabetics patients older than 70 years and comorbid conditions: real-life experience

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Background
Optimal glucose management in older people is currently unclear. Recent guidelines recommend avoiding tight glycemic targets in elderly patients with comorbidities because intensive control is unlikely to achieve benefit and they are at higher risk of hypoglycaemia.
Objective
To estimate the prevalence of potential overtreatment in older adults with diabetes mellitus and comorbidities.
Design
Cross-sectional study.
Patients and methods
The study included 293 type 1 and type 2 diabetic patients that were monitored from 2004 to 2014. At the end of follow-up, 166 (56.7% of final cohort) patients were older than 70 years (DM2: 95.2%; 69.3% female and long-standing diabetes, 26.6 years). Data about treatment, glycemic control, and comorbidities were collected from clinical records of these patients.
Results
Sixty-eight patients (42.5%) had an HbA1c < 7%. These patients had significant advanced mean age (80.2 vs 78.4 years) ($P < 0.05$). Their mean diabetes duration was 25.5 years, most of them were female (70.6%) and almost half (47%) had either macrovascular disease, estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 (< 60) or both.
Anti-diabetic therapy was insulin based in 58 (85%), sulfonylureas or glinide based in 7 (10.8%) and combined both insulin and secretagogues in 4 (5.9%). In insulin-treated patients, more than two-thirds (78%) were on intensified regimen. Among patients with macrovascular disease, eGFR < 60 or both, 21(61%) were treated with intensified insulin regimen. Only one patient received secretagogues.
Conclusions
Our results indicate that nearly half of our elderly patients had a strict glycemic control and the majority of them are being treated with intensified insulin regimen, secretagogues or combination of both and therefore are potentially being overtreated.
In all, more than half of these elderly patients with strict glycemic control and comorbidities are being treated with intensified insulin therapy or secretagogues, putting them at risk of adverse hypoglycemic events.

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EP545

Long-term effects of *Stevia rebaduiana* on glucose and lipid profile, adipocytokines, markers of inflammation and oxidation status in patients with metabolic syndrome

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Introduction
Metabolic syndrome (MetS) is a cluster of interconnected factors that directly increase the risk of DM2 and CVD. *Stevia rebaudiana* (a low calorie natural sweetener) and its compounds are known for anti-hyperglycemic, anti-inflammatory, anti-oxidant, anti-hypertensive effects.
Methods
Thirty-eight patients (age 47.3 ± 10.3 years) (n_{males} = 14, $n_{females}$ = 24) with MetS (NCEP/ATPIII criteria) were included. MetS patients were following the same low calorie diet and were randomly assigned to consume either a Stevia snack (n = 19) four times/week (*Stevia* group) or a sweet of their choice (n = 19) once a week (control group), for 4 months. BMI, W/H ratio, systolic and diastolic blood pressure (sBP, dBP) were measured before and after intervention. Glucose, triglycerides, cholesterol (LDL, HDL), uric acid, renal and liver functions were determined. Insulin was measured with CLIA, and HOMA-IR was calculated. leptin, plasminogen activator inhibitor 1 (PAI1), IL-6,ox-LDL, suPAR were measured with ELISA, HbA1c in DCA BAYER analyzer and total oxidant status: (Perox) photometrically.
Results
After 4 months dietary intervention, a decrease in BMI (P = 0.01) sBP (P = 0.02), SGOT (P = 0.004), γGT (P = 0.035), alk.phospatase (P = 0.008) was observed in the control group while Patients in the *Stevia* group presented significantly lower levels in TCHOL (P = 0.022), *SGOT* (P < 0.001), γ-GT (P < 0.001), ox-LDL(P = 0.016), BMI (P < 0.001), sBP (P < 0.001), dBP (P < 0.001) and W/H (P = 0.001). A marginally significant decrease in suPAR (P = 0.078), as well as in HbA1c (P = 0.07), LDL (P = 0.072), and leptin (P = 0.071) was also observed. Comparing the changes in serum values, BMI, W/H, BP and HOMA-IR between the two groups over the 4 months period, patients in *Stevia* group presented significantly lower levels of ox-LDL (P = 0.01) and sBP (P = 0.003) and marginally significant decrease in fasting Glu (P = 0.058) and leptin (P = 0.054) compared to control group.
Conclusion
The introduction of low glycemic load snacks based on *Stevia* in a low calorie diet in patients with MetS is safe and can lead to a further reduction in BP, fasting glucose, ox-LDL and leptin compared to a hypocaloric diet alone.

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EP546

Evaluation of three continuous glucose monitoring systems during exercise and meal challenges

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Introduction
Continuous glucose monitoring (CGM) has become an essential tool in diabetes management. In order to use CGM for treatment decisions, CGM systems have to be reliable over a wide range of glycemia as well as in situations with rapidly changing glucose levels such as exercise or in the postprandial state.
Design
In this monocentric study we evaluated the performance of three commercially available CGM systems (Abbott Libre, Dexcom G4 Platinum, Medtronic Enlite) in 12 type 1 diabetic subjects (age 33 ± 11 years, 42% women, BMI 22.5 ± 2.4 kg/m^2, diabetes duration 17 ± 12 years, HbA1c 7.6 ± 1.1%) over a period of 12 h. Routine clinical conditions were mimicked by meal and exercise tests. The sensors were inserted 24 h prior to the test in parallel and were calibrated according to manufacturers' instructions. Reference plasma glucose samples were taken every 5 min throughout the study and measured with Super GL analyzer. Glucose measurement accuracy was assessed by mean absolute relative difference (MARD) for each CGM system overall, during exercise and postprandially.
Results
Overall MARD was 13.2 ± 10.9% (Abbott), 16.8 ± 12.3% (Dexcom) and 21.4 ± 17.6% (Medtronic). During exercise (ex) and postprandially (pp) MARD was as follows: 8.7 ± 5.9% (Abbott_ex), and 11.7 ± 10.5% (Abbott_pp), 15.7 ± 14.6% (Dexcom_ex) and 15.1 ± 12.5% (Dexcom_pp), and 19.4 ± 13.5% (Medtronic_ex) and 20.5 ± 17.9% (Medtronic_pp), respectively.
Conclusion
Sensor performance was similar during the whole investigational period compared to exercise or the postprandial state. The Abbott sensor showed superior performance during all study phases. CGM might become an important tool to avoid exercise-related hypoglycemia which needs to be proven in large-scale studies.

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EP547

The effects of vitamin D on advanced glycation end-products in prediabetic and type 2 diabetic patients with vitamin D deficiency

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Aim
There is strong evidence regarding vitamin D being a risk factor for Type 2 Diabetes Mellitus (T2DM). In this study, we aimed to investigate the effects of vitamin D on advanced glycation end-products in prediabetic and type 2 diabetic patients with vitamin D deficiency.
Methods
Forty type 2 diabetic patients, 40 prediabetic patients and 40 healthy controls with the levels of vitamin D < 20 ng/ml were included in the study. All three groups were given oral vitamin D 50 000 U/w as loading dose for 8 weeks and it was tapered to maintenance dose to 1500 U/d. All three groups were evaluated with pretreatment and 12th week measurements of height, weight, waist circumference, systolic/diastolic blood pressures, advanced glycation end-products (AGE) in skin, serum CML, fasting blood glucose, HbA1c, 25(OH) vitamin D, calcium, phosphorus, parathyroid hormone (PTH) and their muscle strengths were assessed.
Results
All three groups showed statistically significant increase in their serum 25(OH) vitamin D levels (P < 0.0001). Serum CML levels increased significantly in all three groups (P < 0.05). Skin AGE deposition was observed significantly higher in diabetic group compared to healthy control group (P < 0.05); however there was no significant decrease in skin AGE levels in any of the groups after vitamin D replacement (P > 0.05). All three groups had statistically significant increase in their muscle strength after treatment (P < 0.0001).
Discussion
Vitamin D replacement increased serum vitamin D levels in all three groups; however it did not result in significant decrease in glycemic parameters after a 3-month treatment. Serum CML levels significantly increased after treatment and this increase was thought to be due to weight gain. This finding is the first in literature. When AGE deposition in skin is considered a long-term effect, longer periods of follow-up and serum AGE measurements may confirm the correlation.

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EP548

Intensive therapy with insulin pump in type 1 diabetes mellitus

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Background
Continuous subcutaneous insulin infusion (CSII), alongside multiple daily injections (MDI) are the most frequent therapeutic of type 1 Diabetes Mellitus (DM). We aimed to evaluate the effects of the transition from MDI to CSII in the treatment of type 1 DM.
Patients and methods
This retrospective longitudinal study analysed patients that received treatment with CSII from 2006 to 2014. Our sample had 85 patients, 35 male (41.2%) and 50 female (58.8%) with ages between 19 and 77 years (mean age 37 ± 11), and duration of disease of 15 ± 9 years. We evaluated values such as HbA1c, serum glucose, lipid profile, creatinine, weekly frequency of hypoglycemias (< 70 mg/dl) and hyperglycemia (> 200 mg/dl) as well the presence of microvascular complications. The effects of CSII were compared according to the following subgroups: HbA1c pre-CSII (≤ 7.0% vs > 7.0%); age (≤ 35 years vs > 35 years); sex distribution; duration of disease (≤ 15 years vs > 15 years); presence of microvascular complications. The statistical analysis was made recurring to Wilcoxon and Mann–Whitney tests. The results presented are means ± S.D., median and percentages. A bilateral value of P < 0.05 was considered statistically significant.
Results
We observed a decrease in the weekly frequency of hypoglycemias [3.0(1.5, −6.0) vs 2.0(1.0, −3.9); P = 0.001] and hyperglycemias [5.5(3.0, −7.0) vs 2.5(1.8, −4.5); P < 0.001]. Comparing patients with HbA1c pre-CSII ≤ 7 and > 7.0%, the latter group had a significant reduction of HbA1c [−0.40(−0.90.0)

vs 0.25(−0.45,−0.80); $P=0.002$] after 6 months. No statistical difference was found on the subgroups of age, sex, duration of disease and microvascular complication. Serum glucose and HbA1c values on patients with HbA1c pre-ISCI ≤ 7.0% had also no statistical difference.
Conclusions
The CSII therapy is more effective than MDI as demonstrated by the significant reduction of hypoglycemia and hyperglycemia episodes. We also observed benefits in the reduction of HbA1c with the CSII treatment in the HbA1c > 7.0% subgroup, which had the worst metabolic control.

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EP549

Potential use of embryonic antitumor modulator (EATM) for diabetes prevention and treatment

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Introduction
Incidence of diabetes mellitus worldwide is on the rise, and better methods of prevention and treatment are needed. We evaluated the possible antidiabetic effect of embryonic antitumor modulator (EATM) created by Mkrtchyan, which reportedly exhibit anticancer, neuroprotective and immunomodulatory properties.
Materials and methods
Rats with streptozotocin (STZ)-induced diabetes (55 mg/kg once i.p.) were injected EATM (1 mg/200 g rat body mass once i.p.) in preventive mode and in therapeutic mode. The activity of cortisol, prolactin, IL-4, −6, −8 in the serum, as well as releasing of NAPDH-oxidase in erythrocyte membranes and exosomes of blood serum were studied. For morphological analysis pieces from the pancreas, liver, kidney and heart were stained with hematoxylin-eosin, aldehyde-fuchsin or Azur II-eosin.
Results
The activity of serum cortisol, prolactin, IL-4, −6, −8, as well as releasing of NAPDH-oxidase in erythrocyte membranes and exosomes in blood largely normalized in treated compared to untreated STZ animals. Compared to control animals (Group 1), there was a 4-fold decline in the number of pancreatic β-cells in STZ rats (Group 2), while preventive injection of EATM (Group 3) animals showed significantly smaller decrease in β-cells, with levels being higher than in Group 2. In the EATM-treatment group (Group 4) the number of β-cells was the highest among the treatment groups ($P>0.05$), and was just 1.4-fold lower than those of control Group 1.
Conclusion
In rats with STZ-induced diabetes both preventive and therapeutic mode of EATM injection revealed definite protective effect. The normalization of studied biochemical, immunological and morphological indices was observed.

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EP550

Effects in weight loss and HbA1c after one year of use of dapaglifozina

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Changes in HbA1c and weight after 1 year on dapaglifozina added to the previous treatment.
SGLT2 inhibitors are becoming a common and useful drug to treat type 2 diabetes.
The inhibition of the sodium-glucose co transporters (SLGT2) inhibits also the glucose reabsorption in the proximale tubule and increases the glucose excreted in the urine.
Therefore hyperglycemia decreases and so does weight as happens with the glycosuria. This is a very convenient side effect since type 2 DM is highly associated with overweight/obesity.
We show the results of HbA1c and weight evolution after starting dapaglifozina added to the previous treatment. We evaluate 46 patients; the medium age was 58 ± 8 years. Males represent the 47%.
Initial medium HbA1c 7.9% ± 1 and medium weight 90 ± 16 kg. After 3 months medium HbA1c was 7.4% ± 0.7 and weight 87 ± 16.4 kg. After 6 months the medium HbA1c was 7.26% ± 0.7 and weight 88.2 ± 17 kg. Twenty of those patients were controlled after 1 year, the medium HbA1c was 7.37% ± 0.86 and medium weight was 87.6 ± 19 kg (initial parameters for this group were HbA1c 8.1% ± 1.2 and weight 92.4 ± 20 kg).
Uric acid levels were assessed, basal medium levels were 5.25 ± 1.6 mg/dl after 3 months decreased a medium of 0.32 mg/dl (4.9 ± 1.1 mg/dl) in 24 patients. A decreased of 1 mg/dl after 6 months was verified in 11 patients.
Three female patients suffered urinary infection during the first 3 months, only one of them had to stop the therapy. No other adverse effects were observed.
Conclusions
Dapagliflozina is an useful drug for treating type 2 diabetes.
In addition, most of the patients get a lost of weight.
A decrease in serum uric acid levels was observed.
The most common side effect was non complicated urinary infection in the first 3 months that was solved with antibiotic therapy.

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EP551

An assessment of factors related with understanding education and knowledge of self-care among patients with diabetes mellitus: a cross sectional prospective study in two cities of Turkey

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Background
The prevalence of the diabetes mellitus is rapidly increasing particularly in developing countries. For effective management of diabetes, patients must be actively involved in their care. The aim of the study was to assess the knowledge and self-care practices and contribution of the education to this knowledge level and glycemic control.
Material methods
We formed patients groups consisting of 15 to 30 diabetic patients. Firstly, patients surveyed diabetes self-care knowledge questionnaire (DSCKQ-30).). Later, a standard power point presentation about diabetes self-management was made to patients. Then, patients surveyed DSCKQ-30 again. All patients were invited to hospital to measure control HBA1c level 3 months later.
Results
Of the total 364 participants 62.9% ($n=229$) were females. Significant increase in percent of correct response was determined in all components between before and after education. There was a significant decline of 1.1 in HBA1c levels after 3 months of education ($P<0.001$). Married or active working patients had better understand the educations of diabetes and had higher knowledge of self-care management regardless of the level of education or income.
Conclusion
Education of diabetes can significantly improve knowledge of self-care management and can help achieving glycaemic control. Continuing education on self-care management and complications is crucial and this should be accompanied by a regular assessment of their diabetic knowledge.

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EP552

Associated antidiabetic treatment in a rural population with type 2 diabetes mellitus

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Objectives
To evaluate the characteristics of patients with type 2 diabetes mellitus (T2DM) attended in a rural primary care setting and to analyze associated antidiabetic treatment and metabolic control.
Methods
Cross-sectional study which included patients with T2DM followed in a rural primary care setting. Data about age, sex, body mass index (BMI), associated antidiabetic treatment, and HbA1c was collected.
Results
Seventy nine patients were included in this study, with a mean duration of T2DM of 5.9 years (S.D. 5), mean age 70.1 years (DE 11.8), 63.3% males, and mean BMI 30.8 kg/m^2 (DE 5.7). 100% of patients were under antidiabetic treatment: oral

antidiabetic drugs (OADs) 74.7%, OADs + insulin 20.3%, insulin alone 5%. Mean number of OADS was 1.3 (65.4% monotherapy, double therapy 28%, triple therapy 6.6%). Most used drugs were metformin (85.3%), DPP4 inhibitors (29.3%) and sulfonilureas (20%). Most used insulin therapy was basal insulin + rapid-acting insulin (55%), followed by basal alone (35) and pre-mixed insulins (10%). Mean insulin dose was 62.3 units (DE 37.1) and mean HbA1c value was 6.8% (DE 0.9). 61% of patients showed adequate metabolic control (defined by HbA1c <7%).

Conclusions

Most patients with T2DM in a rural setting are obese elderly men. Antidiabetic therapy is usually based on oral drugs, being metformin the commonest drug. Metabolic control was adequate in this group of patients, achieving more than 60% of patients HbA1c <7%.

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EP553

Abstract withdrawn.

EP554

Economic impact on the use of insulin pumps in diabetes type I – analysis on Portuguese real life results

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Although, diabetes type I patients in Portugal have complete and free access to HbA1c management (via multiple daily injections) only a few percentage has been provided an insulin pump – priority is given to children and women in fertile age trying to get pregnant. By the end of 2014, 1.150 insulin pumps had already been provided by the National Program of Insulin Pumps, but at least 3.000 patients with indication for insulin pump use were in waiting list. HbA1c pre-pump as well as number of hypoglycaemias and ketoacidosis events have been registered in a database for those patients that were provided an insulin pump. Annual control medical appointments fed this database with post-pump results. Analysis on these results showed important reductions on the number of hypoglycaemias and ketoacidosis events per patient-year (hypo: −1.54; ketoacidosis: −0.05) and a reduction of average HbA1c of these patients by 1%. Collecting Portuguese costs on hypoglycaemia events, ketoacidosis events and main chronic diseases related to diabetes enabled the analysis on the economic impact of the use of insulin pumps on Portuguese patients in a real life setting. Results show that in the short-term, it is expected annual savings of 3.336€ per patient driven by the reduction of acute events. In the long-term, the reduction of the HbA1c significantly reduces the risk of developing chronic diseases saving around 25.553€ per patient. A total of 125.639€ per patient can be saved during 30 years of using an insulin pump. An investment up to 3.585€ per patient per year is possible and justifies the use of insulin pumps given the potential savings per patient that are estimated.

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EP555

Effects of GLP-1 analogues in the treatment of a population with DM2

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The analogues of GLP-1(aGLP1) are a new class of anti-diabetic agents, administered subcutaneously for the treatment of Diabetes Mellitus type 2 (DM2). In the Portuguese market, there are two aGLP1 currently available: Liraglutide (once-daily administration) and Exenatide (once-weekly administration). They mimic the GLP-1, produced in the small intestine, stimulated by foods at this region, increasing the production of insulin, decreasing the satiety and slowing gastric emptying.

Objectives

Impact assessment of aGLP1 in patients with DM2 followed in the consultation of Diabetes.

Methods

Retrospective study of patients with DM2 followed in consultation, using aGLP1, since January 2014 to December 2015. Were evaluated: demographic data, the anti-diabetic medication used before the introduction of the drug, metabolic control and the weight on the 0, 3 and 6 months(M). Data were analysed according to descriptive statistical methods.

Results

Were observed 80 patients, 65% male, with average of 58.4±9.4 years. The initial mean HbA1c was 8.0% (5.1–11.6) and the average initial weight was 109.9 Kg (between 72 and 132). 76.9% of patients were under non-insulin anti-diabetics (NIA), 12.8% under NIA+long-acting insulin, 10.3% under NIA+long-acting insulin+rapid-acting insulin. In 13.3% it was the first therapeutic choice. In 31.4% was done an exchange of pharmacological class and the remaining therapeutic add-on. 12.8% abandoned therapy by gastro-intestinal side effects. The HbA1c to 3 M reduced on average −0.84% (−3.0 and +1.7), however in 15% there was an increase and 6 M a mean variation of −1.3% (−3.8 to +2.5). The weight reduced on average −2.98 kg (−15 to 0) to 3 M, no increased weight and 10% remained weight, and reduced −5.1 kg (−16 to +2) at 6 M.

Conclusions

Patients with DM2 medicated with aGLP1 presented benefits at the level of HbA1c and the weight up to 6 months. The extension of this analysis will assess the long-term results.

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EP556

Effects of SGLT2 inhibitors in the treatment of a population with type 2 diabetes mellitus

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Introduction

The SGLT-2 inhibitors (InibSGLT2) are the newest class of non-insulin antidiabetic drugs (ANI) for type 2 diabetes mellitus (T2DM) treatment. Currently is only available in Portugal, dapagliflozin. This pharmacological class have shown benefits in metabolic control (reduction of 0.5–0.8% HbA1c) and in weight loss (1–3 kg).

Objective

Evaluate the impact of InibSGLT2 in patients with T2DM followed in a Diabetes department.

Methods

Retrospective study of patients with T2DM followed in clinic, treated with Dapagliflozin since December 2014 to December 2015. We evaluated demographic data, antidiabetic medication used prior to Dapagliflozin introduction, metabolic control and weight at 0, 3 and 6 months. Data analyzed by methods of descriptive statistics.

Results

We observed 78 patients, 64.1% male, mean age 64±10 years. Average initial HbA1c was 8.1% (6.5–11.7%) and initial weight was 92.7 kg (72–122 kg). 72.9% were exclusively treated with ANI and 27.1% with insulin therapy. Of patients treated exclusively with ANI, 14.8% were treated with 1 ANI, 40.7% with 2 ANI, 37.0% with 3 ANI and 7.4% with 4 ANI. There was an exchange in pharmacological classes in 13.5% of patients while others had an add-on therapy. 10.9% of patients abandoned therapy, 75% because of genital-urinary complaints. 28.2% have no reassessment after introduction of Dapagliflozin, 53.8% after 3 months and 10.3% after 6 months. After 3 months there was a decreased in HbA1c of 0.57% (−2.1%;+1.2%), with 21.8% patients having an increase in HbA1c. At 6 months, there was an average reduction of 0.25% (−0.8;+0.3%). Weight reduction at 3 months was on average −1.99 kg (−6;+1), of which 14.8% had increased weight. At 6 months, there was an average reduction of −5.2 kg (−10;−0.4).

Conclusions

We conclude that patients with DM2 treated with InibSGLT2 obtained benefits especially in weight loss and metabolic control immediately. The extension of this analysis will assess long-term results.

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EP557

Randomized clinical trial to compare the effects of glargine multidosis versus CSII therapy on metabolic and oxidative stress parameters in people with type 1 diabetes

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Aims
There are few data comparing oxidative stress markers in CSII versus MDI/G We compared after randomization CSII (Continuous subcutaneous insulin infusion) vs MDI/G therapy (multiple doses of insulin with glargine) in DM1 people previously optimized at MDI/G being the primary objective assessment of metabolic control and oxidative stress.
Assess oxidative stress and metabolic control in patients with type 1 diabetes (T1D) after randomization in CSII (continuous subcutaneous insulin infusion) therapy vs MDI/G (multiple daily injections with glargine) previously optimized MDI/G.
Materials and methods
Thirty eight patients (29.8 ± 8.5 years) with type 1 diabetes T1D of long duration (13 ± 7 years), HbA1c 8.4 ± 1.2%, treated with MDI/NPH, were intensified for 6 months at MDI/G and then randomized to MDI/G vs CSII, both with Lispro for rapid analogue, and reviewed monthly during six months. At the end of each phase, metabolic control variables and total antioxidant capacity (TAC) (EIA, Cayman Chemical) were evaluated. Glycemic control was assessed by HbA1c, data derived from the MCG for 72 h CGMS® (Medtronic), rate of mild and severe hypoglycemia, and ketoacidosis.
Results
At 6 months of treatment with MDI/G ($n = 38$), with a larger number of self-test ($P = 0.001$), total insulin daily dose ($P = 0.04$), HbA1c ($P = 0.02$), glycemic variability ($P = 0.04$), number of severe hypoglycemia episodes ($P = 0.01$), and TAC (2.3 ± 1.2 vs 1.3 ± 0.5 mM; $P = 0.001$) decreased while time in normoglycaemia ($P < 0.05$) and BMI ($P = 0.01$) increased.
After 6 months of randomization, TAC and HbA1c improved significantly only in the CSII group reaching at the end of the study better levels than in the MDI/G group (TAC: MDI/G 1.48 ± 0.84 vs CSII1.94 ± 0.58; $P = 0.03$; HbA1c: MDI/G 7.6 ± 0.9 vs ISCI 7 ± 0.6%;$P = 0.006$). No correlations between TAC and variables studied were appreciated.
Conclusions
This randomized study shows that in patients with DM1 previously optimised, CSII therapy may provide additional benefits in HbA1c and oxidative stress markers versus MDI/G. Studies with larger sample size and other oxidation markers must confirm these findings.

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EP558

Dapagliflozin clinical experience and safety on patients with type 2 diabetes and obesity

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Introduction
New treatments of diabetes, such as dapagliflozin, improve global metabolic status beyond glycemic control.
Aim
To evaluate tolerance to dapagliflozin and its effects on metabolic control in type 2 diabetes and obese patients attended in endocrinology offices.
Material and method
A prospective study of patients with type 2 diabetes and obesity. In an intra-subject analysis, clinical and analytical data were evaluated at baseline and after dapagliflozin treatment.
Results
We studied 38 patients (47.4% women) with type 2 diabetes and obesity. Average age was 55.7 ± 1.5 years, average duration of diabetes was 10.7 ± 1.7 years and 40.9 and 91.3% had family history of cardiovascular disease and diabetes, respectively. At baseline, 78.9% of the patients had metformin, 39.5% others oral hypoglycemic agents, 13.2% glp-1 agonists and 44.7% insulin. We re-evaluated the patients 3.9 ± 0.2 months after treatment with dapagliflozin. We found significant improvements in weight ($P < 0.001$), bmi ($P < 0.001$), sbp ($P = 0.008$), dbp ($P = 0.030$), fasting glucose ($P = 0.001$), hba1c ($P < 0.001$), total-chol ($P = 0.011$), ldl-chol ($P = 0.038$) tg ($P = 0.025$), gpt ($P = 0.032$), and lipids drugs ($P < 0.001$). No changes in levels of creatinine and glomerular filtration rate were observed. Regarding tolerance to dapagliflozin, only 7.9% developed urinary tract infections.
Conclusions
Significant improvement of anthropometric parameters and glycemic control in terms of fasting glucose and hba1c, and significant improvements of blood pressure, gpt and lipid profile were observed. Only 7.9% developed urinary tract infections. In addition, we found a significant intensification of lipid-lowering therapy.

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EP559

Lixisenatide effects on liver function, lipids and blood pressure levels

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Introduction
New diabetes treatments, such as lixisenatide, improve global metabolic status beyond glycemic control.
Aim
To evaluate lixisenatide effects on liver function, lipids and blood pressure levels in type 2 diabetes and obese patients attended in endocrinology offices.
Material and method
This is a prospective study with a sample of 106 patients with type 2 diabetes and obesity. In an intra-subject analysis, clinical and analytical data were evaluated at baseline and after lixisenatide treatment.
Results
We studied 106 patients (51.9% women) with type 2 diabetes and obesity. Average age was 57.9 ± 1.1 years and average duration of diabetes was 11.1 ± 0.7 years. At baseline, 66% of the patients used insulin. We re-evaluated the patients 3.8 ± 0.2 months after treatment with lixisenatide. We found significant improvements in weight ($P < 0.001$), bmi ($P < 0.001$), wc ($P = 0.002$), sbp ($P < 0.001$), dbp ($P = 0.001$), fasting glucose ($P < 0.001$), hba1c ($P < 0.001$), total-chol ($P < 0.001$), ldl-chol ($P = 0.040$) tg ($P = 0.047$), got ($P = 0.022$), insulin units ($P = 0.045$), hypertension drugs ($P < 0.001$), and lipids drugs ($P < 0.001$). Bp and lipids improvements were still significant in the hypertension and lipid treated subgroups (sbp, $P = 0.001$; dbp, $P = 0.005$; total-chol, $P < 0.001$, ldl-chol, $P = 0.013$ and tg $P = 0.014$), while only the decrease of sbp ($P = 0.036$) remained significant in the subgroup of patients without hypertension or lipid-lowering therapy.
Conclusions
1) We found significant improvement of anthropometric parameters and glycemic control in terms of fasting glucose and hba1c. 2) Significant decrease of bp, got and lipid profile and less insulin requirements were observed.

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EP560

Predictive factors in the management and the prognosis of Korean women with gestational diabetes mellitus

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Introduction
Gestational diabetes mellitus (GDM) of increasing prevalence, lacks factors known to predict the prognosis of GDM. The correlations between levels of Oral Glucose Tolerance Test (OGTT) and BMI before pregnancy and the clinical progress of GDM were evaluated.

Methods
Data of pregnant women diagnosed as GDM in Busanpaik hospital from January 1, 2010 to February 28, 2015 were studied. Correlations between patients' OGTT in gestational age 24–28 weeks, BMI before pregnancy, and the prognosis of GDM (insulin usage and dose, postpartum 75-g OGTT, neonatal APGAR) were analyzed.
Results
Among 97 patients, 35% required insulin treatment. Initial OGTT had profound effect on prognosis of GDM and complications of the pregnant woman and the fetus. One-hour 50-g OGTT (value: >165.5 mg/dl, sensitivity: 0.840, specificity: 0.420) and 2-h 100-g OGTT (value: >171.5 mg/dl, sensitivity: 0.800, specificity: 0.380) showed affinitive correlations with insulin usage. 75-g OGTT result after delivery in the group that used insulin therapy was significantly higher compared to the group that controlled by just diet modification, all in fasting, after 1-h, and 2-h test. Especially, fasting glucose levels showed affinitive correlation with the usage of insulin ($P=0.043$). For neonatal health, one and two hour 100-g OGTT showed meaningful correlation with 1 min APGAR score ($P=0.042$, $P=0.010$), especially 2-h OGTT showing affinitive correlation with 5 minute APGAR score ($P=0.010$). Unlike OGTT, BMI showed no consequential correlation.
Conclusion
Initial 50- and 100-g OGTT are factors legitimate for prediction of prognosis of GDM such as need of insulin treatment and mother and fetal complications.

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EP561

Non-surgical reversal of type 2 diabetes mellitus

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A 44-year-old woman with a history of Bartters syndrome wanted a second opinion. Her height was 1.54 m, weight 69 kg, waist circumference 102 cm, BP 112/74. A OGTT was arranged because of her waist circumference. Fasting glucose 8.9 mmol/l, 2-hour glucose 20.2 mmol/l, HbA1c 7.9% consistent with type 2 diabetes mellitus. She started taking metformin. However she was keen to pursue lifestyle driven reversal of type 2 diabetes and so a low carbohydrate diet was recommended restricting carbohydrates to <20 g a day.
At 4 weeks follow up she weighed 66.9 kg and her periods became regular. At 3 months her weight was 61.3 kg and waist circumference 88 cm. 6 months later her weight was 57 kg and waist circumference 86 cm. She stopped taking metformin. 4 years later she had managed to maintain her weight and repeat oral glucose tolerance test showed a fasting glucose of 5.8 mmol/l, two-hour glucose 7.6 mmol/L, HbA1c 4.8% or 29 mmol/mol.
This case illustrates the utility of a low carbohydrate; high fat (LCHF) or ketogenic diet in promoting reversal of type 2 diabetes especially when implemented soon after the diagnosis is made. LCHF diets have been shown to be highly effective at reducing weight, triglycerides and elevating HDL-C. They significantly reduce hepatic glucose output and inflammation associated with insulin resistance. In one study, 95.2% of patients on a ketogenic diet reduced or stopped anti-diabetic medications compared to 62% following a low glycaemic index diet. The potential to prevent progression in the disease process is not only extremely beneficial for long term health but to do so in a way that could also prevent a significant number of other co-morbidities associated with insulin resistance such as non-alcoholic fatty liver disease, hypertension and cardiovascular disease risk factors while reducing dependence on pharmaceutical agents is highly attractive and cost-effective.

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EP562

Insulin pump therapy-a different solution for treating diabetes type I

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Introduction and aim
Continuous subcutaneous insulin infusion via insulin pump is the most efficient way of imitating physiological insulin secretion, and it also provides better management of diabetes, lower rate of hypoglicemic episodes, better quality of life and prevention of long-term complications of diabetes mellitus. Aim of the research was to determine effects of subcutaneous insulin infusion therapy on parameters of glycoregulation during the two years trial.
Material and methods
Research was conducted at Clinic for endocrinology, diabetes and diseases of metabolism, Clinical center of Vojvodina, where 80 patients were treated this way during period of time from 2007 to 2015. There are complete results assembled for 60 patients with type I diabetes, from that 45 women, average age $31.67+8.03$ and 15 men average age $26.06+8.25$ years. In all subjects following parameters were monitored: sex, age, medical indications for this kind of therapy, complications of therapy, HbA1c in the moment of insulin pump application, after 6 months, 1 and 2 years of therapy.
Results
After starting with insulin pump therapy, better glycoregulation was notified, through statistically significant decrease in HbA1c rates after 6, 12 and 24 months. The biggest decrease in HbA1c rate was in those patients who had poorly regulated diabetes with HbA1c $>10\%$ in the moment of insulin pump application (usually former pediatric patients).
Conclusion
There is significant decrease in HbA1c rate after application of the insulin pump, and it is also confirmed that the biggest reduction in HbA1c rate (2–3%) was in those patients who had the worst glycoregulation (HbA1c $>10\%$). Reduction of HbA1c did not result in higher rates of hypoglicemic episodes, while ketoacidosis was developed in two patients.

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EP563

Make sense of insulin

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Background
Insulin-related peptides are found in Cnidaria (the most ancient animals with differentiated tissues including a nervous system, dating from 600 million years ago) and their nucleotide sequence has been highly preserved ever since. In mammals the binding of insulin to its receptor causes a cascade of actions, the main one being translocation of GLUT4 glucose transporters to the plasma membrane allowing influx of glucose into the adipose and striated muscle cells. But the fact that glucose can freely enter most other tissues (via non-insulindependent glucose transporters) and that in non-chordates the glucose influx is unrelated to insulin raises the question: Why did fat and muscle need to have GLUT4 and therefore insulin dependency? Better yet, what is the sense of having insulin?
Methods
Review of the literature with emphasis in insulin phylogeny.
Findings
The familiar glucocentric functions of insulin appear with protochordates; however insulinrelated peptides play an essential role in invertebrates activating growth, differentiation, metamorphosis, sexual activity and in general regulating the allocation of energy resources. In the well-studied nematode Caenorhabditis elegans the presence of nutrients releases an insulin-like peptide that activates metabolic and reproductive developments and shortens the lifespan, while the lack of this peptide triggers a long-lasting dormant state (dauer).
Conclusions
The insulin receptor and insulin are lock and key. But having a lock and key in a door only makes sense if sometimes we need to close it. We need insulin, not to allow glucose influx in muscle and fat (in the postprandial state), but in order to be able to close it (in the fasting state) saving glucose for non-dependent tissues. Therefore insulin is the main switch between the anabolic and the catabolic state. This function predates allowing glucose influx by hundreds of millions of years and is well preserved along the evolutionary tree.

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EP564

GLP-1-RAs treatment in type 2 diabetes and obesity patients

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Introduction
Assessing the effect of GLP 1 receptor agonist on metabolic control and weight loss in obesity and type 2 diabetes patients.
Description of methods
A retrospective descriptive study involving type 2 diabetes patients and BMI >30 kg/m^2, who started treatment with GLP-1-RAs during the years 2012–2014. Variables analyzed: weight and HbA1c at the begging, 6 months, 1 and 2 years; regimen at baseline and after GLP-1-RAs; incidence of withdrawal of treatment.
Results
125 patients were included (mean age 55.4 ± 9.7 years old; male 58.4%). GLP-1 agonists: exenatide 24.8%, liraglutide 57.6%, 17.6% lixisenatide. HbA1c at baseline: 8.9 ± 1.37%; HbA1c 6 months: $7.7\% \pm 1.3$; HbA1c 1 year: $7.3\% \pm 1.4$; HbA1c 2 years: $7.3\% \pm 1.3$. Start weight: 16.4 ± 106.4 kg; 6 months weight: 101.6 ± 16.5 kg; 1 year weight: 15.7 ± 98.4 kg; 2 years weight: 15.5 ± 97.4 kg. The difference in HbA1c and weight at baseline and 6 months, 1 year and 2 years follow-up statistically significant ($P<0.001$), not statistically significant difference the first and second years of therapy. 56.8% patients were treated with insulin at start. After addition GLP-1-RAs insulin treatment was finished by 9.9% (45.2% basal bolus therapy who changed baseline insuline and OADs). Therapy discontinued in 25.6% (68.8% in the first-year), the main reason was non-response (75%).
Conclusions
GLP-1 agonist inclusion in type 2 diabetes therapy improves glycemic blood control and loss weight. Improvement already 6 months and holding the first and second year. Treatment helped simplified insulinize, which is reflected in that almost half of those doing intensive treatment could suspend insulin. However, the number of patients we found in whom the treatment brought no improvement was significant, been observed early non-response.

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EP565

The effect of diabetes on the duration and cost of treatment in patients with acute ischemic stroke

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Diabetes is an important risk factor for ischemic stroke. Hyperglycemia observed in acute ischemic stroke is accepted as a poor prognostic factor. In the present study, our aim is to investigate the effect of diabetes on the duration and cost of treatment in acute ischemic stroke.
Three hundred sixty two acute ischemic stroke patients that were hospitalized in the university neurology clinic in 2015 were retrospectively evaluated. Patients that have diabetes ($n=112$) were compared with the non-diabetics in respect to the duration and cost of hospitalization.
There were no significant difference among the age, gender and other vascular risk factors of both groups. We also found no difference between the duration (12.5 ± 7.7, 10.9 ± 7.2 days, respectively) and cost of hospitalization (743.5 ± 588.2, 689.2 ± 657.2 €, respectively).
The co-existence of diabetes does not bring additional load to the treatment cost of acute ischemic stroke that has self-high hospitalization costs due to theincreased mortality and morbidity.

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EP566

Quality of life domains are affected in caregivers of people with type 2 diabetes: results from a literature review

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Background/aims
Caregivers play a crucial role in self-management of long-term conditions. The aim of this literature review was to explore the impact that Type 2 diabetes has on the caregivers' quality of life (QoL) and its significance in integrated healthcare.
Methods
A search was undertaken in CINAHL, MEDLINE, BNI and ASSIA using combinations of the following keywords limited to adults, humans and published in English in the last 10 years: 1: carer, caregiver, family, 'next of kin', spouse*, partner, proxy; 2: 'type 2 diabetes'; 3: 'quality of life', QoL, 'health related quality of life', 'mental quality of life' and 'physical quality of life'. Inclusion criteria were articles that explored aspects inherent to caregivers' QoL and five articles were found and analysed using critical analysis/thematic analysis.
Results
Caregivers QoL domains are affected by type 2 diabetes and overall impact is found to vary: for some it was reported as neutral, while others stated it was negative or positive. The most affected domain is emotional wellbeing specifically related to anxiety and depression. Further domains were economic burden and social functioning. Socio-demographic and cultural differences were also identified as variables that can influence caregivers QoL.
Discussion/implications
The impact of type 2 diabetes on caregivers QoL is apparent in an initial overview of the affected QoL domains. Healthcare professionals' awareness of the impact of type 2 diabetes on caregivers' QoL is essential to enable effective integrated healthcare.
Conclusion
The impact of type 2 diabetes in caregivers' QoL requires further research, especially to take into consideration socio-demographic and cultural and differences. Education programmes are useful to raise awareness of healthcare professionals, and help them to assess the impact of Type 2 diabetes on caregivers QoL.

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EP567

Effects of gender on IGF1 changes after initial basal insulin analog therapy in the type 2 diabetics

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Introduction
Serum IGF1 levels declined particularly with hyperglycemia in diabetic patients and lower IGF1 levels has been suggested to be associated with the development of diabetes. IGF1 levels appear to increase with the improvement in glycemic control in diabetic patients but do not reach normal levels. Also, it affected by gender; in this study we aimed to investigate effects of gender on IGF1 changes with basal insulin analogs.
Methods
The serum total IGF1 levels of the 62 insulin-native type 2 diabetic patients were studied before and after 12 weeks of the started treatment with basal insulin analogs. 42 patients using insulin detemir and 20 patients on insulin glargine were evaluated.
Results
Mean age of patients were 57.0 ± 6.4 in the males ($n=27$) and 55.2 ± 7.1 in the females ($n=35$). Changes in the IGF1 values are calculated as 0.5% decrease in the males and 2.1% increase in the females. Means IGF1 levels were 111.7 ± 38.4 in the males and 111.5 ± 47.5 before insulin therapy and were 107.6 ± 35.9 in the males and 108.8 ± 47.8 in the females at the end of the study. IGF1 change means were -4.1 and -2.6 in the males and females respectively.
Conclusion
In our study, it was observed that, while IGF1 levels remained unchanged or increased in the detemir groups, levels dropped at the level close to significance in

the glargine group. The changes in the IGF1 level were found to be more evident in the males. The change differences between the male and female patients could be explained with the fact that BMI averages were different and that the daily variability in the serum IGF1 level was higher depending on the cyclic estrogen fluctuation in the females.

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EP568

Half of three regimen for treatment of T2 DM in low income populations

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According to the seventh edition of diabetes atlas, 415 million persons all over the world are diabetics requiring more than 680 billion US $ annually for their management. Diabetes affects middle and low socio economic countries than developed countries. The ADA/EASD guidelines included drug price as one of the criteria to choose from different classes. Incretin based therapy are new classes for treatment of T2 DM with low incidence of hypoglycemia and modest weight loss, but its disadvantage is its higher cost compared to other agents.

Aim

The aim of this work is compare the efficacy of treating T2 DM patients with l metformin and DPP4-I fixed combination (full dose) versus continuing on only the half dose plus adding a half dose of an SU.

Methodology

This study included 194 T2 DM patients who achieved glycemic targets (A1c 7%) on fixed dose of DPP4-I and metformin twice daily, but for financial reasons part of them cannot afford to continue. So we had two groups, G1 who continued the same regimen, and G2 who will continue on only half of the dpp4i/metformin dose plus a small dose of an SU. Blood sugar, AIC weight will be measured at the start of the study and after 3 months. Major or minor Hypoglycemic events will be reported, also the treatment cost will be calculated for each group.

Results

Comparing the results of both groups, it was found that in G1 the mean A1c was 6.7 0.$\pm$42 vs 6.8$\pm$0.53 in G2, also there were no statistical significance between G1 AND g2 regarding mean FBS PPBS and weight G1 regimen had significantly fewer events of minor hypoglycemia (0.2 event/patient/3 month) compared to G2 (0.39 event/patient/3 month) (*P*:0.031), that is also one attack of sever hypoglycemia in G2. Also the cost of treatment per patient for 3 months was around 700 Egyptian pounds in G1 and only 420 pound for G2.

Conclusion

In our study patients who cannot afford for the full dose of DPP4-I can continue on the have dose plus a small dose of SU with the same efficacy but mild increase in the incidence of hypoglycemic events.

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EP569

Combined metformin-associated lactic acidosis and euglycaemic ketoacidosis

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Introduction

In metformin-associated lactic acidosis with renal dysfunction inhibition of hepatic gluconeogenesis by drug accumulation may aggravate fasting induced-ketoacidosis. We report the occurrence of metformin-associated lactic acidosis with concurrent euglycemic ketoacidosis in three patients with renal failure.

Cases

The first patient was a 79-year-old woman who suffered from chronic kidney disease stage IIIa after traumatic uninephrectomy, and had been on metformin therapy for over 10 years. She had been vomiting for 2 days, and was admitted to our intensive care unit with acute renal failure (serum creatinine 9.0 mg/dl) and lactic acidosis (pH = 6.89, lactic acid 22 mmol/l). The patient also displayed elevated serum ketoacids of 7.4 mmol/l at blood glucose level of 63 mg/dl. Euglycaemic ketoacidosis receded under treatment with intravenous glucose infusions.

The second patient was a 78-year-old woman who had been treated with metformin for T2DM and presented to our hospital with acute gastroenteritis. She displayed acute on chronic renal failure (serum creatinine 9.0 mg/dl) and lactic acidosis (pH = 6.80, lactic acid 14.7 mmol/l). Again we detected elevated serum ketoacids (6.4 mmol/l), even though blood glucose was in normal range (76 mg/dl). Ketoacidosis abated after infusion of glucose.

The third patient was a 71-year-old man who had been treated with metformin, canagliflozin and liraglutide for T2DM and presented with acute gastroenteritis. He displayed acute renal failure (serum creatinine 13.6 mg/dl) and lactic acidosis (pH = 7.21, lacitic acid 5.9 mmol/l). The patient also displayed elevated serum ketoacids of 16 mmol/l and blood glucose of 152 mg/dl. Ketoacidosis receded with intravenous glucose infusions.

Discussion

The concurrent occurrence of euglycaemic ketoacidosis in patients suffering from metformin-associated lactic acidosis poses a peculiar diagnostic and therapeutic challenge. This case series highlights the parallel occurrence of metformin-associated lactic acidosis and euglycemic ketoacidosis, the latter exceeding ketosis due to starvation, suggesting a metformin-triggered inhibition of gluconeogenesis. Affected patients benefit from glucose infusion counteracting suppressed hepatic gluconeogenesis.

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EP570

The effect of liraglutide in patients with type 2 diabetes mellitus: clinical and metabolic characteristics

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Introduction

In patients with non-controlled type 2 diabetes mellitus (DM2) and obesity treated with oral therapy, liraglutide treatment should improve glycemic and metabolic control.

Materials and methods

Retrospective descriptive study. Liraglutide treatment was started in 46 outpatients with uncontrolled DM2. The effect of therapy was evaluated between September 2013 and January 2016. Age, sex, duration of diabetes, weight, BMI, HbA1c, fasting and postprandial glucose, lipid profile, were extracted at baseline/starting liraglutide, after 1, 3 and 6 months and at the end of follow up.

Results

Average age in 32 females was 59.3$\pm$18.2 years (range 35–82), in 14 males 55.8$\pm$16.3 (range 37–74 years); Duration of DM2 was 2 months–17 years in females, and 6 months–12 years in male patients. Baseline values:

Women: Weight 85–130 kg, BMI 35.2–48.9 kg/m^2, HbA1c 6.5–10.4%, fasting glucose 5.7–11.2 mmol/l, postprandial glucose 7.2–14.2 mmol/l, cholesterol 2.9–6.6 mmol/l, trygliceride 1.1–3.4 mmol/l, HDL 1–1.5 mmol/l, LDL 1.2–4.6 mmol/l.

Men: Weight 90–142 kg, BMI 35.2–41.7 kg/m^2, HbA1c 7.1–14.2%, fasting glucose 6.4–14.3 mmol/l, postprandial glucose 9.8–20.7 mmol/l, cholesterol 3.8–11.3 mmol/l, trygliceride 1.8–22.5 mmol/l, HDL 0.9–1.9 mmol/l, LDL 1.9–9.8 mmol/l.

After 1 month females lost 1–8 kg, males 0–3 kg. After 3 months women lost 1–16 kg, and men 1–4 kg. After 6 months females lost 3–18 kg (1 patient +2 kg), and males 2–4 kg (1 patient +4 kg).

At the end of follow up (21 months for women, and 15 months for men) female patients lost 2–18 kg, males 2–5 kg, although two female and two male had weight gain. At 15 female and six male patients final dose of liraglutide was 1.8 mg s.c., and in five women and two men basal insulin was added. HbA1c was 5.5–7.5% in female, and 5.9–9.1% in male patients.

Conclusion

Liraglutide therapy resulted in glycemic improvement and weight loss in most patients.

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EP571

Analysis and metabolic evaluation in a standard clinical setting of a group of patients 7 years after a clinical trial with sensor-augmented pump (SAP)

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Background and objective
Several trials showed that sensor-augmented pump (SAP) therapy is safe and effective to reduce hypoglycemic events and improve glicemic control with high treatment satisfaction. Nevertheless patient adherence and sensor use in trials usually decrease with time. Our objective was to evaluate metabolic control and adherence and sensor use after initiation of SAP in a clinical trial.
Methods
In 2008 we recruited 25 patients in treatment with insulin pump (CSII) to start SAP for 6 months. After the trial the patients had the opportunity to maintain the SAP treatment, but only 15 patients did desire to goon with SAP therapy despite a high global evaluation of the device. We evaluate the 25 patients again 7 years after returning to clinical trial.
Results
Seven years after returning to standard clinical care, only 5 of the 25 patients (20%) were still continuously using the sensor. The HbA1c in patients with SAP was $6.9 \pm 0.4\%$ and in patients without SAP was $7.3 \pm 0.4\%$ withou statistically significant difference. The patients in SAP therapy made 6.3 ± 0.8 SMBG tests per day and in the no SAP group the number of SMBG per day was 4.9 ± 1.4 ($P = 0.04$). No statistically differences were found in quality of life between SAP and no SAP group. Patients in SAP therapy were using it mean 60% of the time. Most problems about SAP use were referred with accuracy and daily life interference (no SAP group).
Conclusion
Our results show that in a standard clinical setting still long time benefits can be found in type 1 diabetes patients treated with SAP after a clinical trial. Nevertheless, new strategies to improve patient adherence to SAP should be developed.

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EP572

Ameliorative effects of *Treculia Africana* aqueous seed extract on hyperglycemia and testicular histopathological alterations in alloxan-diabetic rats

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Introduction
Treculia Africana (TA) has been used as an anti-inflammatory agent by the Yoruba people of West Africa and is also known to be a component of an ancient anti-diabetic remedy used in the Western and Middle belt areas of Nigeria. This study was conducted to investigate the anti-hyperglycemic property of the aqueous seed extract of *Treculia Africana* (TAE) and also to evaluate the potential of this extract in reversing the toxicity inflicted by experimentally-induced diabetes on the testes.
Methods
Twenty adult male Sprague-Dawley rats were randomly divided into four groups (A-D) of five rats each. Groups A, B and C were injected with alloxan while Group D served as the normal control and received distilled water only. After 4 weeks of sustained hyperglycemia, groups A, B, and C rats were administered TAE (200 mg/kg per day), glibenclamide (10 mg/kg per day) and distilled water, respectively. Body weight and blood glucose concentrations were evaluated. At the end of 8 weeks all animals were sacrificed and the testes were processed for light microscopy.
Results
TAE caused significant reduction (36.27%) in blood glucose concentration at $P < 0.001$ compared to the diabetic control, while glibenclamide caused 70.61% reduction. The weight of the testes of TAE-treated rats showed significant increase compared with the untreated diabetic group. The distorted seminiferous tubules of the diabetic control rats had just a few scattered spermatogonia and spermatids while the testes of the TAE-treated diabetic rats showed seminiferous tubules lined by Sertoli cells, with relatively normal germinal epithelium. Stereologic analysis showed increased germinal epithelial thickness, cross-sectional area and volume for treated groups compared to the diabetic control group.
Conclusion
Histologic and stereologic analysis indicate that TAE would be a good adjunct in the treatment of diabetes mellitus associated with reproductive deficiencies.

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EP573

The influence of α-lipoic acid to endothelial dysfunction and adipokines balance in patients with type 2 diabetes and essential hypertension in the presence of unfavorable genetic polymorphism

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The aim
To establish unfavorable genetic polymorphisms on the development of comorbidity of DM2 and EH in Ukrainian population and to evaluate the effectiveness of α-lipoic acid appointment (α-LC) in complex therapy in patients with 3-4 crossed unfavorable genetic polymorphisms.
The primary examination of 167 patients with DM2 in combination with EH showed that A/C and C/C genotypes of AGTR1, Pro/Pro genotype of PPARγ_2, Arg/Arg and Gly/Arg genotypes of IRS-1, T/T and C/T genotypes of TCF7L2 are characterized by more severe hemodynamic and metabolic disorders, cardiovascular remodeling, thus, these genotypes can be regarded as unfavorable genotypes that are associated with the development of comorbidity. It was proved that in 96 patients with 3–4 crossed unfavorable genetic polymorphisms the severity of these disorders was greater than in 71 patients with 1-2 crossed unfavorable genotypes. Among 96 patients with 3–4 crossed unfavorable genetic polymorphisms two groups were distinguished: 47 patients received standard therapy and 49 patients additionally received α-LC (600 mg/day) for 3 months. It was established that the appointment of α-LC contributed to a more pronounced effect on endothelial dysfunction (ED) that confirmed a greater degree of endothelium-dependent vasodilation and higher levels of oxidative indicators stress (diene conjugates and malondialdehyde) in the inhibition of antioxidant system parameters (superoxide dismutase and catalase) ($P < 0.001$). Furthermore the additional appointment of α-LC impacted more to the functioning of adipose tissue, which showed a more pronounced decrease in leptin ($P < 0.001$) and increase in adiponectin ($P < 0.01$), compared to basic therapy.
Conclusions
A/C and C/C genotypes of AGTR1, Pro/Pro genotype of PPARγ_2, Arg/Arg and Gly/Arg genotypes of IRS-1, T/T and C/T genotypes of TCF7L2 are associated with the development of comorbidity of DM2 and EH. The additional α-LC appointment to standard therapy impacted more to the severity of ED and adypokines balance than basic therapy.

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EP574

Role of community pharmacists in the prevention and management of the metabolic syndrome in Albania

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Background
The metabolic syndrome is a cluster of diabetes and cardiovascular risk factors and its prevalence is alarmingly high in Albania, affecting nearly 20% of the adult population. There is lack of information about the role of community pharmacists in the care of patients with the metabolic syndrome.
Objective
To assess the awareness and opinions of community pharmacists about the metabolic syndrome and identify the services they provide for identification, management and monitoring of patients with the metabolic syndrome.

Setting
25 Community pharmacies in the capital of Albania (Tirana).
Method
A descriptive, cross-sectional study was performed on a randomly selected sample of 52 community pharmacists. Data were collected via face-to-face structured interview of the pharmacists using a pre-tested questionnaire.
Main outcome measures
Pharmacists' knowledge and views on the metabolic syndrome, monitoring services provided, self-reported practices and perceived effectiveness of the various management interventions for the metabolic syndrome.
Results
The response rate was 97.8%. Nine pharmacists claimed to know about the metabolic syndrome, but only one pharmacist could identify the condition correctly. After being given a definition of the metabolic syndrome, 67.7% of respondents strongly agreed that its prevalence was rising in Albania. Nearly two thirds of respondents reported providing height and weight measurement service while 82.7 and 59.5% of pharmacies provided blood pressure and blood glucose measurements, respectively. Waist circumference and lipid profile measurements were the least provided services (1.8%). Respondents claimed to be involved in counseling patients on lifestyle modifications including increased exercise (98.1%) and weight reduction through diet (96.9%). Most pharmacists were involved in encouraging patients' adherence with prescribed treatments (98.6%) and perceived these as the most effective intervention for the management of the metabolic syndrome (95.0%). Respondents were less involved in monitoring patients' response to therapy (75.0%) and documenting patient care services (5.0%).
Conclusion
To the author knowledge this is the first study of this kind in Albania. This study revealed significant deficits in awareness among community pharmacists about the metabolic syndrome. Given the proper education and training, community pharmacists could be important front-line contributors to the control of this emerging epidemic in Albania.
Keywords: metabolic syndrome, community pharmacists, education, Albania
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EP575

Galangin, a dietary flavonoid improves antioxidant status and reduces hyperglycemia mediated oxidative stress in streptozotocin-induced diabetic rats

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Objective
This study was planned to examine the effect of galangin on hyperglycemia mediated oxidative stress in streptozotocin (STZ)-induced diabetic rats.
Methods
Diabetes was induced by intraperitoneal administration of low dose of STZ (40 mg/kg body weight (BW)) into male albino Wistar rats. Galangin (8 mg/kg BW) or glibenclamide (600 μg/kg BW) was given orally daily once for 45 days to normal and STZ-induced diabetic rats.
Results
Diabetic rats showed significantly increased levels of plasma glucose, thiobarbituric acid reactive substances (TBARS), lipid hydroperoxides (LOOH), and conjugated dienes (CD). The levels of insulin, non-enzymic antioxidants (vitamin C, vitamin E, reduced glutathione (GSH)) and the activity of enzymatic antioxidants (superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione-S-transferase (GST)) were decreased significantly in diabetic control rats. These altered plasma glucose, insulin, lipid peroxidation products, enzymatic and non-enzymatic antioxidants ions were reverted to near normal level after the administration of galangin and glibenclamide.
Conclusion
The present study shows that galangin decreased oxidative stress and increased antioxidant status in diabetic rats, which in turn may be due to its antidiabetic and antioxidant potential.
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EP576

Trends and differences between sexes in control of diabetes and cardiovascular risk factors from 2004 to 2014

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Background
Poorer control of risk factors for cardiovascular disease (cvd) has been reported in diabetic women compared with men.
Objective
To investigate whether control of diabetes and risk factors for cvd differ between sexes in a cohort of diabetic patients monitored at an outpatient endocrinology clinic from 2004 till 2014.
Design
Observational, retrospective cohort study.
Patients and methods
A cohort of 424 randomly selected diabetic patients (dm type 2 (dm2) 84.6%; 58.3% female; mean age 63.4 years and mean diabetes duration 15.7 years) was monitored from 2004 to 2014. Final cohort size was 293 patients (dm2: 80.2%; female 59.4%; mean age 69.3 years and diabetes duration 25.1 years). Data about glycaemic, lipid and blood pressure (bp) control, antiplatelet/anticoagulant therapy were collected from clinical records at baseline and 10 years afterwards.
Results
In 2004, 27.8% of the men and 23.5% of the women had an hba1c $< 7\%$. This increased to 36.8% in men and 39.3% in women in 2014 ($P<0.001$). Patients having systolic bp (sbp) $<$ 140 mm hg changed from 79.5% to 75.9% and from 70% to 56.4% in men and women respectively ($P<0.001$). Patients with ldl-cholesterol $<$ 100 mg/dl increased from 44.3% to 81.2% in men and 44.9% to 85.2% in women ($P<0.001$). Obesity increased in men (35.2% to 38.3%) and decreased in women (63.6% to 58.2%) ($P<0,05$). Antiplatelet/anticoagulant therapy increased from 46.9% to 68.4% in men and 39.7% to 68.6% in women ($P<0.001$). In 2014, all patients with cvd were on antiplatelet/anticoagulant therapy. Smoking was more frecuent in men (27.7% versus 4.7%) ($P<0.001$).
Conclusions
After 10 years of follow-up, glycaemic and lipid control and use of antiplatelet agents has improved in both sexes. No significant difference was found in risk factors control between men and women, except for sbp and obesity.
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EP577

Antidepressant treatment worsens metabolic control in type 2 diabetes mellitus

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Objectives
To evaluate the use of antidepressant drugs in patients with type 2 diabetes mellitus (T2DM) and to analyse if these drugs are associated with a more deteriorated metabolic control.
Methods
Cross-sectional study which included patients with T2DM followed in a primary care setting. Data about age, sex, T2DM evolution, body mass index (BMI), HbA1c and associated antidepressant treatment was collected. Statistical analysis was performed with SPSS v 15.0 for Windows.
Results
79 patients were included, with a mean age of 70.1 ± 11.8 years (63.3% men) and a mean duration of T2DM of 5.9 ± 5 years. 47% of patients were under treatment with antidepressant drugs (men 30%, women 65%, $p=0.018$). Metabolic control was more deteriorated in patients with associated antidepressant treatment (HbA1c 7.1% vs 6.6%, $p=0.037$), even after adjustment by sex, age and body mass index.
Conclusions
A high rate of prescription of antidepressant drugs is frequently found in individuals with T2DM, especially in women. T2DM patients under antidepressant treatment show a worse metabolic control.
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EP578

The need of change in the treatment options for diabetes in acute ischemic stroke

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Diabetes that is an important risk factor for ischemic stroke should also be well-treated in acute ischemic stroke patients for the secondary prevention against the next strokes. In the present study, we investigated the rate of the treatment changes in diabetic acute ischemic stroke patients during their stay at hospital.
One hundred twelve acute diabetic ischemic stroke patients that were hospitalized in the university neurology clinic were retrospectively evaluated. HbA1c levels and the need of changes in antidiabetic drugs and doses were noted.
Mean HbA1c levels were 8.2 ± 2.2%. In order to better regulate the blood glucose levels, changes in the antidiabetic drugs had been made in 26.8% of patients. Change of dosage was found necessary in 33.9% of patients. Use of insulin that was seen 29% of patients increased to 37% at the time of discharge from hospital. Diabetes was found undertreated before acute ischemic stroke. The need of change in the diabetes treatment was observed in a significant ratio of the patients. The neurologists who manage the treatment of the primary disease should also be alert for the need of changes in the treatment of diabetes.

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EP579

Effect of short term GLP-1 modifying therapy on intima media thickness

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Atherosclerosis is the major cause of death in type 2 DM. Increased intima media thickness (IMT) denotes subclinical atherosclerosis. Endothelial cells express GLP-1 receptors. There are a few studies regarding the effect of GLP-1 system modifying agents on IMT. Although most of them indicates decreased IMT, the results are contradictory.
We aimed to compare the effect of sitagliptin, vildagliptin, and exenatide on IMT measurement in type 2 DM.
We enrolled 24 patients (7 male, 17 female, aged 53.5 ± 8.2 years, DM duration 4.63 ± 4.46 years, 15 hypertensive, mean initial hemoglobin A1c %7.66 ± 1.43) with type 2 DM. The patients were already using various combinations of oral antidiabetic drugs including metformin, sulphonylurea, or pioglitazone. The data of patients were collected from the records. IMT at baseline and after 6 months of therapy were compared in 6 patients on sitagliptin, 9 on vildagliptin, and 9 on exenatide. Initial and 6th month data (age, DM age, glucose, hemoglobin A1c, calcium, LDL, HDL, triglyceride, TSH, and IMT) were similar in 3 groups. 3 groups differed significantly in terms of initial and 6th month BMI ($P = 0.003$ and $P = 0.001$, respectively). When initial and 6th month data were compared in each group, the difference did not persist.
3 drug groups had similar rates of plaque formation.
Right- and left-side IMT and mean IMT were similar between 3 groups both at baseline and after 6 months of therapy. But when baseline and 6th month IMT values were evaluated in each group, only right side IMT (lower) differed significantly after 6 months of exenatide therapy ($P = 0.046$).
Although groups are small in size, sitagliptin and vildagliptin has no and exenatide has slight impact on mean IMT in short term of therapy.

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EP580

Protocol for the hyperglycemia and diabetes mellitus in hospitalization

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Introduction and objectives
Hyperglycemia is present in about 25% of hospitalized patients. His control is common deficient. Consequently it increases the average stay, infection rates and mortality. In order to improve we present a comprehensive protocol.

Methods
We developed algorithms of subcutaneous insulin therapy for non-critical patients, insulin therapy i.v. for critical patients, management of hypoglycemia, fasting situations, diabetic ketoacidosis/hyperosmolar state, and performance at hospital discharge.

Results
1. Subcutaneous insulinization for patient not critical. *Patient previously with insulin:* basal/24 h (glargine/detemir) + bolus(glulisine/lispro/aspart) breakfast, lunch and dinner + correction bolus a(<40u), b(40–80u), c(>80u). *Patient previously within insulin*: regular insulin regimen breakfast/lunch/dinner/6–8 h in fasting. >16u/24 h pass to basal-bolus-correction. *Fasting*: *<24 h: suspend bolus and maintain basal + bolus correction *> 24 h: serum-insulina i.v./6 h.
2. Insulin i.v. for critical patient. *1. fluid line*: glucosaline 5% 60–100 ml/h ± 1.2 meq/kg of clk. *Insulin line 2*: saline 0.9% 100 ml with 100 u regular insulin. Insulin infusion (ml/u/h) by patterns 1, 2, 3, 4 based on blood glucose and variation. *Transition to subcutaneous insulin*: insulin last 6 h×4, 50% basal insulin – 50% bolus insulin, maintain perfusion three hours after putting basal insulin.
3. Management of hypoglycemia (<70 mg/dl). *Patient conscious and can ingest*: 200 ml water with two sugar packets. *Patient unconscious or unable to ingest:* 10 g glucose (i.v.) or glucagon 1 mg (sc/im). Repeat procedure if blood sugar below 70 mg/dl in 15 min.
4. Diabetic ketoacidosis and hyperosmolar state. *1. fluids*: 1000 ml 0.9% saline/1 h, after 250–500 ml/h. When glucose <200 mg/dl glucosaline 5% 100–150 ml/h. *2. insulin:* 0.1 u/kg of regular insulin bolus directly. i.v. insulin infusion beginning with pattern 2. *3. potassium*: k<3.3 meq/l: 20 meqk/500 ml, k3,3–5,3 meq/l: 10 meqk/500 ml. K>5.3 meq/l: not manage. *4.bicarbonate*: if ph <7% half deficit administer 1/6 m in 4–6 h and revaluate.
5. Performance at hospital discharge. Apply for hba1c if not available in last three months. *Dm known and hba1c <8%*: pretreatment. *Dm unknown or hba1c>8%*: initiate/intensify treatment.

Conclusions
We believe that this protocol will contribute to better management of blood glucose by different professionals in hospitalization. It remains to evaluate their impact after his introduction.

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EP581

Diabetic hyperlipidemia: from guidelines into clinical practice

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Diabetes mellitus (DM) is associated with significant morbidity and mortality despite steadily improving standards of care. Coronary heart disease (CHD) is by far the most common cause of death in individuals with diabetes.
A characteristic pattern, termed diabetic dyslipidemia, consists of specifically mild to marked elevation of triglyceride-rich lipoproteins (VLDLs) and VLDL remnants concentrations and low levels of HDL-C. Raised serum triglycerides and low HDL-C often precede the onset of T2DM for many years. In addition, LDL particles are converted to smaller, perhaps more atherogenic, lipoproteins termed 'small-dense LDLs'.
Different mechanisms are responsible for the development of dyslipidemia in individuals with diabetes. Defects in insulin action and hyperglycemia could lead to dyslipidemia in patients with diabetes. In the case of T2DM, the obesity/insulin-resistant state that is at the basis of the development of this disease can in itself lead to lipid abnormalities independently of hyperglycemia. In poorly controlled T1DM hypertriglyceridemia and reduced HDL-C commonly occur, but in most cases insulin replacement in these patients correct these abnormalities. In T2DM, this phenotype is not usually fully corrected with glycemic control, suggesting that insulin resistance and not hyperglycemia *per se* are associated with this lipid abnormality.
Primary therapy should be directed towards lowering LDL-C levels. A statin should be chosen depending on the LDL-C reduction needed to achieve the target value (<70 mg/dl) and upon the judgment of the physician. Although usually not very effective for raising HDL-C levels, statins might be effective at reducing moderately elevated triglycerides, thus reducing the need for combination therapy. Addition of fibrates may be indicated when triglycerides are high and HDL-C is low.
This review will give an update regarding management of dyslipidemia of diabetic patients to achieve the best clinical outcome regarding reduction of CVS mortality.

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Endocrine Disruptors

EP582

Epithelial-mesenchymal transition and estrogen receptor-dependent pathway are linked with ovarian cancer cell growth and migration caused by cigarette smoke extracts in human ovarian cancer cells

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Cigarette smoke contains over 60 well established carcinogens. There are strong links between some of these carcinogens and various types of smoking-induced cancers. In this study we investigated whether cigarette smoke extracts (CSEs) affects the cell proliferation, migration, and invasion of BG-1 human ovarian cancer cells by alteration of epithelial-mesenchymal transition (EMT). We confirmed that CSEs increased the ovarian cancer cell viability in a dose-dependent manner. Also the protein expression of cyclin D1 and cyclin E1 was increased while p21 and p27 expression was decreased by treatment of all CSEs (3R4F and two-domestic commercial cigarettes). Additionally the alteration of EMT markers such as E-cadherian and N-cadherin was examined. The expression of E-cadherin was reduced by the treatment of CSEs while its reverse transition marker N-cadherin was increased. EMT-associated transcriptional factors, Snail and Slug were also up-regulated by CSEs treatment. These results indicate that CSEs can increase EMT process in BG-1 ovarian cancer cells, which is associated with cancer cell migration. We examined the migration activity through scratch assay and fibronectin coated trans-well invasion assay, in which CSEs increased cancer cell migratory propensity. These functional alterations were associated with changes in the metastasis-related genes. Upon CSEs stimulation, the expression of MMP-9 and cathepsin D was increased. Taken together, we confirmed that CSEs increased the growth of human ovarian cancer cells and the development of metastasis by stimulating cell cycle and EMT process through up- and down-regulation of a multiple cellular markers and signaling proteins and that CSEs exposure might have a higher risk of ovarian cancer than nonsmokers. Based on the results of this *in vitro* study, we will examine the in vivo risk assessment of CSEs in a xenografted mouse model transplanted with BG-1 human ovarian cancer cells.

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EP583

Thyroid diseases in the 'Land of Fires': results of a single center screening in Acerra (Naples)

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Introduction
Environmental toxins, including those deriving from illegal and hazardous disposal of urban and chemical waste, are known to act as endocrine disruptors and to increase the risk of malignancy and cancer mortality. The present study aimed at investigating prevalence and characteristics of thyroid diseases in the area of Acerra, a town in the perimeter of the so called 'Land of Fires'.
Methods
The screening included subjects aged $\geq$15 yrs living in Acerra. Overall, 787 consecutive subjects (631 F, 156 M, aged 39.6$\pm$16.3 yrs) were recruited on a voluntary basis. Iodine supplementation, thyroid palpation, hormonal testing (TSH, fT3, fT4, antithyroid antibodies), ultrasound and fine needle cytology (FNC, when necessary) were investigated. According to the age tertiles, subjects were classified as Group A (age $<$24 yrs, no$=$236), Group B (Age 25–52 yrs, no$=$310) an Group C (age $>$ 52 yrs, no$=$241).
Results
Prevalence of Hashimoto's thyroiditis and nodular goiter was 13.5% and 17.5% of the whole cohort, respectively, being not different as compared to that of the Italian general population. Hashimoto's thyroiditis was significantly prevalent in C compared to A ($P=0.021$), and hyperthyroidism in C compared to A ($P=0.003$) and B ($P=0.03$). Prevalence of nodular goiter was higher in C as compared to A ($P<0.001$) and B ($P<0.001$), and in subjects who did not use iodine supplementation ($P=0.032$) as compared to those who did. Among subjects undergone FNC, none had thyroid cancer and all were classified as benign nodular disease (THY2).
Conclusion
These findings suggest that subjects living in the area of Acerra had a similar prevalence of thyroid diseases as compared to the Italian general population and did not present with an increased prevalence of thyroid cancers despite chronic exposure to environmental pollutants.

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EP584

Estimation of bisphenol A influence on obesity

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Introduction
Obesity is a global health problem. More than half (54%) of the adult population in Serbia and 58.5% of adult population in the north province, Vojvodina is obese or overweight. Hence, it is urgent to identify environmental factors which may contribute obesity. Bisphenol A (BPA) is one of the most extensively used chemical in production of food and beverage containers, epoxy resins, polycarbonate plastics and well known endocrine disruptor. The aim of this study is to determine the prevalence of BPA in urine samples in women in Vojvodina and to determine the association between BPA and obesity in women.
Method
The study was conducted in the Clinical Centre of Vojvodina and 103 women age between 18 and 55 were enrolled in the study and in their urine samples BPA was determined. Women were divided according to their body mass index (BMI) into two groups: N-normal weight (BMI $<$ 25 kg/m^2) and O-obese group (BMI $\geq$ 30 kg/m^2).
Results
BPA was detected in 36% (37/103) women, 31% (16/52) in the N-group and 41% (21/51) in the O-group. The average concentration of BPA was 12.24$\pm$10.55 μg/g creatinine. The groups were additionally divided into two subgroups: BPA positive (BPA$+$) and BPA negative (BPA$-$). There was statistically significant linear correlation between BPA concentration in the urine sample and BMI ($r=0.59$, $P=0.003$) as well as between waist circumference and BMI ($r=0.45$, $P=0.02$) in the O-group. However, no statistical difference was found between BMI, waist circumference, or lipid status: HDL, LDL and total cholesterol among BPA$+$ and BPA- subgroups in both N- and O-group. The highest BPA concentrations were detected in younger women with highest BMI.
Conclusion
BPA is one of the most important factors which may contribute the increment of BMI and waist circumference, while HDL, LDL and total cholesterol may be associate factors which additionally influence obesity.

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EP585

Impact of EDCs on cation transporter channel in the mouse placenta during pregnancy

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Placenta exchanges vital factors including oxygen, carbon dioxide, cation (copper, iron, calcium) and glucose that are essential to fetal growth. Copper, iron, calcium cation and glucose transfer genes are regulated by reproduction-related hormones, vitamin D and human placental lactogen. These molecules are transferred by specific receptors located on cell membrane or cytoplasm in placenta. These substances disturb action of reproduction-related hormones (ex$>$ estrogen, progesterone) by interacting with their receptors, or affecting the expression of transporting genes for cations. To examine the effects of EDCs exposure during pregnancy, we conducted the in vivo model study using Pregnancy mouse. We used different doses of octyl-phenol (OP; 50 mg/kg/day), and bisphenol A (BPA; 50 mg/kg/day) in pregnancy mice for GD 11.5$\sim$16.5. Ethinyl estradiol (EE; 0.2 mg/kg/day), which activates estrogen receptors, was used as a positive control. ICI 182 780 (70 ug/kg) were used with estrogen antagonist. Transcription of calcium transporting genes, copper transporting genes, and iron transporting genes was quantified by qRT-PCR. Treatment with EE, OP, BPA in a mouse placenta affected expression of calcium transporting

genes (PMCA1, TRPV6), copper transporting genes (CTR1, ATP7A), and iron transporting genes (IREG1, HEPH). Expression of the gene was confirmed in the control group and the experimental group. In the result of real-time PCR, relative mRNA expression levels of PMCA1, TRPV6, ATP7A, CTR1, HEPH, IREG1 in some group were decreased or increase compared to the vehicle control. We concluded essential cation transporting genes in placenta are modulated by EDCs.

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EP586

2,4,6-tribromophenol inhibit overall thyroid function in mouse

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Synthesized chemicals that not existed in the environment have been troubled endocrine physiology. These endocrine disruptors (EDs) had been noted and replaced with other chemicals. Most of compound banned for production act as an estrogen. But other than estrogen, especially thyroid hormone related EDs are noted for early brain and neural development. Brominated flame retardants (BFRs) are representative known as thyroid disruptor because of its structural similarity. 2,4,6-tribromophenol (TBP), one of BFRs, has been produced bulky for reagent of thermostable plastic. Its effect to thyroid system related with transthyretin (TTR) is studied in vivo. TTR is blood protein that has a high binding affinity to thyroid hormones. ICR female mouse, post-natal 16 days, were exposed to TBP with or without triiodothyronine (T3) or thyroxine (T4). Liver and pituitary gland were dissected and RNA was extracted by Trizol. mRNA level of each pituitary gland and liver was quantified using quantitative real time PCR. Serum level of each free thyroid hormone was measured by Immulite 1000. Dio1 was increased in pituitary gland and liver by TBP. Reduction of thyroid hormone receptor beta, isoform 2 (Thrβ2) and Dio2 inductions of Gh and thyroid stimulating hormone β (Tshβ) were observed in pituitary gland. Thyroid hormone receptor beta, isoform 1 (Thrβ1) was reduced by TBP in liver. Each free thyroid hormone level was decreased by TBP and its inhibition effect was also observed when treatment with thyroid hormones. TBP was shown anti-thyroid effect in some way such as Dio1, Dio2, Tshβ and Thrβ2 in pituitary gland. TBP inhibited expression of Dio1 and Thrβ1 induced by thyroid hormones in liver. Finally, TBP decrease the hormone level in blood. Like other BFRs, TBP also shown interfering effect to thyroid system.

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EP587

The effects of endocrine disruptors on the *in vitro* AVP hormone regulation

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Introduction
Endocrine disruptor compounds (EDCs) are chemicals that may interfere with the endocrine system and produce adverse developmental, reproductive, neurological and immune effects.These agents can be found in household, in the industry and in our environment.Endocrine disruptors are substances that interfere with the synthesis, secretion, transport, binding, action, or elimination of natural *hormones* in the body that are responsible for development, behaviour, fertility, and maintenance of homeostasis.Our **aim** was to investigate the effects of uron herbicides EDCs/fenuron (PU), monuron (MU), diuron (DU)/on the normal endocrine regulation; particularly the monoamine activated arginine-vasopressine(AVP)release from neurohypophyseal cells.
Materials and methods
The primary monolayer cell cultures were the neuroendocrine regulated models. These were prepared from the pituitary of normal Wistar rats (♂).The separated neurohypophysis (NH) tissues were dissociated by enzymatic (trypsine, collagenase, DNA-se I; II) and mechanic methods. The 14 days old cultures were standardized for cell-viability and AVP content in NH cultures. The NH cells were tested for functionally AVP hormone volume by aspecific osmotic stimulus (30 mM K^+). Untreated cultures were used as controls while further cultures were treated with:- ***I.:*** 1 hour 0,1 μg/ml EDCs: MU, DU, PU -***II.:*** 10^{-6}M monoamines (norepinephrine, dopamine, histamine) alone -***III.***: the monoamines agents with EDCs combined. The AVP release was measured from supernatant media by RIA method.
Results
The uron herbicides alone did not have significant effects on the AVP release in the NH cell cultures. The monoamine activated hormone release strongly changed by the EDCs, mainly the dopamine and histamine.
Conclusion
The psycho-neuro-endocrine-immune system modulated by various environmental factors can lead to the development of different diseases in connection with this complex network. This work was supported by: TÁMOP-4.2.2.D-15/1/KONV-2015-0010, TÁMOP-4.2.4.A/2-11-1-2012-0001

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Endocrine Nursing

EP588

Managing Children with Diabetes within the Family: Movement in the orbit of diabetes

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Background
Diabetes is the disease of family and parents of children with diabetes face different problems which concerns meeting the developmental needs of children and daily control of children with diabetes.
Purpose
This article aims to explain how to manage diabetes around the child's life within the family.
Methods & materials
In this qualitative study, data was collected through semi-structured interview technique and was analysed using Grounded Theory approach. The process of data collection was carried out by purposeful sampling. The participants included 13 individuals from nine families (11 parents and two children with diabetes). The research environment was health canters in Iran providing care to the families of children with diabetes. Data analysis was performed using Corbin and Strauss approach. Data was analysed with using MAXQDA software (version 10).
Results
The core category of "Movement in the orbit of diabetes" addresses the story of how to keep track of managing children with diabetes within the family which included Main categories "ride in the waves of care", "provision of diabetes backpack", and "movement focused on children with diabetes".
Conclusion
The outcome of "Movement in the orbit of diabetes" results capturing the control of diabetes. The findings of the present study may play an integral part to help households with practicing appropriate strategies for the management of children with diabetes.

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Endocrine tumours and neoplasia

EP589

Proposal of a two-step dynamic prognostic stratification for stage IV sporadic pancreatic neuroendocrine tumors

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Purpose
To validate a prognostic stratification system of overall survival (OS) in stage IV pancreatic neuroendocrine tumors (pNETs) *naïve* of therapy by analyzing

1) prognostic parameters at the time of stage IV diagnosis; 2) the role of spontaneous tumor slope.
Patients and Methods
Multicenter retrospective study including consecutive patients diagnosed with stage IV pNET from January 1997 to March 2014. Inclusion criteria were: 1. pNET with well-differentiated morphology; 2. measurable stage IV disease; 3. diagnosis and follow-up entirely performed at the participating center. Exclusion criteria were: 1. systemic treatment prior work-up; 2. hereditary syndromes. The primary endpoint was OS. Univariate and multivariate analyses were performed: *model 1* "at the time of stage IV diagnosis"; *model 2* "after the definition of spontaneous tumor slope".
Results
Two hundred and eight patients with stage IV pNET were included. Median follow-up was 45 months. Parameters independently associated with OS were: *model 1*. T parameter (T4, $P=0.04$), metastatic tumor load (2 sites, $P=0.004$; >2 sites, $P=<0.0001$), liver involvement ($>70\%$, $P=<0.0001$), grade (ki67 and/or mitotic index >10, $P=0.01$); *model 2*. T parameter (T4, $P=0.04$), metastatic tumor load (2 sites, $P=0.006$; >2 sites, $P<0.0001$), liver involvement ($>70\%$, $P=0.0002$), grade (ki67 and/or mitotic index >10, $P=0.03$), and spontaneous tumor slope (progressive disease, $P=0.001$).
Conclusions
Based on these results a two-step prognostic stratification of stage IV pNET patients is proposed. This includes the number of tumor organs, liver involvement, T4 and the grade at diagnosis, empowered by tumor slope at the time of first imaging monitoring in patients subjected to watchful follow-up.

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EP590

Localization of benign insulinomas using glucagon-like peptide-1 receptor (GLP1-R) SPECT/CT and PET/CT in a prospective clinical study

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Purpose
The aim of our study is to compare the detection rate of GLP-1R PET/CT and GLP-1R SPECT/CT in patients with a biochemically proven endogenous hyperinsulinemic hypoglycemia. Preliminary results of an ongoing study are reported.
Methods
Thirty-three patients (25 females, 8 males, age range 18–80 years, mean 49 years) with neuroglycopenic symptoms due to endogenous hyperinsulinemic hypoglycemia were enrolled (ClinicalTrials.gov, NCT02127541).
Results
Previously performed cross-sectional imaging (CT/MRI) was negative or not conclusive in 25/33 (76%) of patients. 22 patients have been operated. In this collective, the histological diagnosis of a benign insulinoma was confirmed in 19 patients, one patient had adult islet cell hyperplasia. In one patient both intraoperative palpation and histological diagnosis did not confirm an insulinoma. In one patient symptoms of endogenous hypoglycemia ceased postoperative but histological diagnosis did not confirm the diagnosis. This patient was excluded from evaluation as the final diagnosis remained unclear. Two patients refused surgery. Five patients are awaiting surgery. In four patients PET/CT, SPECT/CT as well as the previous performed conventional imaging did not find any suspicious lesion and were thus not operated up to date. In this interim analysis PET/CT showed an overall pooled sensitivity of 93% SPECT/CT at 72 h showed an overall pooled sensitivity of 75% PET/CT was the only modality which correctly identified the area of islet cell hyperplasia (adult nesidioblastosis) within the pancreas.
Conclusion
Our interims analysis suggests that GLP-1R PET/CT performs better than GLP-1R SPECT/CT at a lower radiation dose and shorter examination time.
GLP-1R PET/CT will be a useful diagnostic tool in patients where cross sectional imaging (CT/MRI) fails to localize the insulinoma.

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EP591

Mtor inhibitors responsiveness associates with Akt/Mtor pathway activation in pancreatic neuroendocrine tumors

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Introduction
Medical therapy of Pancreatic neuroendocrine tumors (P-NETs) may take advantage from mammalian target of rapamycin (mTOR) inhibitors. However, so far, the extent of therapeutic response cannot be predicted.
Aim
To investigate the possible predictors of sensitivity to mTOR inhibitors in P-NETs.
Materials and methods
P-NET primary cultures were treated with IGF1 and/or Everolimus. Cell viability and caspase activity were evaluated. Protein profiling for PI3K/AKT/mTOR pathway components was assessed by alpha screen. Validation by Tissue microarray and immunohistochemistry (IHC) was performed on 11 P-NETs. Molecular and clinico-pathological characteristics of the patients were collected.
Results
Everolimus significantly reduced cell viability and induced apoptosis up to 30% (Responder; P-NET-R) in 6 P-NETs, where the proliferative and antiapoptotic effects IGF-1 were blocked by Everolimus. On the contrary, 14 P-NETs were resistant to Everolimus and IGF-1 treatments (Non Responder; pNET-NR). Furthermore, we found that phosphorylated IGF1R, AKT, mTOR and 4EBP1 protein levels were >2 fold higher in P-NET-R as compared to P-NET-NR. Among the 11 P-NETs analysed by IHC, 2/3 P-NET-R tissues were positive for p-AKT and p-mTOR, On the contrary, 6/8 P-NET-NR tissues were negative for p-mTOR independently of the phosphorylation state of p-AKT, confirming alpha screen data. Furthermore, clinical characteristics associated with responsiveness to Everolimus *in vitro* were higher ki67 ($\geq 10\%$) and higher grade (G3).
Conclusions
The lack of response to mTOR inhibitors associates with an inactive mTOR protein, suggesting that mTOR phosphorylation status assessed by IHC may represent a predictive marker of responsiveness to mTOR inhibitors. However, further studies are needed to confirm these data.

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EP592

Bone morphogenetic protein signaling as novel therapeutic target in pheochromocytoma

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Introduction
Rats affected by the MENX syndrome develop bilateral pheochromocytoma (PCC) with complete penetrance. Transcriptome profiling of rat PCC identified *Bmp7* (bone morphogenetic protein 7) as highly expressed in the tumors. Interestingly, 72% of human PCCs also showed elevated BMP7 expression. BMP7 plays pro- or anti-oncogenic roles in cancer in a cell type-dependent manner. To address the role of *Bmp7* in PCC, its level was modulated in PCC cell lines and functional assays were conducted. The results showed that Bmp7 promotes oncogenic features in PCC.
Methods
We modulated Bmp7 expression and checked for integrin b1 expression. We knocked-down integrin b1 and performed *in vitro* functional assays. We treated PCC cell lines, primary PCC cells and tumor tissues with DMH1, a small molecule inhibitor of BMP type I receptors. Following DMH1 treatment, functional *in vitro* assays or immunohistochemistry were performed.
Result
Integrin b1 mediates Bmp7-dependent increase in PCC cell motility. Treatment of MTT cells with DMH1 suppressed cell proliferation and migration in a dose- and time-dependent manner. Concomitantly, a down regulation of molecular readouts of active BMP signaling in PCC cells was observed. The treatment of rat primary PCC cells with DMH1 was associated with a dose-dependent decrease in cell viability. Isolated rat tumor tissues were inserted into a rotary cell culture system

(RCCS, Synthecon™) and treated with DMH1. Immunohistochemistry on the fixed tissues confirmed the downregulation of BMP signaling by the inhibitor.
Conclusion
BMP signaling may represent a novel therapeutic target in PCC. Pathway blockade by DMH1 elicits anti-proliferative and anti-migratory responses in PCC cells *in vitro* and should in the future be evaluated in PCC models *in vivo*.

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EP593

Prognostic factors of recurrence-free and overall survival in 52 patients with adrenocortical carcinoma

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Adrenocortical carcinoma (ACC) is a rare and very aggressive tumor with poor prognosis. The aim of the study was to identify prognostic factors of recurrence-free (RFS) and overall survival (OS) in patients with ACC.
We present a retrospective analysis in 52 patients diagnosed with ACC. A number of factors both histological and clinical were analyzed. Recurrent disease was defined as a new lesion confirmed in imaging. Kaplan-Meier method and multivariate Cox proportional hazard regression model was performed with adjustment for sex, age and ENSAT staging as covariates.
The study included 36 females and 16 males of median age 48 and 57 respectively. Forty six patients underwent surgical resection, six had unrespectable disease. Forty six patients received adjuvant mitotane. Twenty eight patients suffered from recurrent disease. Thirty four patients died due to disease progression. The 5-year overall survival for stage I, II, III and IV disease was 75, 66.5, 29.2 and 0%, respectively. The median of recurrence-free survival was 24.4 months (1.5–132.8) and 43 months (2.3–165.18) for overall survival. Age, male sex, stage, mitotic rate $>20/50$ high power fields, tumor necrosis, tumor invasion of vessels, neighbouring structure or adjacent organs and time from first imaging to surgery over 70 days were associated with decreased both RFS and OS. Unrespectable disease, macroscopically involved margins or tumor infiltration of capsule with crossing its border were only related to poor OS. Ki67, hormonal activity, tumor size, thrombus in vena cava had no influence on RFS or OS.
Our study indicates a major role of prognostic factors on survival in patients with ACC. The 5-year survival, median of RFS and OS were worse than previously reported. Due to the aggressive behavior of ACC and high percentage of relapse it is crucial to conduct more studies in order to help improving survival.

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EP594

Sentinel lymph node biopsy in medullary thyroid microcarcinoma using methylene blue dye mapping – a pilot study

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Introduction
Serum calcitonin level (sCT) is a precise marker for medullary thyroid carcinoma (MTC). However, lymph node (LN) metastases can be found in lower sCT, as well, and preoperative ultrasound may provide false negative findings on regional LNs. The aim was to present original technique of sentinel lymph node (SLN) biopsy of jugulo-carotid regions, after methylene blue dye mapping procedure, and its usefulness for selection of clinically N0 patients with MTC for modified radical neck dissection (MRND).
Materials and methods
From 2007 to 2015th, 14 patients were operated in our surgical clinic due to MTC with sCT lower than 1000 pg/ml, tumors under or 10 mm in size and clinically negative regional LNs. Central dissection was done in all patients. SLN mapping was performed with 0.2–0.5 ml of 1%-methylene blue dye. Levels II and III were explored on both sides, blue stained SLNs were removed and examined by frozen section analysis. If benign, additional surrounding non-colored LNs were removed for more precise evaluation. If SLNs were positive, MRND was performed.
Results
One patient had hereditary form of MTC, with bilateral subcentimeter tumors, while others had sporadic, unilateral MTC. Sporadic MTCs showed no central nor lateral LN metastases on bilateral SLN biopsy, with no indication for MRND. Hereditary MTC had central LN metastases, with positive SLNs on both sides, thus one-time bilateral MRND was performed. This patient had metastases in other dissected LNs, as well, and sCT of 200 pg/ml. Frozen section and definite pathological analysis were 100% match.
Conclusion
SLN biopsy after methylene blue dye injection can be precisely used for intraoperative assessment of lateral LNs. It optimizes surgery for patients with MTCs, selecting clinically N0, but true positive patients for MRND. This pilot study is the first reported experience with SLN biopsy of jugulo-carotid regions in MTC, using methylene blue dye.

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EP595

Biochemical assessment of disease control in acromegaly: reappraisal of the glucose suppression test in somatostatin analogue (SA) treated patients

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Context
The nadir serum GH level during glucose suppression (OGTT) is recommended in patients treated by surgery, but not during SA treatment. We have shown that patients considered controlled by SA don't suppress serum GH during OGTT and have impaired disease-specific QoL as compared to patients controlled by surgery. We hypothesize SA treated patients also don't suppress GH in response to mixed meals.
Aim
To compare GH levels during two mixed meals in patients considered controlled by either surgery alone or SA.
Patients and methods
Patients controlled by surgery alone ($n=22$) or SA ($n=12$) for $\geq$ 12 months were studied twice in the following order: 1) during a 6 h (8–14 h) GH profile including two standardized mixed meals (at 8 and 12 h), and 2) during a 3 h (8–11 h) GH profile with OGTT at $t=9$ h. At least 6 months elapsed between each study.
Results
The two groups were comparable at diagnosis as regards gender distribution, serum GH and IGF-I levels and adenoma size. The mean$\pm$S.E.M. IGF-I levels (μg/l) at study start were 169 ± 13 (surgery) and 197 ± 13 (SA) ($P=0.15$). During profile 1 (mixed meal) no suppression was observed in the SA treated group and the mean serum GH levels (μg/l) were elevated [1.55 ± 0.77 (SA) vs 0.68 ± 0.48 (surgery) ($P<0.0001$)]. During profile 2 (OGTT) fasting GH levels (μg/l) were comparable [1.73 ± 1.30 (SA) vs 1.47 ± 1.57 (surgery) ($P=0.60$)], but the SA group failed to suppress during the OGTT [2.00 ± 0.90 (SA) vs 0.73 ± 1.0 ($P=0.008$).
Conclusion
1) Patients controlled by SA don't suppress GH in response to either OGTT or mixed meals, 2) This likely implies relatively elevated GH levels during everyday life in SA patients, 3) We recommend that SA patients are assessed with GH measurements during an OGTT and hypothesize that this will reveal under treatment in a substantial proportion of patients.

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EP596

The role of insulin, IGFBP-3, folic acid, 25-OH-D, CA 19-9 and CA 72-4 as potential tumor's predictors of the gastrointestinal tract in patients with acromegaly

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Introduction
Patients with acromegaly have increased risk of developing tumors of the gastrointestinal tract. There are some data that insulin, IGFBP-3, folic acid and 25-OH-D may influence the development of these tumors.

Aim
To study the influence of insulin, IGFBP-3, folic acid and 25-OH-D, CA 19-9, CA 72-4 in the development of tumors of the gastrointestinal tract, and the frequency of neoplasms detection.
Materials and Methods
The study included 120 patients with acromegaly. All patients underwent gastroscopy and colonoscopy with biopsy of revealed tumors. The levels of neoplasms also were studied in all cases.
Results
Neoplasms were found in 43 patients (35.8%). Histologically hyperplastic and adenomatous polyps (24/12), two patients had villous and tubulo-vesicular adenoma, serrated polyp was found in one case, and five patients had cancer of stomach and colon. Thus, the frequency of malignant tumors was 4.2%. Insulin levels higher than 48.6 mU/ml lead to significantly increased risk of developing tumors. The level of Insulin more than 30.1 mU/ml and diagnosed neoplasm significantly increased risk of malignancy (sensitivity 80%, specificity 95.2%). In addition, the level of IGF-GB3 $\geq$ 3510 mg/ml was also significantly increased the risk of malignancy (sensitivity 80%, specificity 98%). The level of CA-19-9 $\leq$ 8.8 U/l also increased the risk of tumors of the gastrointestinal tract in patients with acromegaly (sensitivity 79.3% and specificity 42.3%). Patients with tumors and without them were comparable by CA 72-4, folic acid and 25-OH-D levels.
Conclusion
Patients with acromegaly have the increased risk of neoplasms formation, including malignant tumors. Levels of insulin, IGFBP-3, and CA 19-9 can be used as the diagnostic criteria of tumors of the gastrointestinal tract in patients with acromegaly.

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EP597

Phaeochromocytomas and paragangliomas: A comparative study between sporadic and familial cases in a reference care center in Spain

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Introduction
Hereditary phaeochromocytoma (PCC) and paraganglioma (PGL) account for 30–35% of cases and have some clinically relevant peculiarities.
Material and methods
Retrospective, unicentric cohort study that included all genotyped patients ($n=36$, 27 with PCC and 9 with PGL) diagnosed at Hospital Clínico San Carlos (Madrid) between 1984 and 2013; 33% were germline mutation carriers (25% pseudohypoxic [PH] phenotype, 75% MAP-kinase [MAPK] phenotype). Median follow-up was 98 (IQR 56-141) months. A comparative analysis was performed using the Mann–Whitney U test, the χ^2 test and the log-rank test.
Results
Median age at diagnosis was 35.3 (21.9–45.1) years in familial cases, and 64.4 (48.2–73.0) in sporadic cases ($P=0.02$). Most of the sporadic cases were diagnosed incidentally (61% vs 17%, $P=0.01$). Multifocality was more frequent in familial cases (50% vs 8%, $P=0.01$). Recurrent disease after surgery was present in 40% of familial cases and in no sporadic cases ($P=0.006$, median time 73 [30–85] months); it was more frequent in the PH group (67%) than in the MAPK group (17%). Progression-free survival (PFS) was longer in sporadic cases ($P=0.009$).
Conclusions
Age at diagnosis was significantly lower in familial cases of PCC/PGL. Malignant behaviour and multifocality were associated with familial cases. Genetic testing allowed for early diagnosis in asymptomatic mutation carriers, although sporadic cases had significantly longer PFS.

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EP598

Norepinephrine transporter (NET) as a predictive marker of response to PI3K/mTOR inhibition in pheochromocytoma

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Phaeochromocytomas (PCs) are neuroendocrine tumors derived from neural crest-derived chromaffin cells of the adrenal medulla and sympathetic ganglia. About 10% of all PCs can be malignant.
Currently, there is no effective therapy for malignant PCs.
In many neuroendocrine tumors, including PCs, the PI3K/AKT/mTOR survival pathway is hyperactivated. Therefore, the inhibition of this signaling cascade may exert an antitumor effect.
In our study we evaluated the efficacy of a dual PI3K/mTOR inhibitor, BEZ235, against PC *in* vivo to avoid the re-activation of upstream AKT signaling following mTOR inhibition. We took advantage of a unique *in vivo* model of endogenous PCs: MENX-effected rats.
Beside antitumor effects of BEZ235 on PCs cells, gene expression analyses of tumors from rats treated with placebo or with BEZ235 identified the *Slc6a2* gene, encoding the norepinephrine transporter (NET), as being down-regulated following drug treatment. NET is responsible for the intracellular re-uptake of norepinephrine in chromaffin cells. The fact that NET is expressed by PC cells has been extensively exploited for the functional imaging of these tumors using radiolabeled norepinephrine analogues. We observed a dose-dependent reduction of both *Slc6a2* (by TaqMan) and NET (by immunohistochemistry) expression in rat PCs following BEZ235 administration, which associated with decreased uptake of the radiolabeled norepinephrine analogue 18F-LMI1195 *in vivo*. To assess the relationship between NET levels and response to BEZ235, we generated a drug-resistant derivative of the MPC cell line. While incubation with BEZ235 reduced NET expression in MPC cells, no reduction was observed in the resistant derivative cells, suggesting that decreased NET expression associates with the ability of PC cells to respond to PI3K/mTOR inhibition.
Altogether, our data demonstrate that targeting PI3K/mTOR signalling is effective against PCs and suggest that NET levels may represent a surrogate marker of therapy response to PI3K/mTOR inhibitors, which can be monitored by functional PET imaging.

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EP599

Dual targeting of PIK3/AKT/mTOR and IGF1/KRAS/BRAF pathways in an *in vitro* model of ovarian cancer: strategies for cell proliferation control

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Ovarian cancer (OC) is the most lethal gynecological cancer. Debulking surgery and platinum-based chemotherapy are the cornerstone of OC management; however, after a partial initial response, tumors invariably relapse. Therapeutic approaches should account for interindividual heterogeneity since OC histiotypes show distinct genetic profile. A2780 cell line has been annotated as high grade serous ovarian cancer (HGSOC); nevertheless, recent research underlined that the genetic and molecular background of these cells are much closer to the clear cell/endometrioid histiotypes, characterized by mutations in PIK3/AKT/mTOR and IGF1/KRAS/BRAF pathways, that are partially responsible for their chemoresistance. The aim of the current study was to assess the *in vitro* effects on cell proliferation of the mTORC1 inhibitor everolimus, the mTORC1/mTORC2 inhibitor OSI027 and the IGF1-R inhibitor OSI906, alone and in combinations, in A2780 cells. Dose-time response curves were obtained in A2780 treated for 24, 48, and 72 hours and 6 days with compounds given at concentrations from 1 μM to 1 pM. Everolimus significantly inhibited cell proliferation in a dose-time dependent manner (maximum inhibition 95%). OSI027 significantly inhibited cell proliferation at the highest concentrations of 1 μM and 100 nM (maximum inhibition 95%). OSI906 displayed a non-significant dose dependent trend in the inhibition of cell proliferation. Cells

were then treated with combinations of drugs administered at intermediate concentrations: everolimus at 100 pM, 1 pM and 10 fM was combined with OSI906 at 100 nM, 10 nM and 1 nM; OSI027 and OSI906 were combined at 100 nM, 10 nM and 1 nM. All the co-treatments showed a higher inhibitory effect on cell proliferation compared to single compounds. These preliminary results suggested that the dual targeting of PIK3/AKT/mTOR and IGF1/KRAS/BRAF pathways may be a potentially effective approach to the management of OC. Additional experiments are being performed to further characterize the interplay between these pathways in OC.

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EP600

Immunohistochemical study of AuroraB proves association with differentiation and expression of crucial progression markers in gastroenteropancreatic neuroendocrine neoplasms

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Objective
Gastroenteropancreatic neuroendocrine neoplasm (GEP-NENs) are rare and heterogeneous in their tumor biology. Therapeutic options to prevent growth and dissemination are still not satisfactory. As shown previously, survivin and aurora kinases (members of the mitotic chromosomal passenger complex) play a role in cell cycle progression; FOXM1 is a transcription factor that regulates G2/M progression and is associated with grading and metastasis in GEP-NENs. Aurora kinases, survivin and Ki-67 have been described as transcriptional targets of FOXM1. Here, we immunohistochemically analyzed this protein network as potential tumor markers.
Methods
Tumor tissues from 128 patients were studied immunohistochemically with anti-survivin, anti-FOXM1, anti-STAT3, and AIM 1 (auroraB) antibody (>5%: positive). The expression pattern war correlated with follow up data such as tumor progression, time of death and cause of death.
Results
The immunohistochemical analysis of auroraB revealed an association with survivin, as both nuclear scores were positively correlated ($P=0.000$). We further found associations with the expression of STAT3. AuroraB-expression was related to high FOXM1 expression ($P=0.046$). In accordance with the strong association of survivin/FOXM1 expression with grading and differentiation, we found cytosolic AuroraB almost exclusively in G1/G2 tumors, nuclear AuroraB expression in G3 tumors (both: $P=0.000$).
Conclusion
Our study shows that the expression of AuroraB is associated with differentiation, progression and aggressiveness of GEP-NENs. The association of AuroraB with STAT3, which is involved in tumor-stroma communication, deserves further investigation. AuroraB is strongly associated with other markers of the mitosis regulatory network, including survivin, FOXM1 and Ki-67. We therefore propose to include this set of proliferation markers into routine diagnostics in order to individualize therapeutic strategies in this tumor entity in the future.

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EP601

Adrenal incidentalomas: functionality study

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Introduction
Due to the widespread use of imaging studies performed in hospitalised patients for other indications, adrenal incidentalomas (AI) are frequent findings in the everyday clinical practice. The objective of this research is to describe the prevalence of hormonally active and malignant AI.
Patients and methods
Observational retrospective study of a cohort of patients who consulted in the Endocrinology service between 2005 and 2015 because of an AI. The statistical analysis was performed with SPSS 19th version for Windows.
Results
Two hundred and one patients presented with an AI. Seventy four of them had multiple AI so that the number of AI analysed was 239. The median age of the patients was 58.85±11.55 years, 74.1% of which were older than 50. 56.9% of them were women.
Imaging study where the AI was found: 73.6% CT scan, 40% abdominal ultrasonography, 7.1% MRI, 0.8% PET and 0.4% surgical finding. Size: 29.36± 20.96 mm. 54.4% of the masses were located in the left adrenal gland. After the biochemical testing for hormone production and radiology study were conducted, 71.6% of the AI were non-functioning, 14.4% subclinical Cushing's syndrome 6.8% myelolipoma, 3.2% Cushing's syndrome, 1.4% pheochromocytoma, 1.4% adrenal cancer, 0.9% hematoma, 0.5% metastatic masses. Surgical treatment was performed in 37 patients (15.5%). The size of the mass was the most frequent reason for the intervention (36.7% of the AI removed), followed by radiological findings suggestive of malignancy (26.7%), growing AI (13.3%), Cushing's syndrome (13.3%), pheochromocytoma (6.7%) and history of previous malignancy (3.3%).
Conclusions
The AI is more frequent in women and in patients in the fifth decade of life. In our study, the predominant location was the left adrenal gland. Most of the AI studied were non-functional, being the percentage of hormonally active masses found similar as previous and larger studies.

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EP602

Synergistic anti-tumour effects of 13-cis retinoic acid and lovastatin in pancreatic neuroendocrine tumour (BON1) cells through enhanced EGFR inhibition

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Introduction
In our previous studies we found that the combination of 13-cis retinoic acid (13cRA) and lovastatin significantly reduced tumour growth in a mouse phaeochromocytoma allograft model, with the lowest microvessel density in the combination-treated tumours. We have now investigated the effect of 13cRA plus lovastatin on neuroendocrine (BON1, H727) and non-endocrine tumour (HepG2, Huh7) cell viability and signalling pathways (*EGFR*, AKT, ERK, p70S6K) to elucidate the underlying mechanism of action.
Methods
Cell viability was assessed with the MTS assay, the effect on signalling pathways by Western blotting. For cell viability data, the multiple-comparison Kruskal-Wallis-Test was used, followed by pairwise comparisons with the Mann-Whitney-Test. Interaction effects were analysed with Linear-Mixed-Effects-Models. Statistical significance was defined at $P\leq0.05$.
Results
3.75 μM or 7.5 μM 13cRA significantly reduced endocrine and non-endocrine tumour cell viability ($P\leq0.001$). The combination of 10 μM lovastatin plus 7.5 μM 13cRA showed synergistic inhibition of BON1 cell viability ($P\leq0.05$). We found similar results in the non-endocrine tumour cells ($P\leq0.01$). In H727 cells, 10 μM lovastatin plus 3.75 μM or 7.5 μM 13cRA significantly more strongly reduced cell viability than each drug separately ($P\leq0.05$), but this effect was not synergistic. In BON1, HepG2 and Huh7 cells, combination-treatment decreased pEGFR by more than 50% relative to each drug separately, and by more than 80% relative to the untreated control. This effect on pEGFR was less pronounced in H727 cells. In all cell lines investigated, combination treatment reduced pAKT by more than 50% compared to each drug separately, and strongly up-regulated pERK relative to the control.
Conclusion
We found a synergistic effect of 13cRA plus lovastatin in BON1 cells at clinically relevant doses, associated with enhanced EGFR inhibition. This is compatible with our recent *in vivo* data in a phaeochromocytoma allograft model showing slowest tumour growth and lowest microvessel density after 13cRA/lovastatin-treatment suggesting a novel potentially highly effective therapy.

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EP603

Medullary Thyroid Cancer: a comparative study between sporadic and familial cases in a reference care center in Spain

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Introduction
Hereditary Medullary Thyroid Cancer (MTC) accounts for 20–30% of cases and has some clinically relevant peculiarities.
Material and methods
Retrospective, unicentric cohort study that included all genotyped patients with MTC ($n=48$) diagnosed at Hospital Clínico San Carlos (Madrid) between 1984–2013; 42% were germline mutation carriers (45% moderate risk (category MOD), 45% high risk (category H), 10% highest risk (category HST)). Median follow-up was 61 (IQR 22–104) months. A comparative analysis was performed using the Student's *t*-test, the χ^2 test and the log-rank test.
Results
Mean age at diagnosis was 37.6 (s.d. 20.4) years in familial cases, and 62.5 (12.2) in sporadic cases ($P<.001$); local or distant metastases were present in 44% of familial cases and 61% of sporadic cases ($P=$NS). Most of the familial cases (55%) were asymptomatic and diagnosed after genetic screening. Six months after total thyroidectomy, 24% of sporadic cases and no familial cases showed progression. During follow-up, 27% of sporadic cases and 6% of familial cases developed distant metastases (median time 30 (8–56) months). Progression-free survival (PFS) and distant metastases-free survival (DMFS) were longer in familial cases ($P=$NS). Attributable mortality due to MTC was 23% in sporadic cases and 0% in familial cases; overall survival (OS) was longer in familial cases ($P=0.03$).
Conclusions
Age at diagnosis was significantly lower in familial cases of MTC. Genetic testing allowed for early diagnosis in asymptomatic mutation carriers, therefore familial cases had a better outcome and a longer survival.

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EP604

Evaluation of differential genes expression of ARHI, FAM129A, KCNQ1, STT3A, CDH1, TIMP3, TFF3 and PTEN in thyroid tissue lesions and in biopsies obtained intraoperatively

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Malignant transformation of the thyroid follicular cell in nodular goiter (NG) can lead to development of follicular adenoma (FA) or progression into: papillary thyroid carcinoma (PTC) or thyroid follicular cancer (FTC). Distinguishing follicular cell-derived thyroid tumors (FCDT) from NG on the molecular level can be especially helpful for underdetermined cytology (Bethesda III–IV) or FNAB with 'follicular neoplasm'.
Aim
Comparison of expression levels of *ARHI, FAM129A, KCNQ1, STT3A, CDH1, TIMP3, TFF3* and *PTEN* genes - as candidate biomarkers in differentiation of FCDT - in intraoperative FNAB and in mass of lesion.
Material
RNA isolated from FNAB of the indicated nodule and thyroid tissue neoplasms (obtained during total tyroidectomy) from 56 patients with preoperative FNAB diagnosis: 'follicular neoplasm'/PTC. Final diagnoses: FA ($n=6$), PTC ($n=22$), FTC ($n=5$) and NG ($n=23$).
Methods
RNA isolation, cDNA synthesis, mRNA expression evaluation (RQ), V600E BRAF mutation analysis.
Results
From analysed genes *TFF3, FAM129A, KCNQ1, STT3A* and *CDH1* were expressed on the comparable level in tumor tissue and in biopsies. Expression of *KCNQ1* was elevated in NG, when compared to group of cancer lesions. Expression of *FAM129A*, *CDH1* were the highest in PTC, and *TFF3* in FTC. Differences in expression levels of *TIMP3*, *ARHI* and *PTEN* were observed between cancer tissue and FNAB, what exclude the possibility of using these genes as differentiating markers for biopsies. *ARHI* and *PTEN* expression was significantly elevated in FNAB and *TIMP3* was decreased in FNAB, when compared to cancer tissues. *BRAF* mutations V600E/V600A were observed in six patients, no correlation with gene expression or pathological features.
Conclusions
TFF3, FAM129A, KCNQ1, STT3A and *CDH1* gene expression analysis in biopsy flushes may have diagnostic potential due to the expression on comparable levels in thyroid nodule biopsy and thyroid lesions after thyroidectomy. Search for new molecular diagnostic markers is essential especially for the FNAB with 'follicular neoplasm'.

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EP605

Real life data on Lanreotide Autogel in the treatment of patients with neuroendocrine tumors (NET) – an interim analysis from SOPRANo study

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Introduction
This non-interventional study assesses real-life use and potential predictive parameters for lanreotide (LAN) in pts with either acromegaly (ACRO) or NET over a period of 24 months. We present a pre-specified interim analysis after first 6 months of therapy.
Methods
The primary objective is to evaluate the long term treatment response under LAN and to correlate it with early changes of biochemical markers. The planned sample size is 152 (76 ACRO and 76 NET) pts. Pts/disease characteristics, disease markers, treatment effectiveness are also analysed. The baseline (except CgA) and safety data are presented on 50 enrolled NET pts, other analyses are performed on the main NET analysis population ($n=37$).
Results
At baseline, median ($\pm$ s.d.) age and duration of NET were 68.5 ($\pm$13.2) and 0.9 ($\pm$5.4) yrs, median ($\pm$ s.d.) CgA level was 393.9% of ULN ($\pm$1409.7). Main tumor locations included ileum (46%) and pancreas (22%); 90% of pts had metastases. G1 and G2 tumors were observed in 51% and 43% respectively, G3 in 6%. Scintigraphy was positive in 58% pts. 89% of pts had prior therapy (88% surgery, 22% biotherapy). After first 6 months of therapy 70% and 85% of pts showed stability or improvement of carcinoid syndrome/diarrhea and flush, respectively. 22 adverse events (AEs) were reported in 16 pts (32%), wherefrom 11 pts developed a total of 16 serious AEs (15 unrelated and 1 related (choledocholithiasis)).
Conclusions
The study reflects the routine use of LAN in advanced/metastatic NET. This interim analysis shows favorable effectiveness with stabilization of disease related symptoms and good tolerability of LAN.

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EP606

Novel mutations p.V220E and c.30G>T in menin gene are associated with hereditary predisposition to multiple endocrine neoplasia type 1

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant condition characterized by varying combinations of endocrine tumors and commonly

accompanying hyperplasia within the parathyroid gland, anterior pituitary and gastrointestinal tract. Heterozygous germline mutation of the tumor suppressor gene MEN1 is the most common cause of the disease. Molecular genetic testing of menin gene, in which mutation is known to cause MEN1 syndrome, detects pathogenic variants in approximately 80%-90% of probands with familial background and in approximately 65% of sporadically occurring cases.
Aims
Identification and characterization of pathogenic mutations in 2 separate families presenting symptoms of MEN1.
Methods
Detailed family history of both pedigrees was investigated and followed up. In Family 1, pituitary tumor, parathyroid gland adenoma and neuroendocrine tumor appeared. The Family 2 presented with parathyroid gland adenoma. Genomic DNA was extracted by conventional methods from peripheral leukocytes. The entire coding sequence, together with the intron-flanking sequences of the MEN1 gene was analyzed.
Results
In both families, novel pathogenic mutations were identified. The Family 1 is affected by the missense mutation leading to single AA substitution V > E at position 220. In the Family 2, a novel splice site mutation c.30G > T was revealed. Both mutations and locations were searched in the literature and genomic databases but so far no such abnormalities were reported.
Conclusions
Patients who present solid components of potential MEN1 syndrome should be routinely screened for genetic abnormalities. There is limited understanding of tumor biology, behavior, and heterogeneous clinical presentation in MEN1. Abundance of genetic alterations in menin as well as lack of mutational hot spots, prompt the usage of wider genetic analysis including other genes. This work also indicate the necessity of thorough analysis of synonymous alterations as potentially pathogenic splice site mutations.

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EP607

Glucagon-like-1 Receptor imaging specifically localizes insulinomas in patients with Multiple Endocrine Neoplasia Type 1 (MEN-1)

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Introduction
Surgery is often the only treatment option that can effectively treat patients with insulinoma in MEN-1. However, the surgical intervention should be limited as surgery can not cure patients with MEN-1. It is, therefore, mandatory to correctly localize insulin secreting tumors from other neuroendocrine tumors.
Materials and Methods
In this report we include 6 patients with proven endogenous hyperinsulinemic hypoglycemia and neuroglycopenia in the context of MEN-1. All patients received abdominal SPECT/CT after the injection of a standard activity of ^{111}In-Exendin-4. Four patients underwent additional imaging with a standardized contrast media enhanced 3T MRI and a ^{68}Ga-DOTA-exendin-4 PET/CT scan as part of the study.
Results
Six patients (4 females and 2 males) were included (age range 18–49 years). Until today 5 of 6 patients have been operated. One patient refuses surgery until today. In the operated patients conventional imaging revealed a total of 11 suspicious pancreatic or peripancreatic lesions. PET/CT and SPECT/CT imaging together revealed 6 lesions with a high expression of Glucagon-like Peptide-1 receptors (GLP-1R) suspicious for an insulinoma. Based on the GLP-1R imaging all insulinoma suspicious lesions were surgically removed. Histology confirmed that all GLP-1 receptor positive lesions were insulinomas and all five patients presented with normalized postoperative blood sugar levels.
Conclusion
Adding GLP-1R imaging to conventional imaging is a helpful tool in differentiating insulinomas from other pancreatic islet tumors expressed in MEN-1 patient and may guide the surgical intervention.

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EP608

Pituitary magnetic resonance imaging in pituitary apoplexy

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Introduction
Pituitary apoplexy is a rare endocrine emergency characterized by the sudden onset of severe headaches, vomiting, visual abnormalities and pituitary dysfunction secondary to an acute hemorrhage or infarction within a pituitary adenoma.
Subjects and methods
We report a retrospective study from 2000 to 2014 of 23 cases with pituitary apoplexy. Their mean age was 38.7 years ±10 years, with a male to female ratio of 2:1. All patients benefited Magnetic resonance imaging (MRI).
Results
Pituitary (MRI) showed macroadenomas in all cases. These macroadenomas invade the optical chiasma in 87%, the cavernous sinuses in 48%, the sphenoidal sinus in 39% and have multidirectional extension in 22%. Areas of intratumoral hemorrhage were evident on MRI in 94% leading to the positive diagnosis of pituitary apoplexy which confirms the Importance of pituitary MRI when investigating pituitary apoplexy.
Conclusion
Pituitary apoplexy is a rare life-threatening clinical syndrome caused by infarction or hemorrhage within a pituitary adenoma. Magnetic resonance imaging (MRI) is the investigation of choice and has been shown to confirm the diagnosis in 94% of patients which is compatible with guidelines and results of the literature. Once pituitary apoplexy is diagnosed a multidisciplinary team approach is mandatory in order to improve the outcome of this condition.

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EP609

Craniopharyngioma registry for adult patients, an initiative of the pituitary workgroup of the DGE

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Introduction and Objective
Adult craniopharyngioma as a rare neoplasm of the central nervous system is still very poorly understood. The clinical implications for affected patients are numerous, ranging from endocrine dysfunction to visual loss and neurological impairment. Although the progress of this tumor entity is slow by nature, affected patients often suffer from multiple symptoms even after successful treatment with a strong impact on their individual quality of life. In order to achieve a better understanding of the course of the illness and the effect of modern treatment options a registry for long-term observation of these patients is introduced by the pituitary workgroup of the DGE.
Material and Methods
Based on the childhood craniopharyngioma registry already in place in Germany, modified case report forms (CRF) were developed to provide a better fit for disease related problems in the adult population. A standardized evaluation of the patients including MRI and CT Scans is performed, where location and dimensions as well as mass effects of the tumor are assessed. Each patient is requested to regularly fill out standardized QoL questionaires. Regular follow ups, beginning 6 months postoperative and after that period according to the endocrinologist/neurosurgeon in charge shall ensure detailed data acquisition.
Results
So far, 10 prospective patients from a single institution have been enrolled since April 2015 (2 male, 8 female, mean age 46 y, range 27 y–69 y, mean BMI 24.2, range 17.7–34.7, 50% ($n = 3$) adamantinous and 50% ($n = 3$) papillary tumors, the remaining tumors were not yet classified.
Conclusion
7 centers are recruiting, 1 is still awaiting approval by their ethics committee Further participation by other treatment centers is greatly appreciated in order to

achieve a better understanding of adult craniopharyngioma and to further optimize our patients' treatment and life quality in the future.

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EP610

Effect of 17β-estradiol on the expression of cytochrome P450 1A1 gene via an estrogen receptor dependent pathway in cellular and xenografted ovarian cancer models

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Cytochrome P450 (CYP) 1A1 plays a major role in the metabolic activation of procarcinogens to carcinogens via aryl hydrocarbon receptor (AhR) pathway. In estrogen responsive cancers, 17β-estradiol (E2) may influence on AhR dependent expression of CYP1 family via the interaction between estrogen receptor (ER) and AhR. In the present study, the effect of E2/ER on the expression of AhR and CYP1A1 genes was investigated for BG-1 ovarian cancer expressing ER. In reverse transcription (RT)-PCR and western blot analysis, mRNA level of AhR was not altered, but its protein level was increased by TCDD or E2. The transcriptional and translational levels of CYP1A1 appeared to be increased by TCDD or E2. The increased expression of AhR and CYP1A1 induced by E2 was restored to the control level by the co-treatment of ICI 182,780, indicating that E2 induced the protein expression of AhR and CYP1A1 like TCDD via an ER dependent pathway. In an *in vivo* xenograft mouse model transplanted with BG-1 cells, the protein levels of AhR and CYP1A1 of tumor masses were also increased by E2 or TCDD. Taken together, these results indicate that E2 may promote AhR dependent expression of CYP1A1 via ER dependent pathway in BG-1 ovarian cancer expressing ER in the absence of TCDD, an agonist of AhR. The relevance of E2 and ER in CYP1A1 activation of estrogen responsive cancers may be targeted for developing more effective cancer treatments.

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EP611

Obstructive sleep apnea syndrome in patients with Cushing's syndrome

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Aim
Obstructive sleep apnea syndrome (OSAS) has been studied rarely in patients with Cushing's syndrome. We investigated the possible association between Cushıng's syndrome and OSAS in this study.
Method
Thirty female patients with newly diagnosed Cushing's syndrome and 30 female obese control subjects were included in this study. All the participants were evaluated by polysomnography. OSAS was defined as apneahypopnea index (AHI) of $\geq$5 events/hour. Body mass index (BMI) of the subjects was recorded and insulin resistance were calculated by HOMA score.
Results
The mean age and BMI of patients with Cushing's syndrome and control subjects were similar. However, the mean fasting glucose, HOMA score and apnoea-hypopnoea index were higher in patients with Cushing's syndrome compared to the control obese subjects (Table 1). 42% of patients with Cushıng's syndrome and 10% of control subjects had OSAS.
Conclusion
The risk of OSAS increased in patients with Cushing's syndrome, compared to control subjects with similar age and BMI. Insulin resistance and hypercortisolemia may have a meaningful role for this increment. Cushing's syndrome is a strong risk factor in the development of OSAS. Therefore Cushing's syndrome should be excluded in patients with OSAS and vice versa.

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EP612

Human endometrial adenocarcinoma: growth hormone involvement in cancer chemoresistance

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Introduction
It is known that growth hormone (GH) may influence neoplastic development of endometrial epithelium. GH is produced by normal and neoplastic endometrial cells and elevated levels have been observed in endometrial epithelium of patients with endometriosis and endometrial adenocarcinoma (EA). Moreover, endometrium cancer is one of the most occurring tumors in acromegalic patients. Furthermore, autocrine GH increases the oncogenicity of EA cells and is considered fundamental in neoplastic progression. Since chemoresistance often develops in advanced EA, we aimed at investigating whether GH might influence the development of chemoresistance to drugs routinely employed in EA treatment.
Description of methods
To this aim we employed two EA cell lines: HEC-1-A and AN3 CA cells. Cell viability and caspase activation were assessed by CellTiter-Glo Luminescent Cell Viability Assay (Promega) and Caspase-Glo 3/7 Assay (Promega), respectively. The expression of protein chinase C delta (PRKCD) was investigated by Western-blotting.
Results
We demonstrated that GH increases the viability of EA cell lines, while doxorubicin, cisplatin and paclitaxel significantly reduce this parameter. GH was capable to blunt the effects of doxorubicin and cisplatin, but did not influence paclitaxel effects on cell viability. GH also protects EA cells from caspase activation induced by doxorubicin and cisplatin. In addition, doxorubicin and cisplatin induce PRKCD expression, an effect counteracted by GH.
Conclusion
All together our results suggest that GH may contribute to EA chemoresistance by interfering with apoptotic mechanisms. This may provide new insights on novel therapies against EA chemoresistant aggressive tumors.

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EP613

Silent incidental adrenal pheochromocytoma

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Introduction
The widespread use of abdominal ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) has led to a predictable rise in the discovery of incidental adrenal lesions, some of which will be silent pheochromocytoma. Thus, about ten en percent of pheochromocytoma cases were diagnosed incidentally.
Methods
We studied retrospectively the notes of 23 patients with histologically confirmed pheochromocytom. Demographic information, pre-existing medical conditions, and the presence of classic pheochromocytoma symptoms (headache, sweating, palpitations, febrile sense, or episodic hypertension) were recorded. The aim of our study was to investigate the clinical characteristics and functional status of those who were asymptomatic.
Results
We recorded seven patients with silent pheochromocytoma (30% of confirmed pheochromocytoma). Mean patient age at presentation was 39 ± 11 years. The seven patients had unilateral enlargement on the left side. The Average maximum tumor diameter, as detected by CT was 4.2 ± 0.9 cm. Mean Washout on delayed enhanced CT was 64 ± 14%. All the adrenal masses were heterogeneous and necrotic in 4 cases. The urine fractionated metanephrine measurements were elevated at least 2 to 4 times above normal levels in 5 cases.
Conclusion
Every incidentally discovered adrenal mass should be investigated for pheochromocytoma even in the lack of symptoms. The literature indicates that incidental pheochromocytoma cases that are smaller than 1 cm have no clinical symptoms. Rarely, some large pheochromocytoma cases do not show any clinical symptoms but in our study the size of the adrenal masses is greater. Sublaboratory pheochromocytoma are rare. CT can show features of suspicious morphology

(calcifications, necrotic or cystic changes, and inhomogeneity) used as a screening tool for pheochromocytoma.

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EP614

Nestin and Klotho protein expression in neuroendocrine tumors of the lung

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Introduction
Neuroendocrine tumors of the lungs comprise 20% of primary lung tumors. Nestin is an intermediate filament protein, expressed in stem cells during fetal development. It is also described as a potential cancer stem cell marker, angiogenesis marker and indicator of poorer survival probability for patients with some types of malignancies. Adversely, Klotho gene is a potential tumor suppressor. Aberrant expression of Klotho have been recently noticed in a number of cancers. The knowledge of neuroendocrine tumors of the lung is scarce, so that in our study we aim at finding a marker which can possibly be used to establish prognosis and help to adjust the treatment to the type and stage of tumor.
Methods
We assessed immunohistochemically the expression of nestin and Klotho in 40 patients: in 20 cases of large cell neuroendocrine cancer (LCNEC), and in 20 cases of carcinoid tumors. We retrospectively reviewed patient charts and analyzed multiple variables like tumor size, metastases and overall survival time.
Results
We did not disclose any correlation between Klotho, nestin expression and Ki-67, initial tumor size, TNM stage in carcinoid tumors. In LCNEC there was no correlation between Klotho, nestin expression and overall survival time or metastases. Nestin expression was correlated with the patient's age in LCNEC group ($P=0.048$, $r=-0.44$). When comparing the level of expression of Klotho in carcinoids and LCNEC, it was significantly higher in the first group ($P<0.0001$). Additionally, nestin expression was more pronounced in LCNEC then carcinoids ($P<0.0080$).
Conclusion
Carcinoids usually characterized by indolent clinical behavior are characterized by higher Klotho expression, then LCNEC. Adversely, nestin expression is more pronounced in aggressive LCNEC. It points to a conclusion that, both Klotho and nestin might be useful as a possible biomarkers. Further studies, on a larger group of patients should be conducted.

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EP615

Genetic predisposition to breast cancer occurring in a male-to-female transsexual patient

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Introduction
Breast cancer affects less than 1% of all male cancer patients. In 5–20% of cases, genetic predisposition is involved, mostly due to mutations of the *BRCA2* gene. Hormonal imbalance between oestrogens and androgens is another predisposing factor. Male-to-female (MtF) transsexual patients usually undergo long-term cross-sex hormone therapy, which could expose them to higher risks of developing hormonally-dependent cancers.
We report the case of a MtF transsexual patient diagnosed with breast cancer. A pathogenic *BRCA2* mutation was found in the patient and their family.
Case report
Diagnosed with sexual identity dysphoria, the patient sought endocrine treatment at the age of 46 in order to start hormonal therapy. For 7 years, the patient was administered anti-androgens associated with oestrogens. The physical transformation was found satisfactory by the patient and the treatment was followed unremarkably. After 7 years, a routine mammography revealed a suspicious region with microcalcifications on the right breast. Biopsy was performed and the analysis found a high grade ductal *in situ* carcinoma without obvious signs of infiltration. Hormone therapy was interrupted and the patient underwent right mastectomy. A focally undifferentiated ductal carcinoma was found, estrogen and progesterone-receptors positive. 2 years later, local recurrence was diagnosed on the mastectomy scar.
Genetic analysis revealed the heterozygous c.9117G>A mutation of the *BRCA2* gene. The same mutation was known in a kindred bearing the same family name as our patient and living in the same region.
Conclusion
This is the first report of breast cancer occurring in a MtF transsexual patient with a proven genetic abnormality. It raises awareness of the particular care required by MtF patients due to their modified hormonal environment.

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EP616

Clinical benefit of patients with advanced adrenocortical carcinoma (Acc) treated in phase I clinical trials: the royal marsden hospital (Rmh) experience

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Introduction
After progression on conventional treatment options, some patients with advanced ACC are offered experimental Phase I therapies. The outcomes of these patients have not yet been formally evaluated. This study aims to describe the experience of refractory ACC patients treated on Phase I clinical trials at the RMH.
Methods
We retrospectively reviewed the records of metastatic ACC patients consecutively treated in our Drug Development Unit between January-2003 and December-2014.
Results
Sixteen patients (43.8% males) with median age of 45 years (23–62) were treated on 24 Phase I clinical encounters: 18 (75%) patients received targeted therapy (55.5% insulin-like growth factor pathway inhibitors), 3 (12.5%) chemotherapy and 3 (12.5%) chemotherapy combined with targeted agents. Overall response rate was 8.4% and clinical benefit rates at 4 and 6 months were 37.5% and 8.4%, respectively. Median progression-free survival and overall survival (OS) were 3.1 months (95% CI, 1.7–4.4) and 7.2 months (95% CI, 4.2–20.8), respectively. ECOG PS 1 versus 0 ($P=0.009$), >2 metastatic sites ($P<0.001$), peritoneal metastases ($P=0.016$), high platelet count ($\geq 410\times10^9$/l) ($P=0.014$), albumin <35 g/dl ($P=0.026$) and elevated LDH ($P=0.019$) were significantly associated with shorter OS. Patients with RMH score 0–1 (good prognosis) had superior median OS (14.1 months, 95% CI, 7.8–24.8) than those with a score 2–3 (bad prognosis) (5 months; 95% CI, 3.5–6.6) ($P=0.001$). Three (18.8%) patients experienced drug-related grade 3–4 toxicities. There were no toxicity-related treatment discontinuations or deaths.
Conclusions
Phase I clinical trials can be considered a reasonable therapeutic approach for ACC patients who failed conventional treatments due to low risk of toxicity and the potential for clinical benefit. The RMH prognostic score can help to identify patients most likely to benefit from these investigational agents.

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EP617

Dual inhibition of PI3K and mTORC1/C2 by PKI-587 (PF-05212384) as a promising therapeutic option for pulmonary neuroendocrine tumor disease

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Background
Pulmonary neuroendocrine neoplasms are heterogeneous in their clinical behavior and therapeutic options are still not satisfactory. The 'crosstalk' of

different signaling pathways in NEN cells appears to be more complex as known already. PKI-587 is a highly potent novel dual inhibitor of PI3K and mTORC1/C2.
Aim
Therefore, we assessed the effects of PKI-587 in different pulmonary NEN cell lines compared to the established mTORC1 inhibitor RAD001 and the non-neuroendocrine lung cell line A549.
Materials and Methods
We treated the cell lines NCI-H727, NCI-H69 and A549 with increasing concentrations of the inhibitor PKI-587, compared to RAD001 and DMSO. We performed MTS cell proliferation assay to determine efficacy and growth inhibition. The induction of apoptosis was shown by caspase 3/7 activation and cell cycle was analyzed by FACS. A JC-1 assay was additionally held out to show occurrence of early apoptosis.
Results
In all cell lines PKI-587 inhibited dose-dependently proliferation with an IC50 of approx. 30 – 6000 nM, whereas RAD001 was less effective. Treatment with PKI-587 led to cell cycle arrest in all cell lines and induction of apoptosis in NCI-H727 and NCI-H69 cells, whereas no apoptosis was observed in non-neuroendocrine A549 tumor cells.
Conclusion
PI3K/mTOR dual targeting is a promising new therapeutic approach in neuroendocrine tumor disease. Protein analysis with Western Blot will be held out in the next weeks and presented at the meeting. The efficacy of PKI-587 should be evaluated in further clinical trials.

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EP618

The prevalence of pancreatic neuroendocrine neoplasms with dedifferentiation during their natural history

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Introduction
Neuroendocrine neoplasms (NENs) are neoplasms with a slow progression and a 5-year survival 77–95%. It is well known that secondary deposits of NENs may dedifferentiate during the natural history of the disease, presenting a more aggressive biological behaviour.
Aim of the study
The prevalence of secondary foci dedifferentiation of pancreatic NENs (p-NENs).
Methods
From the NENs database of 414 patients, 160 (38.6%) had pNENs. Patients with dedifferentiation were identified by a new biopsy of metastatic foci and a high proliferation index Ki-67 MIBI (%) that indicated a poorly differentiated NENs that originated from a primary site with a lower Ki-67.
Results
Five (3%) (mean age($\pm$s.d.): 58.8$\pm$4.3 years, two males (40%)) patients, all with sporadic NENs presented dedifferentiation during the natural history of their disease as compared to 155 (52.9$\pm$15.8 years, 94 males (58.8%)) patients with NENs and no dedifferentiation (120 with sporadic NEN). At presentation, 1 patient had a stage III NEN, while 4 had a Stage IV NEN; 1 patient had Ki-67 1%, while 4 had 5% (grade 1 and 2, respectively) while when dedifferentiation was seen, 1 patient had Ki-67 30%, 2 had 50%, 1 had 60%, and 1 had 70%. At presentation, all five patients had metastases: 3 only liver metastases, 1 liver along with bone metastases and 1 liver along with ovaries and breast metastases; all 5 patients had a positive Octreoscan; 2 had a functional syndrome (one carcinoid syndrome and one insulinoma). At presentation 2 patients were candidates for a surgical approach. As first line treatment 2 patients received somatostatin analogs (SSAs) plus everolimus, 1 SSAs plus everolimus plus peptide receptor radionuclide therapy (PRRT), and 1 SSA monotherapy, while another one was followed-up without treatment. Progression free-survival (PFS) for 1st line treatment was 39.3$\pm$25.9 months, while PFS o further therapies varied from 13.4$\pm$11.2 months to 6.3$\pm$7.0 months (eight lines of treatment were registered). At the last follow-up, 3 (60%) patients were alive with an overall survival 158.73$\pm$50.91 months.
Conclusions
The dedifferentiation of NENs implies a more aggressive biological behaviour and worse overall survival despite the use of different therapies.

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EP619

Referral of patients from Lithuania to determination of dehydroepiandrosterone sulphate and no clinical consequences of results

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The 1772 patients were referred for the dehydroepiandrosterone sulphate (DHEA-S) concentration assessment in Lithuania during 2014. We investigated 309 clinical history cases of which 162 presented with normal DHEA-S concentration and 147 with elevated one.
One hundred twenty-three women with increased DHEA-S were examined. The following symptoms were found: hirsutism $-$39%, menstruation disorders $-$23%, weight gain $-$8%, and the rest $-$12 different items. One hundred forty-two women with normal DHEA-S complained of: menstruation disorders $-$32.3%, hirsutism $-$21.7%, infertility 10.6%, elevated blood pressure 8.1% and the rest $-$20 different items.
From 44 men, 24 had increased DHEA-S levels. 33.3% of them complained of elevated blood pressure and 29.2% had adrenal tumour. Of 20 men with normal DHEA-S, 25% cases of adrenal tumour and 10% cases of elevated blood pressure were found.
The body weight of women with elevated DHEA-S was higher as compared with women with normal DHEA-S (mean$\pm$s.d.) 80.72$\pm$20.85 kg vs 72.54$\pm$22.41 ($P<0.005$) and analogically was the BMI. Concentration of DHEA-S in women with normal DHEA-S was lower than the same parameter in women with high DHEA-S: 5.7$\pm$3.05 micromol/l vs 12.49$\pm$3.81, ($P<0.001$). The DHEA-S ratio (patient's concentration of DHEA-S/highest level according to age) was 0.54$\pm$0.23 vs 1.3$\pm$0.35 ($P<0.001$) respectively. Testosterone concentration in above mentioned two female groups was 3.29$\pm$1.36 nmol/l vs 4.27$\pm$1.83 ($P<0.00001$).
The percentage of analysed women with normal and high DHEA-S concentration who underwent the diagnostic imaging was always the same. The abdominal ultrasonography was used for 26.1% and 27.6%, the adrenal computed tomography was used for 14.8% and 17.1% and the magnetic resonance imaging was applied for 2.1% and 2.4% of women with normal and increased DHEA-S levels, respectively.
This suggests that finding of even high DHEA-S concentration does not increase diagnostic imaging use and has no influence on the further clinical decisions.

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EP620

Potential role of the adrenolitic drug mitotane in the treatment of hepatocarcinoma (HCC): effect on cell proliferation in HCC cell lines

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HCC is one of the most common malignancies worldwide. Local approaches are generally preferred for patients whose disease is restricted to the liver. In patients with extrahepatic disease systemic therapy can be considered. Chemotherapy did not demonstrate convincing survival advantages in several trails for HCC patients. Presently, the kinase inhibitor sorafenib is the only approved systemic target therapy for the treatment of advanced HCC. Mitotane (dichlorodiphenildichloroethane or o,p'DDD), a chemotherapeutic agent, is the only drug approved for the treatment of advanced adrenocortical cancer (ACC) but no data are available concerning its cytotoxic role in different cancers, including HCC. The aim of this study was to evaluate the effect of mitotane on cell proliferation in HCC cell lines. HepG2, HuH-7, JHH-6, PLC/PRF/5 HCC cell lines, and H295R, ACC cell line, were used for the study. DNA assay was conduced to evaluate the rate of inhibition after 6 days of treatment with mitotane in a concentration ranging between 10^{-6} and 10^{-5} M, beneath the plasma mitotane levels achieved by ACC patients. Western blot analysis for PARP cleavage was performed to evaluate apoptosis. Mitotane was able to inhibit cell proliferation in a

dose-dependent manner with a maximal effect of 54%, at 10^{-5} M ($P<0.001$) and minimum effect of 35%, at $5*10^{-6}$ M ($P<0.01$) in PLC/PRF/5; maximal effect of 49%, at 10^{-5} M ($P<0.001$) and minimum effect at 32%, at $7.5*10^{-6}$ M ($P<0.001$) in JHH-6; maximal effect of 45.5%, at 10^{-5} M ($P<0.001$) and minimum effect of 20%, at $5*10^{-6}$ M ($P<0.001$) in HuH7; maximal effect of 36%, at 10^{-5} M ($P<0.001$) and minimum effect of 15.4%, at $5*10^{-6}$ M ($P<0.01$) in HepG2. In H295R, that were used as control, maximal effect was 82%, at 10^{-5} M ($P<0.001$) and minimum effect was 52%, at $5*10^{-6}$ M ($P<0.001$). In each HCC cell line mitotane induced apoptosis as demonstrated by PARP cleavage after 2 h of treatment. In conclusion, these preliminary data demonstrated the *in vitro* antiproliferative role of mitotane in HCC cell lines suggesting its potential use in the treatment of HCC.

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EP621

Body image perception in acromegaly is not associated with objective acromegalic changes, but depends on depressive symptoms

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Objective
Diagnosis of acromegaly is often delayed up to 10 years after disease onset despite obvious visual changes, *bone* and soft-tissue deformities. We hypothesized that a reduced sense of body perception in acromegaly, possibly mediated by psychiatric or cognitive alterations, might contribute to the delayed initiation of a diagnostic work-up.
Design
Cross-sectional study.
Methods
We investigated perceived body image by standardized questionnaires (FKB-20: Fragebogen zum Körperbild; FBeK: Fragebogen zur Beurteilung des eigenen Körpers) in 81 acromegalic patients and contrasted them to a) a clinical control group of 60 patients with non-functioning pituitary adenomas (NFPA) who lack severe facial and physical alterations and b) normative values of healthy controls. We further evaluated subjective body image perceptions in relation to objective acromegalic changes as judged by medical experts and psychiatric pathology such as depression and cognitive impairment.
Results
Acromegalic patients differed from NFPA patients in only one of the tested body image scales (vital body dynamics, FKB-20), although NFPA patients hardly exhibit any physical/bodily changes. Despite objective acromegalic changes as judged by medical experts, body image scales were similar, indicating a lack of subjective perception of the disease state. Depression was associated with worse scores of body image perception, while no associations were found between body image and cognitive decline, time of hormonal excess or treatment status.
Conclusions
Disturbed body image perception in acromegalic patients is unrelated to their objective appearance and similar to those of NFPA patients without major bodily changes. This fact might contribute to late disease diagnosis.

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EP622

The role of immunohistochemical assessment of somatostatin receptor expression in case of patients with well differentiated neuroendocrine neoplasms with symptoms of carcinoid syndrome and negative somatostatin receptor imaging

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Introduction
Over expression of somatostatin receptors (SSTR) is the characteristic feature of well differentiated neuroendocrine neoplasms (NENs). We present two patients with well differentiated NENs of the large intestine with negative SRS and without SSTR expression confirmed with immunohistochemical (IHCH) examination and symptoms of carcinoid syndrome with good clinical response to the therapy with long acting somatostatin analogs.
Case reports
53 years old man after right-sided hemicolectomy due to NETG2 (Ki67 5%) of the ileo-cecal valve with mesenteral lymph nodes and liver metastases. Patient presented with flushes. Therapy with long-acting somatostatin analog led to release of symptoms. Laboratory findings prior to the therapy: 5OHIAA 545.7 umol/24 h (N: 10-40) and CgA 112 ng/ml (N: 0-6). While somatostatin receptor scintigraphy (SRS) revealed increased pathological uptake only in the single mesenteral lymph node IHCH examination was performed. IHCH examination confirmed only low focal SSTR 1–5 expression.
Sixty four years old man with inoperable NETG1 (Ki67 $<2\%$) of the cecum with lymph nodes and liver metastases. Patient also presented with severe flushes. Therapy with long-acting somatostatin analog led to release of symptoms. Laboratory findings prior to the therapy: 5OHIAA 287 umol/24h and CgA 248 ng/ml. While SRS did not reveal any pathological uptake of the tracer in the lesions visualized with CT IHCH examination was performed. IHCH did not reveal any SSTR expression.
Conclusions
Presented case reports indicate the necessity of immunohistochemical assessment of the expression of SSTR in case of patients with well differentiated NENs and negative SRS results. Confirmed lack of SSTR expression make it necessary to change the imaging modalities and therapeutic options used for patients' management. However we would like to emphasize the observed release of symptoms of carcinoid syndrome in response to the therapy with long acting somatostatin analogs in case of presented patients.

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EP623

Dual face of sex-steroid hormones, estrogen and progesterone, on ovarian cancer metastasis via the regulation of epithelial-mesenchymal transition

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Ovarian carcinoma is the most deadly and leading cause of cancer death occurring in the female reproductive tracts. 17β-estradiol (E2) has long been considered as one of the effective causes of ovarian cancer through its actions via estrogen receptors (ERs). In contrast, progesterone (P4) offers protective effect against ovarian carcinogenesis. We predicted that P4 would inhibit the metastasis of BG-1 human epithelial ovarian cancer cells, which was induced by E2. In the present study, we confirmed that E2 increased BG-1 cell viability in a dose-dependent manner, while the effect of E2 was inhibited by the co-treatment of P4. Also we showed that P4 decreased the metastatic potential of BG-1 cells. P4 treatment clearly led to functional changes in cancer cell migratory and invasive propensity. We performed scratch assay and invasion assay to evaluate these functional changes. The results showed that P4 inhibited the migration and invasion activity of BG-1 ovarian cancer cells, which was increased by E2 via its receptor interaction. These alterations were also related with changes in the epithelial-mesenchymal transition (EMT) markers such as E-cadherin, Vimentin, and N-cadherin and EMT-associated transcriptional factors, Snail and Slug, too. Upon P4 stimulation, the expression of the epithelial marker E-cadherin was strikingly increased, whereas the expression of mesenchymal makers like N-cadherin and Vimentin was decreased. EMT-associated transcriptional factors, Snail and Slug, were also significantly down-regulated. These results indicate that P4 can inhibit the migration of BG-1 ovarian cancer cells by reducing EMT. Consequently, the present results represent that P4 is a potent substance which may inhibit the growth of human ovarian cancer cells and metastasis via regulation of PR. Therefore, the hormone therapy using P4 may be a clinically effective tool for the treatment of human epithelial ovarian cancer.

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EP624

Inferior petrosal sinus sampling in the differential diagnosis of ACTH-dependent Cushing's syndrome

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Introduction
Bilateral sampling of the inferior petrosal sinuses is an accurate test to diagnose Cushing's disease and distinguish it with the ectopic ACTH syndrome. The aim of the study was to review the petrosal sinus samplings carried out during last 10 years in our hospital.
Methods and material
The medical histories of patients admitted for suspected Cushing's disease in the last 10 years (from 2005 till 2015) were reviewed. There were selected the 18 cases of inferior petrosal sinuses samplings. The studied variables were: sex, age, previous Magnetic Resonance Image (MRI), results of the petrosal sinus sampling, complications, subsequent therapeutic attitude and evolution of the patient after the treatment.
Results
The mean age of the patients was 44.8 years and 83.3% were women. In 62% of patients MRI was normal. In 61.1% left lateralization occurred, and in 22.2% there was a bad catheterization of the sinus (most often the left). In 16 cases the pituitary origin was confirmed, in 1 case that source was rejected and in another case the origin is waiting for being determined. In the cases with pituitary origin, neurosurgery was carried out, except in one case in which conservative treatment was preferred. With regard to the complications, there were two cases of posterior bleeding and one case of binocular diplopia due to a stroke. Petrosal sinus sampling had to be repeated in one case of cyclical Cushing and in another case of recurrence without clear image in the MRI. There were 2 cases of postoperative recurrence and one case of not recovery after the surgery.
Conclusions
Inferior petrosal sinus sampling is a very useful technique in the diagnosis of Cushing's disease, with a low complication rate. The most frequent is the left lateralization, and it is more frequent a bad catheterization of the left sinus.

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EP625

Four cases of hyperparathyroidism-jaw tumor syndrome in young patients with primary hyperparathyroidism in Russia

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Introduction
Hyperparathyroidism-jaw tumor (HPT-JT) syndrome is a rare autosomal-dominant disorder caused by mutations in *CDC73* tumor suppressor gene. To date about 80 mutations in *CDC73* have been described.
Case reports
Four patients among a cohort of young patients (<40 y.o.) with primary hyperparathyroidism (PHPT) underwent next-generation sequencing (NGS) (Ion Torrent^{TM} PGM^{TM}, Thermo Fisher Scientific–Life Technologies, USA) using a custom-designed Ion AmpliSeq^{TM} gene panel.
Case 1. A female with PHPT manifestation at age 20, osteitis fibrosa cystica (OFC), kidney microlithiasis, serum Ca 4.09 mmol/l (2.15–2.55), parathyroid hormone (PTH) 2440 pg/ml (15–65) due to parathyroid carcinoma, and endometrial polyp at diagnosis. At age 26 her PHPT recurred as lung metastases of parathyroid carcinoma, requiring surgical intervention. Case 2. A female with PHPT manifestation at age 24, severe OFC, kidney microlithiasis, serum Ca 3.36 mmol/l, Ca^{2+}1.56 mmol/l (1.03–1.29), PTH 558.8 pg/ml due to parathyroid carcinoma. A patient had *positive* family history, with polycystic kidney disease in her mother. Case 3. A male with PHPT manifestation at age 22, severe OFC, serum Ca 3.9 mmol/l, Ca^{2+}1.84 mmol/l, PTH 1441 pg/ml due to parathyroid carcinoma. Case 4. A female with mild PHPT manifestation at age 30, serum Ca 2.94 mmol/l, Ca^{2+}1.24 mmol/l, PTH 125.1 pg/ml due to single parathyroid hyperplasia.
NGS revealed four heterozygous germline *CDC73* mutations, respectively: a novel nonsense mutation in exon 3 p.R91X, a nonsense mutation in exon 6 p.Q166X, a novel nonsense mutation in exon 7 p.R229X and a novel missense mutation in exon 8 p.R263C.
Conclusion
We describe four cases of HPT-JT in young patients with PHPT in Russia. 3 of 4 mutations are described for the first time. Occurrence of nonsense *CDC73* mutations in patients with parathyroid carcinoma and a missense mutation in a patient with parathyroid hyperplasia may reflect various degrees of parafibromin dysfunction.

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EP626

Efficiency of cabergoline suppressive therapy in young patients with prolactinoma

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Aim
The aim is to study the clinical and hormonal peculiarities of PROL (prolactinoma), manifesting in people under the age of 18 and monitoring the effectiveness of suppressive CAB (Cabergoline, Dostinex) therapy during 12 months period.
Materials and methods
The total study included 11 patients with PROL, manifesting in childhood. There were also examined 54 healthy volunteers (25 males and 29 females) aged 15–19 to determine the range of normal PRL blood values. It were assessed TSA (total secretory activity, ng/ml), PaSA (partial secretory activity, ng/ml/cm^3) and SpTG (the speed of tumor growth, cm^3/yrs).
Results and their discussion
At initial examination PRL blood levels was (Me = 89.6 ng/ml): macroPROL (Me = 52.3 ng/ml); microPROL (Me = 200.0 ng/ml). Before treatment PaSA in the whole group was (Me = 81.3 ng/ml/cm^3); in group with macro- and giant PROL(Me = 47.1 ng/ml/cm^3); with microPROL (Me = 98.9 ng/ml/cm^3) ($P < 0.05$). SpTG was (Me = 0.8 cm^3/yrs). Univariate regression analysis showed that the average therapeutic CAB dose was (Me = 1.0 mg/week); the average cumulative dose-(Me = 44.2 mg/yrs). A statistically significant reduction of PRL levels after 1 month of therapy was found, but the most positive effect was achieved after 3 months therapy ($n = 9$). The high efficiency of high start doses of CAB were confirmed by MRI: after 12 months of therapy the decreasing of the pituitary volume by 50% or more was marked in 5 patients, in 2 patients - by 30–49%, and 2 girls became pregnant.
Conclusion
Prescription of high start doses of CAB is safe and effective in treatment of PROL in children, as evidenced by the absence of side effects, the normalization of the pituitary-gonadal axis and growth hormone function, rapid sustained reduction in the concentration of PRL level to 5 percentile norm age in most patients (90.1%), statistically significant reduction of PaSA in all patients, decrease of pituitary tumors by 50% or more in 54.5% patients.
Keywords: prolactinoma, prolactin, children, adolescents, cabergoline (Dostinex) therapy.

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EP627

RSUME regulates tumorigenesis and metastasis in pancreatic neuroendocrine tumors

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The factors triggering pancreatic neuroendocrine tumor (PanNET) progression are largely unknown. Here we investigated the role and mechanisms of the sumoylation enhancing protein RSUME in PanNET tumorigenesis. Immunohistochemical studies showed that RSUME is strongly expressed in normal human

pancreas, in particular in β-cells. RSUME expression is reduced in insulinomas and is nearly absent in other types of PanNETs suggesting a role in PanNET tumorigenesis. In human pancreatic neuroendocrine BON1 cells, RSUME stimulates hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor-A (VEGF-A), which are key components of tumor neovascularisation. In contrast, RSUME suppresses nuclear factor-κB (NF-κB) and its target interleukin-8 (IL-8). Correspondingly, PanNET cells with RSUME knockdown showed decreased HIF-1α activity and increased NF-κB and IL-8 production leading to a moderate reduction of VEGF-A release as reduced HIF-1α/VEGF-A production is partly compensated by NF-κB/IL-8-induced VEGF-A. Notably, RSUME stabilizes the tumor suppressor PTEN, which is frequently lost in PanNETs and whose absence is associated with metastasis formation. *In vivo* orthotopic transplantation of PanNET cells with or without RSUME expression into nude mice showed that PanNETs without RSUME present reduced PTEN expression, grow faster and form multiple liver metastases. In sum, RSUME differentially regulates key components of PanNET formation suggesting that the observed loss of RSUME in advanced PanNETs is critically involved in PanNET tumorigenesis, particularly in metastasis formation.

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EP628

Potential role of vitamin D in restoring sensitivity to mTOR inhibitors in hepatocellular carcinoma (HCC): 1,25(OH)vitamin D (VITD) reverts everolimus (EVE) resistance in a HCC cell line

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HCC is a difficult-to-treat- cancer with poor prognosis. The recent EVOLVE-1 trial demonstrated that EVE did not improve overall survival in molecularly and clinically unselected patients with advanced HCC resistant to sorafenib treatment. In selected patients, the well-established antitumor effect of EVE could make this drug a potential adjuvant therapy. Unfortunately, the acquired resistance to this molecule due to the tumor adaptation to chronic drug use is a current challenge. VitD has been deemed as potential regimen to treat a variety of cancers alone or in combination with other drugs. The aim of this study was to assess the antiproliferative effect of the combined treatment with EVE and VitD in JHH-6, a model of HCC cell line, and to explore the role of VitD pre-treatment in the re-sensitization to EVE in JHH-6 cell line resistant to EVE (JHH-6 RR). JHH-6 RR were obtained after 4 months of treatment with EVE 10^{-8} M. Messenger and protein VitD receptor (VDR) expression was confirmed by RT-qPCR and immunofluorescence. DNA assay was established to evaluate the proliferation rate in basal and resistant cells after EVE treatment (from 10^{-14} M to 10^{-8} M) alone or in combination with VitD (10^{-7} M). In basal condition, EVE significantly reduced the proliferation index in a dose-dependent manner after 6 days of treatment and VitD did not improve EVE effect. JHH-6 RR cells no longer responded to EVE treatment but 12 h of VitD pre-treatment was sufficient to significantly restore the efficacy of EVE at concentration ranging from 10^{-14} M to 10^{-8} M with a minimum effect of 14% of inhibition at 10^{-14} M ($P<0.01$) and a maximum effect of 35.3% at 10^{-8} M ($P<0.001$). These preliminary data suggested the use of VitD to overcome the acquired resistance to EVE in HCC.

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EP629

Circulating levels of survivin in acromegaly

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Introduction
Acromegaly is a chronic disorder characterized by chronic growth hormone (GH) excess. In most of cases, GH hypersecretion is derived from somatotroph cell tumors. Survivin is a member of apoptosis protein family, which was recently showed to be expressed in different benign and malignant human tumors. A number of studies showed overexpression of survivin in pituitary adenomas. This study is intended to determine circulating levels of survivin in patients with acromegaly.
Methods
The study group was composed of 19 newly diagnosed patients with acromegaly. Concurrently, 19 healthy individuals were included in the study as control group. Serum survivin levels, GH, insulin like growth factor-1 (IGF-1) and, some other biochemical parameters as fasting glucose, creatinine, alanine aminotransferase, cholesterol, triglyceride, highdensity lipoprotein cholesterol, lowdensity lipoprotein cholesterol were measured in each subject. Correlation analysis was performed between survivin and GH, IGF-1.
Results
Serum survivin levels tended to be higher in acromegaly group, but this was not reach statistical significance ($P>0.05$). Serum survivin levels were comparable among acromegaly patients and controls. Neither GH nor IGF-1 correlated with serum survivin.
Conclusion
Larger scale studies are needed concerning the circulating levels of survivin in patients with acromegaly.

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EP630

A thymic carcinoid tumor causing Cushing syndrome in the setting of a multiple endocrine neoplasia syndrome type 1

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Introduction
Multiple endocrine neoplasia syndrome type 1 (MEN1) associated thymic carcinoids (Th-NETs) are rare and have poor prognosis. Cushing syndrome (CS) caused by Th-NET in MEN1 syndrome is extremely rare.
Case report
We report a case of a 55-year-old man with CS at presentation due to ectopic ACTH production in MEN1 syndrome. Thirty years ago, this patient had total gastric resection due to Zollinger-Ellison's syndrome and extirpation of two tumors of pancreas, when diagnosed with gastrinoma. Three years prior to the manifestation of CS, the patient was diagnosed with primary hyperparathyroidism (PHPT) and thus treated with parathyroidectomy, near-total cervical thymectomy and total thyroidectomy. Histological analysis revealed hyperplasia of parathyroid glands, papillary thyroid carcinoma and regular thymic morphology. Based on gastrinoma and PHPT, the patient was diagnosed with MEN1 syndrome and the germline mutation of MEN1 gene was detected. This time, the patient presented with weakness, weight loss and hypokalemia. MDCT of the thorax revealed the large mediastinal mass. Subsequently, the percutaneous biopsy of the tumor was done and the histopathological analysis revealed neuroendocrine carcinoma. The tumor was operated and the diagnosis of atypical thymic carcinoid with high proliferative activity index Ki 67 was confirmed. Eight months after the operation control MDCT revealed recurrent mediastinal tumor that was reoperated. Three months after the reoperation the patient developed mediastinal lymphadenopathy.
Conclusion
The presented case of MEN1 is peculiar because the majority of Th-NETs in MEN1 are nonfunctional and ectopic secretion of ACTH seldom occurs. Although Th-NET did not show immunohistochemical staining for ACTH, level of ACTH in the blood significantly decreased after the operation. Therefore, it is not impossible that the carcinoid tumor may secrete ACTH precursors and/or CRH instead of ACTH. The present case highlights the importance of screening MEN1 patients for thymic carcinoid and reinforce the notion that subtotal transcervical thymectomy was not effective profilactic tool in this case.

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EP631

Clinical characteristics, survival and prognostic factors of patients with adrenocortical carcinoma: a tertiary centre experience

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Adrenocortical carcinoma (ACC) is rare malignancy associated with poor prognosis. The aim of this study was to present clinical characteristics and survival of patients with ACC and to analyse the effect of prognostic factors on survival.
We retrospectively analysed 69 patients (46 female and 23 males) with pathologically confirmed ACC who were treated in our hospital between January 2005 and December 2015. The median age at diagnosis was 51,0 years (range 14–74), mean tumour size was 11.3 cm (range 3.1–30 cm) and median follow up duration was 36 month (range 3–240). Patients with hormone secreting ACC (43.5%) mainly presented with isolated Cushing's (21.7%), or combined with hyperandrogenism (20.3%); 56.5% of patients had non-functioning tumour. The group included 50% low-stage tumours (4 stage I, 29 stage II) and 50% high-stage tumours (no stage III, 33 stage IV). Metastatic disease was present in 33% of patient at the time of diagnosis and 39% had acquired metastasis. Surgical resection was performed in 89.9% of patients; 78.9% of patients were treated with mitotane, and 24% with chemotherapy. Median overall survival (OS) was 71 months (95%CI 41-100) with 5 year OS 51% (75.1% in stage II, 26% in stage IV). The 5-year OS for hormone secreting and nonsecreting tumours were 33% and 62%. Median disease free survival was estimated 6 months (95%CI 0–12). The results of univariante Cox regression analysis showed that gender, age and tumour secretory activity were significant variables with patient survival and surgical resection, disease stage and presence of metastatic disease at the diagnosis were highly significant. The results of multivariate Cox regression analysis showed that the surgical treatment (HR-7.16, 95%CI = 1.48-34.55, $P = 0.014$), age (HR-0.409, 95%CI = 0.177-0.947, $P = 0.037$), and presence of metastatic disease at the time of diagnosis (HR-0.217, 95%CI = 0.101-0.729, $P = 0.010$) were independent prognostic factors for survival.

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EP632

Evaluation of the incidence and clinical characteristics of glucose metabolism alterations during the follow-up of surgically treated insulinomas

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Introduction
The incidence of glucose metabolism alterations during the follow-up of surgically treated insulinomas is largely unknown. Our aim was to evaluate the incidence, and the clinical characteristics, of diabetes and prediabetes in this population.
Methods
We retrospectively analyzed the cases diagnosed as insulinomas in a Central Hospital in Portugal in the period between January 1980 and December 2015.
Results
We identified 19 patients, 68% women, with a median age at onset of symptoms of 49 years. Enucleation of the tumor was performed in 4 cases and the remaining 15 were submitted to partial pancreatectomy. In one patient, the surgery did not remove the tumor and so total pancreatectomy was performed. All tumors were solitary, with a median diameter of 1.8 cm. Ten tumors were located at the head of the pancreas, 4 at the body, 4 at the tail and 1 at the uncinate process. The median of follow-up was 48 months, with only 4 patients with a follow-up inferior to 6 months because of loss of follow-up or recent intervention. A total of 9 patients presented glucose metabolism alterations on follow-up. Four patients presented diabetes in the immediate postoperative period, 1 presented diabetes 4 months after surgery, 3 presented diabetes 10–12 years after surgery and 1 patient present prediabetes 54 months after surgery. The mean age at diagnosis of glucose metabolism alterations was 54 years. Regarding treatment, 3 patients were treated with insulin, 3 were with oral antidiabetic drugs, 1 with insulin and oral antidiabetic drugs and 2 with lifestyle interventions. Concerning microvascular and macrovascular complications, only 1 patient presented microalbuminuria.
Conclusion
Glucose metabolism alterations are a frequent complication during the follow-up of insulinomas. Prevention, early diagnosis and treatment of diabetes in patients with surgically treated insulinomas must be a priority during the follow-up of these patients.

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EP633

Mechano growth factor (MGF) expression increased in secondary compared to primary foci in well neuroendocrine neoplasms

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Introduction
Insulin-like growth factor-I (IGF-I) has a role in cell proliferation, differentiation, migration, and survival. By alternative splicing different IGF-I mRNA transcripts as IGF-IEc (mechano growth factor, MGF) or IGF-IEa variants are produced. MGF induces muscle hypertrophy and implicated in the pathophysiology of various types of cancer. Aim of the study was to investigate the role of MGF in the pathophysiology of neuroendocrine neoplasms (NENs).
Methods
We have used immunohistochemistry in 39 specimens of patients with NENs to show the expression status of MGF. Proliferation index ki-67 MIBI (%) was also evaluated. Specimens were divided in three subgroups: in 15 samples Ki-67 was $\leq 2\%$, in 15 2-20%, and in 9 $> 20\%$.
Results
Specimens from 8 gastric, 11 pancreatic, 2 appendiceals, 7 small intestine, 1 colic and 1 retrosigmoidal, 1 gallblader and 3 lung NENs, 2 undifferentiated unknown primary (UPO), 3 UPO were studied. No MGF staining was found in 19 specimens while cytoplasmatic staining was found in 20 specimens: focal staining was seen in 13 (65%) and diffuse in 6 (30%) and dot like in 1 (5%). Ki-67 and MGF expression were positively correlated in all the samples studied reaching a trend difference ($r = 0.29$, $P = 0.07$); the same correlation was seen only in the subgroup with $\leq 2\%$ ($r = 0.48$, $P = 0.07$) but not in the other subgroups studied. MGF staining did not differ between primary and secondary foci in total sample population but staining was increased in secondary compared to primary foci in samples with ki-67 2–20%.
Conclusions
Our preliminary data indicate that MGF expression may have a limited role in the pathophysiology of NENs. Further studies will shed light to the exact role of MGF in NENs.

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EP634

Hypoglycaemia unawareness – a challenge in the management of a Von Hippel-Lindau patient

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Background
The key physiologic defences against hypoglycaemia are the decrease in insulin and the increased secretion of glucose counterregulatory hormones, namely glucagon and epinephrine. The absence of warning signs of impending neuroglycopenia is known as hypoglycaemic unawareness.

Case report
Male, 26 year-old, without relevant medical history and with normal body mass index, presented with hypertension, palpitations and diaphoresis. Clinical suspicion of pheochromocytoma was confirmed by abdominal CT scan and 24-hour urinary catecholamine levels: normetanephrine 8304 µg/24 h (ref.88–444), norepinephrine 2511 µg/24 h (ref.15–80) and vanillylmandelic acid 33.5 mg/24 h (ref.1.4–6.5). He was diagnosed with bilateral pheochromocytoma and underwent bilateral adrenalectomy without perioperative complications (both benign tumours in anatomopathological study). Treatment with hydrocortisone and fludrocortisone was then initiated. Genetic testing revealed a missense mutation (arg167gln) at exon 3 of VHL gene compatible with Von Hippel-Lindau disease. His family history revealed pheochromocytoma in 3 members (mother, uncle and cousin), but genetic testing was not previously performed in any of them. Six years later the patient developed a pancreatic endocrine tumour of uncertain behaviour and was submitted to proximal pancreatectomy. *De novo* pancreatic lesions appeared 4 years later, leading to a total pancreatoduodenectomy. Postoperatively the clinical management of secondary diabetes was very difficult. He was treated with multiple daily insulin injection regimen (detemir twice daily plus prandial lispro). Given the absence of adrenal cortisol and catecholamines secretion, and of glucagon secretion by the pancreas, his hypoglycemic counterregulatory responses were impaired, leading to severe and recurrent hypoglycaemia unawareness. These episodes frequently had severe neuroglycopenic symptoms, seizures and loss of consciousness requiring glucagon or parenteral glucose therapy. Currently he is learning carbohydrate counting with symptoms improvement and use of an insulin pump was proposed.
Conclusion
This case report highlights the difficult and challenging management of hypoglycaemia unawareness in a patient with Von Hippel-Lindau disease previously submitted to bilateral adrenalectomy and total pancreatectomy.

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EP635

Thyrotoxicosis leading to adrenal crises reveals primary bilateral adrenal lymphoma – case report

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Introduction
Amiodarone use may be associated with secondary severe organ dysfunction. Thyrotoxicosis develops in 15% cases. Primary bilateral adrenal lymphoma is a rare malignancy. If frequently presents bilaterally and with symptoms of adrenal insufficiency. Symptomatology for both conditions is nonspecific, especially in the elderly, and a high suspicion index is necessary for appropriate diagnosis.
Case report
A 78 year old female presented to the emergency department due to confusion, nausea and vomiting. She had history of Diabetes Mellitus, Hypertension and atrial fibrillation. She had been recently treated for urinary infection associated with vomiting and acute hypochloremic hyponatemia. Leucocyturia persisted and due to TSH 0.01 uU/ml, fT4 68 (10–18) pmol/l, fT3 6.34 (4–8) pmol/l, the patient was admitted to the Endocrinology ward. Further evaluation supported amiodarone-induced type 2 thyroiditis. Despite appropriate therapy, thyroid function further aggravated. She synchronously developed a septic state associated with nosocomial pneumonia. Hemodynamic instability, hyponatremia, hypoglycemia and vomiting raised the suspicion of concomitant adrenocortical insufficiency. Fluid resuscitation and hydrocortisone led to clinical improvement, with high dose glucocorticoid requirements. Adrenal insufficiency was admitted. Abdominal echography showed right and left justa-renal heterogeneous solid nodules (6.6 and 7 cm respectively) and left pleural effusion. Fluid analyses was negative for malignant cells. Thoracoabdominal contrasted-tomography suggested an endobronchic primary, also suspected during bronchofibroscopy, with hepatic and adrenal secondary deposits. The left mass compressed the ureter and seemed to penetrate the kidney and vascular structures. 24 h-Urinary metanephirnes were normal but the adrenals were not accessible to biopsy. After a period of seemingly favourable evolution the patient died. Autopsy confirmed primary adrenal non-hodgkin lymphoma.
Conclusion
Primary adrenal lymphoma is a rare cause of adrenal insufficiency but progression is often fast and fatal. This entity must integrate the differential diagnosis, especially in the elderly patient.

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EP636

Hyperparathyroidism-jaw tumour syndrome in Adolescence

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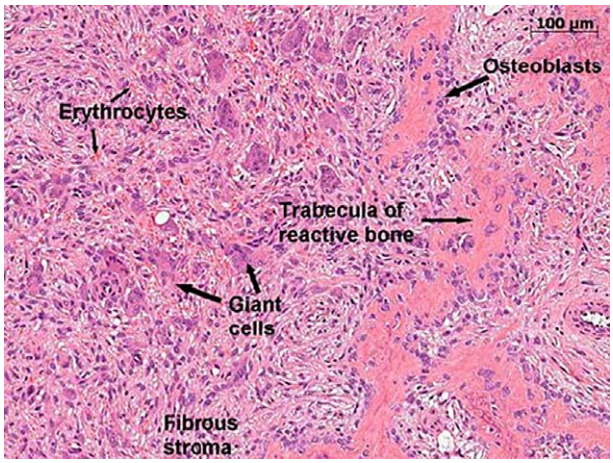
Introduction
The hyperparathyroidism-jaw tumour syndrome is a rare autosomal, dominantly inherited disorder characterized by neoplastic or cystic lesions in parathyroid gland, jaws and the kidneys. With approximately 200 reported cases in literature this condition remains a challenge both diagnostically and in guiding further management.
Case report
Seventeen year old scholar was seen by the maxillofacial department at Medway Hospital with 2 painless swellings in his mouth, present for 2–3 months. Dental X-ray (OPG) showed resorption of bone at the sites of the swellings. Routine blood tests showed serum corrected calcium of 4.12 mmol/l (16.48 mg/dl), plasma PTH of 628 ng/l (10–65) and normal renal and thyroid functions. He had experienced significant polyuria and polydipsia for at least 2–3 years prior to this presentation. A CT scan of neck showed 2.5 cm × 2 cm right lower lobe parathyroid adenoma; ultrasound scan of his kidneys was normal. The tumour was resected: histology confirmed a benign parathyroid adenoma. There was no family history of any tumours.
Post-operatively the patient developed severe and prolonged 'hungry bone syndrome'. He required prolonged HDU admission for intravenous calcium infusions despite high dose Alfacalcidol (4 mcg/day) and then oral calcium supplement at home. These are being reduced stepwise, at present as plasma PTH remains suppressed.
Soon after the parathyroidectomy the maxillary swellings were biopsied. The histology showed spindle cells, osteoclast giant cells and substantial bone formation.



Genetic tests showed the characteristic mutation in the CDC73 gene, confirming the diagnosis of the 'hyperparathyroidism-jaw tumour syndrome'.
Discussion
On review of literature, in HPT-JT syndrome, jaw tumours are mostly composed of fibro cellular tissue without giant cells. In contrast our patient had multiple giant cell granulomas. In most cases, an affected person has one parent with the condition. This case illustrates consideration of genetic testing in younger patients presenting with primary hyperparathyroidism.

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EP637

Analogues of somatostatin in preoperative treatment of rare NET

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Analogues of somatostatin are widely used in management of neuroendocrine tumors. The "classic" indications for this treatment are: acromegaly and NETs of midgut to diminish symptoms caused by hormonal overproduction and slow down

the tumors' growth. However we consider the use of this medication also in the other cases in which we confirm the presence of somatostatin receptors in tumor by somatostatin receptor scintigraphy.
We would like to present three cases of symptomatic, resistant to pharmacological therapy, neuroendocrine tumors, in which only preoperative treatment with long-acting Octreotide enabled successful surgery.
Case 1. 40-years-old man with profound hypoposphataemia caused by GF-23 secreting tumor in the right maxillary sinus (glomangiopericytoma). The treatment with phosphorus and active vitamin D metabolites was ineffective. The improvement of phosphorus concentration was necessary for safety of anesthesia and proper function of respiratory muscles after the extubation, so waiting for surgery patient was treated with long acting Octreotide, and phosphorus level increased to proper values.
Case 2. 44-years-old woman with paroxysmal tachycardia and hypertension up to 200/140 caused by catecholamine secreting tumor localized in mediastinum (paragandglioma). The preoperative treatment with alpha, beta and calcium channel blockers and also ACI and diuretics was ineffective. On the second day after the Octreotide injection the blood pressure fell down and directly before surgery only the alpha and beta blockers were used.
Case 3. 50-years-old woman with paroxysmal sweating and hypertension up to 240/140 caused by pheochromocytoma of the left adrenal gland. The treatment as in the case above – also ineffective; she was twice disqualified from the operation due to blood pressure > 200/120. After the Octreotide injection the blood pressure fell down, however the reduction of the medications before surgery was impossible.
These cases exemplify possibility of unconventional use of long acting somatostatin analogues in preoperative treatment of rare neuroendocrine tumors.

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EP638

A case of tumor-induced osteomalacia in which recurrence and bilateral lung metastases occurred following tumor resection

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A 32-year-old woman with a nine-year history of right hip pain was admitted after she became unable to walk. Based on marked hypophosphatemia as indicated by serum phosphate of 1.4 mg/dl, intactPTH;29 pg/ml, TmP/GFR;1.14 mg/dl, and fibroblast growth factor 23 (FGF23) increased to 713 pg/ml, tumor-induced osteomalacia (TIO) was diagnosed. Systemic venous sampling of FGF23 performed for locating the tumor revealed an elevated level of 1600 pg/ml in the right femoral vein, and MRI of the right leg showed a tumor 26mm in size on the dorsal side of the right knee. In June 2011, the tumor in the right knee was surgically resected. Hypophosphatemia promptly improved following surgery, and FGF23 also returned to normal. The patient became able to walk independently and was able to reintegrate into society. The pathological diagnosis was phosphaturic mesenchymal tumor. However, serum phosphate again decreased in April 2013 to 2.6 mg/dl. FGF23 also increased to 221 pg/ml. Leg MRI was performed, and a tumor 25 mm in size was again detected on the dorsal side of the right knee. FDG PET/CT revealed significant uptake that was consistent with the tumor on the dorsal side of the right knee, as well as multiple nodules seen in both lung fields on CT. The tumor in the right knee was surgically resected in September 2013. However, FGF23, which was elevated to 1500 pg/ml preoperatively, remained high postoperatively at 950 pg/ml. Hypophosphatemia also did not improve, and phosphate treatment is being continued. Because she tested positive for somatostatin receptor 2 on RT-PCR using a resected sample, treatment using a somatostatin analog is being considered.
Summary: Malignant TIO is extremely rare, and no effective treatment exists for this condition. We herein report our experience with a case of malignant TIO in which recurrence and metastases to both lungs were observed two years after tumor resection.

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EP639

Effects of genetically engineered human neural stem cells expressing cytosine deaminase and interferon-beta on the growth of lymph node metastatic colorectal adenocarcinoma

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Genetically engineered stem cells may be advantageous for gene therapy against various human cancers due to their inherent tumor-tropic properties. In this study, we employed human neural stem cells (HB1.F3; hNSCs) transduced with genes expressing Escherichia coli cytosine deaminase (HB1.F3.CD) and human interferon-beta (HB1.F3.CD.IFN-β) as a treatment strategy for human lymph node metastatic colorectal cancer. CD can convert the prodrug 5-fluorocytosine (5-FC) to its active chemotherapeutic form, 5-fluorouracil (5-FU), which induces a tumor-killing effect through DNA synthesis inhibition. IFN-β also slightly inhibits tumor growth by inducing apoptotic process. In RT-PCR analysis, we confirmed that HB1.F3.CD cells expressed CD gene and HB1.F3.CD.IFN-β cells expressed both CD and IFN-β genes. A modified transwell migration assay showed that HB1.F3.CD and HB1.F3.CD.IFN-β cells selectively migrated toward SW-620 human lymph node metastatic colorectal cancer cells. When co-cultured with HB1.F3.CD or HB1.F3.CD.IFN-β cells in the presence of 5-FC, the viability of SW-620 cells were significantly reduced. In a xenografted mouse model, hNSCs treatment significantly inhibited the growth of tumor mass and the expression of proliferative marker without any harmful effects on the animals. In addition, fluorescent-labeled hNSCs could be found in the excised tumor mass. The tumor-tropic properties of these engineered hNSCs were found to be attributed to chemoattractant factors secreted by SW-620 cells, SDF-1, c-kit, uPAR, uPA and CCR2. Consequently, the present results represent that engineered hNSCs and prodrug treatment inhibits the growth of human lymph node metastatic colorectal cancer. Therefore, hNSC therapy may be a clinically effective tool for the treatment of human lymph node metastatic colorectal cancer.

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EP640

gp91-phox in differential diagnosis of hyperplastic lesions in parathyroid gland

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Introduction
Glycoprotein gp91-phox is an essential component of the NADPH oxidase. The superoxide-generating NADPH oxidase is present in phagocytes, neuroepithelial bodies, vascular smooth muscle cells and endothelial cells. It includes a membrane-bound flavocytochrome containing two subunits, gp91-phox and p22-phox. gp91-phox is a significant element of the membrane-bound oxidase of phagocytes that generates superoxide. It is the terminal component of a respiratory chain that transfers single electrons from cytoplasmic NADPH across the plasma membrane to molecular oxygen on the exterior. This glycoprotein participates in the regulation of cellular pH and is blocked by zinc. gp91-phox could be potentially useful in diagnosis of primary hyperparathyroidism which is one of the most common endocrine disorders caused by adenoma (80%), hyperplasia (15%) and carcinoma (5%).
Methods
For immunohistochemistry, parathyroid specimens of patients undertaken surgery due to primary hyperparathyroidism caused by adenoma and primary hyperplasia were investigated. Normal healthy tissues served as a control. Frozen sections were incubated with purified mouse monoclonal antihuman antibodies anti-gp91-phox. The dilution of the primary antibodies was 1:50 and was verified in a series of pilot experiments. The immunohistological investigations were performed by the BrightVision method from ImmunoLogic. The sections were counterstained with Mayer's haematoxylin. The number of positively stained cells were counted and expressed as a mean value of at least 10 high power fields (400×).

Results
Positive gp91-phox immunoreaction was significantly increased in parathyroid adenomas, whereas gp91-phox was up-regulated in parathyroid hyperplasias compared to healthy parathyroid glands. Positively stained cells were localized in the well vascularized region of the parathyroid nodule.
Conclusions
The immunohistochemical assessment of gp91-phox complements conventional methods in distinguishing between parathyroid hyperplasia and adenoma, however, there is an overlap between these parathyroid lesions and there is no definite cutoff value.

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EP641

Myelolipoma in a rheumatoid arthritis patient – report of a case

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Introduction
Adrenal myelolipoma is an extremely rare benign adrenal tumor. Adrenal myelolipoma is characterized by the presence within the adrenal gland of mature adipose tissue and active bone marrow elements. Owing to their non-functional nature most cases are incidental, either at autopsy or through computer tomography scan. Occasionally the lesions attain a large size to become clinically apparent. Seropositive rheumatoid arthritis is a disorder affecting approximately 1% of the population.
Aim
The aim was to describe the case of a patient with an adrenal myelolipoma who later developed seropositive rheumatoid arthritis.
Case report
A male patient, aged 42, presented with bilateral symmetric polyarthitis affecting the small joints of the hands, knees and shoulders. He had morning stiffness lasting >1 h. Rheumatoid factor was positive and anti-CCP antibodies were positive. The patient had a history of an adrenal myelolipoma, which was discovered incidentally at the age of 31 and was removed surgically. The patient underwent further evaluation for polyarthritis and the diagnosis of rheumatoid arthritis was made. Methotrexate was administered in a weekly regimen.
Conclusion
Adrenal myelolipoma is a rare benign tumor of the adrenal. Many cases do not require surgical treatment. In the case described, myelolipoma was surgically removed, the patient later incidentally developing severe seropositive rheumatoid arthritis.
Reference
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EP642

A case of multiple endocrine neoplasia type 2A with a C634A mutation and a L769L polymorphism in RET proto-oncogene

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Introduction
Multiple endocrine neoplasia type 2A (MEN2A) is an autosomal dominant condition characterized by the presence of a medullary thyroid carcinoma, pheochromocytoma and hyperparathyroidism. The germ-line mutations of the RET proto-oncogene cause MEN2A. Specific RET mutations correlate with the onset of age and the aggressiveness of the disease. It has been reported that polymorphisms of RET may have a modifier effect on the presentation.
Case report
We experienced a case of 27-year-old woman who presented with palpitation and orthostatic hypotension and was diagnosed with bilateral pheochromocytoma. On evaluation, each one medullary thyroid carcinoma in both thyroid lobes and a parathyroid adenoma were found. Genetic testing detected a mutation in codon 634 (C634A, 1900T>C) at exon 11 and a polymorphism in codon 769 (L769L, 2307T>G) at exon 13 of the RET proto-oncogene. Her father died in a car accident in youth. Her mother remembered patient's aunt (father's sister) living in Canada, had never seen, had total thyroidectomy in youth.
Conclusion
Patients of MEN2A with a C634A mutation and a L769L polymorphism in RET proto-oncogene may be presented in younger age and have poor prognosis.

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EP643

Multiple endocrine neoplasia type 1: an underdiagnosed disorder

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Introduction
Multiple Endocrine Neoplasia type 1 is an underdiagnosed autosomal dominant disorder, with inter and intrafamilial variability without a genotype-phenotype correlation.
Case report
A young female (born in 1986) presented with galactorrhea and secondary amenorrhea in 2002, and investigation revealed a prolactinoma. Her brother (born in 1982) presenting gynecomastia and erectile dysfunction at age 21, was also diagnosed with prolactinoma. The female was referred to our appointment in 2013 due to pancreatic tumors, treated with cabergoline. Laboratory: prolactin 44 ng/ml [1.9–25], GH 25.8 ng/ml [0.06–5], IGF1 1.208 ng/ml [117–329], OGTT: GH basal/nadir 18.5/12.1 ng/ml; calcium 11.3 mg/dl [8.4–10.2], PTH 95 pg/ml [10–70]. VIP, gastrin, glucagon, insulin, chromogranin-A: normal. Thoraco-abdominopelvic-CT: lesions on pancreatic tail with 40×27×36 mm and 7 mm; heterogeneous liver mass 48×49×51 mm. Octreoscan: two focus of hyperfixation in pancreas. Biopsy: pancreatic neuroendocrine tumor with liver infiltration. MRI revealed diffuse pituitary hyperplasia. Subtotal parathyroidectomy, distal pancreatectomy and liver metastasectomy were performed. Histopathologic examination: pancreatic neuroendocrine tumors, Ki-67<2%; secondary infiltration of liver. After surgery: IGF1 424 ng/ml, OGTT basal/nadir 0.6/0.25 ng/ml, calcium 10.3 mg/dl. Octreoscan and abdominal-CT were negative 4 months later. MRI revealed regression of pituitary hyperplasia. GHRH immunohistochemical study on pancreatic tumors was negative. Family study was performed: brother underwent total pancreatectomy due to non-functioning pancreatic tumors; 60-year-old father: evidence of bronchopulmonary carcinoid tumor, non-functioning pancreatic tumors, primary hyperparathyroidism. Family DNA sequence analysis of the *MEN1* gene identified a germinal mutation on exon 2: deletion of 4bp involving codon 88, not yet described.
Conclusions
The occurrence of *prolactinoma* at a young age in two siblings should have prompted a genetic basis investigation, possibly implying a different prognosis in this family. The diagnosis of acromegaly in the female patient, its etiology and pituitary imaging need to be further elucidated.

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EP644

A case of recurred parathyroid carcinoma with multiple lymph node metastasis: concurrent with papillary thyroid cancer

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Parathyroid carcinoma, a rare endocrine malignancy, accounting for only 1–2% of patients with primary hyperparathyroidism (HPT). In addition, a few case have been reported coexistence of parathyroid carcinoma and papillary thyroid cancer. Here, we present a case of recurred parathyroid cancer with multiple lymph node metastasis. A 57-year-old women was presented with high serum calcium level (14.4 mg/dl) in medical check-up. Hyperparathyroidism was considered to be the reason of hypercalcemia because of significantly increased parathyroid hormone (PTH, 1275 pg/ml) levels. Neck ultrasonography (US) at that time showed 0.7∼4.5 cm sized multiple thyroid nodules at both lobes. Tc-99m sestamibi scan

demonstrated marked increased radiotracer activity in the region of the inferior left lobe of the thyroid. She underwent left parathyroidectomy, total thyroidectomy and central compartment lymph node dissection. Histopathology revealed that the 4.5 cm mass adjacent to the left thyroid lobe was a parathyroid carcinoma with evidence of vascular invasion. As well, she was found to have a 1.3 cm papillary thyroid cancer in the right thyroid lobe and a 1.5 cm follicular adenoma in the left side. Serum calcium and PTH returned to the normal range after surgery, but she developed a recurrence 2 years later (2 × 0.5 cm, isoechoic nodule at left operative bed). Re-exploration revealed recurrence at the previous surgery site. Positron emission tomography-computed tomography (PET-CT) revealed intense hypermetabolic lesions on Left operative bed and cervical level VI, VII, and whole body bone, which were thus thought to be local recurrence of parathyroid cancer. At third operation, 5×9 cm sized soft, well demarcated mass was found at previous op site, and enlarged lymph nodes were detected at level coincide with PET-CT image. Pathologic report confirmed diagnosis of metastatic parathyroid carcinoma.

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EP645

Postprandial hypoglycemia in the presence of insulinoma – case report

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Background and aim
Although insulinoma typically causes fasting hypoglycemia, postprandial hypoglycemia occasionally reported in these patients. We aimed to report a rare case of insulinoma who atmitted to outpatient clinic with postprandial hypoglycemia.
Case report
A 31-year-old woman was admitted to outpatient clinic with postprandial hypoglycemia. Capillary blood glucose levels were found 25 and 27 mg /dl during typical hypoglycemic symptoms such as blurred vision, palpitations, and weakness. These hypoglycemic episodes occured about 2 hours after eating and eliminated with sugary foods. The symptoms of hypoglycemia were decreased with diet modification and increase in meal frequency. After 6 months, hypoglycemic symptoms reappeared by exercise and delayed meals. Her physical examination was normal except hepatomegaly. Blood samples were taken after an overnight fast and serum blood glucose 91 mg/dl, insulin 5.64 uU/ml, kortizol 19.3 µg/dl, and c-peptide 1.14 ng/ml. Hb A1C, thyroid function tests, insulin like growht factor-1, anti- insulin antibody, liver and renal function tests were in normal range. Prolonged- 72 hours- fasting test was performed. After 56 hours, inappropriately high serum insulin concentration was showed during hypoglycemia. Endoscopic ultrasound showed 9,8 mm hypoechoic lesion in the head of the pancreas. Present findings suggested the presence of insulinoma. Operation was planned but not yet carried out.
Conclusions
Fasting hypoglycemia is the common clinical manifestation of insulinoma. However, postprandial hypoglycemia rarely observed in this situation. It is important to consider insulinoma as a cause of postprandial hypoglycemia.

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EP646

A novel mutation of the menin gene in a family with multiple endocrine neoplasia type 1

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Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant genetic disorder characterized by parathyroid adenomas, enteropancreatic endocrine tumors and anterior pituitary adenomas. It is caused by inactivating mutations of the *MEN1* tumor suppressor gene, encoding menin (chromosome 11q13). A large family with several members affected were evaluated for clinical and genetic characteristic of MEN1.

The index male patient (42 yr) presented with symptoms of hypoglycemia and hypercalcemia. Abdominal MRI revealed a mass at distal pancreas. Distal pancreatectomy was performed. Glucagon, synaptophysin and chromogranin were positive on immunostaining, but insulin was negative. Total parathyroidectomy was performed and on pathology, parathyroid hyperplasia was diagnosed. His pituitary MRI and hormone levels were normal. Because the index patient had developed two tumor types associated with MEN1, genetic analysis was performed. Genetic analysis identified a novel mutation on chromosome 11q13.1 which was c.218insGGCGGCAC heterozygote.
Case 2 (21 yr) is the son of index case. He had primary hyperparathyroidism. Total parathyroidectomy was performed. Two neuroendocrine tumor was defined at pancreas.
Case 3 (45 yr) is the sister of index case. She had primary hyperparathyroidism with parathyroid hyperplasia.
Case 4 (50 yr) is the other sister of index case. She had primary hyperparathyroidism. She has four non-fonctional neuroendocrine tumor on pancreas, all of which are stable in size.
Case 5 (27 yr) is the son of case 4. He had primary hyperparathyroidism. He went to surgery for parathyroid hyperplasia. He is waiting for pancreas surgery for 21 mm pancreatic neuroendocrine tumor.
Case 6 (24 yr) is the daughter of case 4. Despite in-vitro fertilization methods, she was unable to conceive. After parathyroid surgery, she became pregnant spontaneously.
We conclude that MEN1 in this large family was associated with a previously unidentified mutation of the menin gene. MEN1 genetic analysis facilitates clinical management and provides benefits to patients and families with MEN1.

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EP647

Multiple liver-directed therapy including theraspheres for recurrent metastatic jejeunal carcinoid tumor

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Introduction
Majority of patients with neuroendocrine tumors (NET) harbor hepatic metastases at presentation, posing therapeutic challenge. Multiple liver-directed treatment modalities have been employed with variable success. Herein is presented successful outcome in a patient whose recurrent metastatic liver metastases from NET was managed using multidisciplinary approach.
Case report
We present long-term18-years course of a patient with liver metastases from midgut carcinoid. She had successful outcome using repeated surgery, radiofrequency ablation, octreotide, and therasphere therapy in succession. Minimally invasive therapy of therasphere using transarterial yettrium 90 can be used safely for recurrent hepatic metastatic neuroendocrine tumor.
A 61-year old female with hepatic metastases from non-functioning jejunal carcinoid had resection of 25 cm of small bowel containing 5 cm of carcinoid tumor, resection of 5 cm mesenteric metastatic lymph node, resection of hepatic segments 3 and 4 containing the tumor measuring 7.5 cm. This was followed 10 years later by resection and radioablation of recurrent hepatic metastases. Two years later MRI and octreoscan revealed multiple liver metastases, with abnormal circulating CGA (100 ng/ml; Ref. <93) and received on going monthly octreotide injections. Four years later liver metastases progresses with additional lesions. Liver biopsy revealed metastatic neuroendocrine grade 2 tumor (Ki-67 index 4.5%). In view of her diabetes PRRT was not given; instead she received therasphere therapy. 90 yttrium, tumor dose 164 Gy was injected into left hepatic artery. Patient tolerated it well with no side effects. A year later MRI showed resolution of tumor with atrophic left lobe, and hypertrophic right lobe.
Conclusion
Majority of patients with neuroendocrine tumors present with liver metastases. Despite therapeutic challenge; hepatic metastases can be managed by a combination of surgical, radioablation, medical and radioembolization therapy using Yttrium 90.

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EP648

Clinical case of rare adrenal tumor – schwannoma

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Background
Schwannoma (Sch) is a rare peripheral nerve sheath tumor comprised entirely of neoplastic Schwann cells. Adrenal Sch are extremely rare. Most adrenal Sch are incidental, and patients with Sch may not have any complaints. Here we present the clinical case of giant adrenal Sch, which caused hematuria and had indiscriminating organ origin on MRI.
Clinical case
Woman, 58 y.o., was consulted by urologist because of painless macrohematuria. Abdomen MRI was performed, it revealed giant mass (14×13×11 cm) with cystic degeneration and calcification, which was located in retroperitoneum. Patient was consulted by endocrinologist, typical testing was done. Plasma cortisol after 1-mg DST was 48 nmol/l (<50 nmol/l), 24-hour urinary fractionated metanephrines were 59 μg (<320 μg), 24-hour urinary fractionated normetanephrines were 144 μg (<390 μg). Because of heterogeneous structure, normal level of catecholamine metabolites, absence of known cancer in anamnesis, adrenocortical carcinoma was strongly suspected. Right laparotomic adrenalectomy was performed without any intraoperative and postoperative complications. Immunohistochemical assay showed that tumor cells were positive for S-100 protein and vimentin, which was consistent with schwannoma. Since Sch may be associated with syndromic diagnosis of schwannomatosis or neurofibromatosis type 2, the genetic testing was performed. No any associated mutations were revealed. Therefore, the diagnosis of sporadic adrenal Sch was established. Further follow up during a year didn't show signs of recurrence.
Conclusions
Firstly, because of rarity of adrenal Sch, it is of great importance to describe any case in order to understand true prevalence and natural history of the disease. Secondly, Sch as may be discovered incidental, as may be non-specific symptomatic. In latter case, it is very important that different specialists tightly interact with each other. Thirdly, the preoperative diagnosis of Sch is impossible in most cases, that's why strict following to diagnostic protocols is demanded in order to exclude all other causes of incidentalomas firstly.

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EP649

The contribution of fast test in the diagnostic approach of hypoglycemia in non-diabetic patients

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Introduction
Hypoglycemia is an uncommon complaint among non diabetic patients. The aim of this study was to determine the role of fast test in the diagnostic approach to hypoglycemia.
Patients and methods
It was a retrospective study, including 40 patients admitted in the endocrinology department from 2001 to 2015 for hypoglycemia signs. We collected clinical and biologic data, fast test results and final diagnosis of hypoglycemia.
Results
The mean age was 46 years [±19.1]. 57.5% of the patients were women. The mean duration of symptoms was 33 weeks [±55]. Sixty five percent had neuroglycopenic signs. The mean capillary blood glucose was 0.38 g/l [±0.15]. Two patients had adrenal insufficiency, and 3 had sulfamid induced hypoglycemia. Supervised fast test was undertaken in 20 patients. In 2 patients hypoglycemia occurred in the first 24 h, and final diagnosis was insulinoma in both cases. In 3 patients fast test was stopped because of non hypoglycemic symptoms, and 5 patients stopped voluntarily the test. five hours glucose tolerance test was performed in 25 patients: Reactive hypoglycemia was diagnosed in 77.5%; 68% had glucose tolerance abnormalities.
Conclusion
Insulinoma was diagnosed in 5% of the patients admitted for hypoglycemia. The two cases was identified by a hypoglycemia occurring during the first day fast test. To confirm organic hypoglycemia, fast test is a chief pattern but other investigations are often necessary.

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EP650

Evaluation of postmenopausal hyperandrogenism – case report

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Introduction
Evaluation of postmenopausal hyperandrogenism may be a challenge for physicians as it is necessary to exclude the presence of the relatively rare but potentially life-threatening underlying tumorous causes. We report the case of a postmenopausal woman who presented with clinical and biochemical hyperandrogenism.
Case Report
We present the case of a 65 year-old woman being followed at our clinic because of mild hypothyroidism. At inspection we observed severe hirsutism (20 points on Ferriman-Gallway scale). Patient referred increased facial hair in the last year. No other signs such as baldness or voice changes were detected. She referred regular menses until menopause at the age of 49. Total testosterone levels were increased (2.28 ng/ml) with normal concentration of adrenal androgens (DHEA-S) in several determinations. A vaginal ultrasound was performed showing no alterations, CT-scan showed a 2 cm lesion in left adrenal gland suggestive of adrenal adenoma. Abdominal MRI showed a nodule of 2.2 cm on the right ovary suggestive of mioma and less likely of an ovary tumor. Despite the presence of an adrenal adenoma, suspecting ovary hyperandrogenism we decided to perform laparoscopic bilateral oophorectomy. An steroid cell tumor of 1.5 cm was detected on the right ovary on histological evaluation. After surgery, testosterone levels returned to normal and our patient has observed improvement in hirsutism and other signs of virilization.
Conclusions
Hyperandrogenism after menopause is a rare condition that needs careful evaluation in order not to misdiagnose an underlying androgen-secreting tumor. Clinical phenotype and symptom onset do not reliably permit discrimination between tumorous and nontumorous causes, but may help to guide the diagnosis. Imaging tests not always show the origin of hyperandrogenism and occasionally may mislead the diagnosis.

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EP651

Hirsutism with rapid onset presenting in a 62-year-old postmenopausal woman

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Introduction
Virilizing tumors are rare, but frequent cause of virilization in postmenopausal women.
Case report
A 62-year-old postmenopausal woman presented with a rapid onset of hirsutism with increased terminal hair growth, particular on chin and abdomen, frontal male pattern balding in the last 5 months. Physical examination revealed a low-pitched, deepened voice and clitoromegaly. The Ferriman–Gallwey score was 18. Laboratory evaluation: Testosterone: 11.2 ng/ml (nr for women 0.07–0.65), DHEAS 154.4 μg/dl (24.6–182.3), 17OHP 0.5 ng/ml (0.19–0.71), Δ4A 1.4 ng/ml (0.3–3.7), FSH 11.6 IU/l (27.7–93.3), LH 1.6 IU/l (14.4–52.8), PRL 6 ng/ml (1.9–17.9), E_2 91.7 pg/ml (6–53). On a 48-h low-dose (2 mg/day) dexamethasone-suppression test, testosterone showed only a 24% reduction from baseline, while DHEAS was practically unchanged. A pelvis MRI scanning revealed normal adrenal glands and enlargement of the right ovary with an echogenic solid mass measuring 3.6×3.7×4 cm and a laparoscopic right salpingo-oophorectomy was performed. Histopathology revealed a Leydig cell tumor with no malignant features.
Conclusions
Hyperandrogenism and especially virilization in menopausal women has to be investigated thoroughly, since the percentage of virilizing tumors of adrenal or ovarian origin is much higher in menopause than during reproductive age. Ovarian virilizing tumors are usually benign and the treatment of choice is surgical removal.

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EP652

Clinical presentations and genetic analyses of patients with multiple endocrine neoplasia type 2A: a single thai tertiary center experience

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Introduction
Multiple endocrine neoplasia type 2A (MEN 2A) is an autosomal dominant disorder from a RET proto-oncogene mutation, characterized by the presence of medullary thyroid carcinoma (MTC), pheochromocytoma and/or primary hyperparathyroidism.
Materials and Methods
A retrospective study of 5 probands (3 males and 2 females, age range 31–46 years) and 6 family members (2 males and 4 females, age range 2–50 years) diagnosed as MEN 2A at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, during 2000–2015 was performed. Direct sequencing of the RET gene successfully identified all mutant alleles of the affected individuals. Demographic data, clinical profiles, mutation types and genotype-phenotype correlation were analyzed.
Results
At the diagnosis, four probands had pheochromocytoma and MTC whereas the other one developed all three. Of the pheochromocytoma, all of them were benign, 60% (3/5) were bilateral and 60% (3/5) were the presenting tumors. Two of the probands initially presented with MTC with multiple foci at the diagnosis. Hyperparathyroidism due to hyperplasia was identified in one case. All the affected subjects responded well to standard treatment of each tumor except one that was delayed in diagnosis resulting in fatal outcome. Two distinct mutations which all located in codon 634 of exon 11 in RET gene, C634S (60%) and C634R (40%), were detected. A prophylactic thyroidectomy based on a classification of RET mutations in an asymptomatic MTC 10-year-old girl was performed successfully.
Conclusions
Screening and early detection of MEN2A mutation carriers are very effective clinical intervention. As described in the literature, MTC is usually the first manifestation in patients with MEN 2A; however, pheochromocytoma may be the presenting tumor due to its alarming symptoms. In this study the identified frequent loci of the RET gene will facilitate the molecular diagnosis of MEN 2A in Thai patients.

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EP653

Multiple complications of severe hyperandrogenism in a postmenopausal woman

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Introduction
Severe hyperandrogenism is not only associated with cosmetic concerns but it also increases the risk of neoplastic (endometrial, breast cancer), cardiovascular, respiratory and metabolic complications.
Case report
A 68 years-old woman with a recent history of severe arterial hypertension, cardiogenic pulmonary edema, diabetes mellitus, severe respiratory failure, marked obesity was referred to our department due to the markedly androgenic phenotype.
Clinical examination showed android obesity, severe male-pattern alopecia, marked hirsutism involving the face and the trunk, deepening of the voice. Severe, resistant arterial hypertension with hypertrophic cardiomyopathy and congestive heart failure was present. The patient associated chronic respiratory failure, severe obstructive sleep apnea syndrome, diabetes mellitus. The endocrine evaluation revealed an extremely elevated serum testosterone level (>16.6 ng/ml), high serum estradiol (186 pg/ml) with low gonadotropins (FSH 0.3 mIU/ml, LH 0.42 mIU/ml), normal adrenal function, with normal androstenedione, DHEAS and 17OHP levels. Computed tomography of the abdomen showed normal adrenal glands, right ovarian tumor, markedly increased uterine volume with severe endometrial hyperplasia. Surgery was recommended and performed very recently with significant clinical improvement.
Conclusions
The presence of severe hyperandrogenism in postmenopausal women is frequently the result of an androgen-secreting tumor and can be associated with important complications

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EP654

Incidentaloma. Myxoid adrenal adenoma

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Introduction
Myxoid tumors of the adrenal glands constitute an unusual entity and should be part of the differential diagnosis of atypical adenomas in the study of adrenal incidentaloma.
Description of methods
We report the finding of myxoid adrenal adenoma in left adrenal gland in a 38-year-old woman.
Case
PMH: Active smoker. Non hypertension, type 2 diabetes or dyslipidemia. No constitutional symptoms.
Physical examination: no signs of hypercortisolism. Weight 164 kg, BMI 18 kg/m^2, MAP 120 – 70 mmHg.
38-year-old woman studied by mixed urinary incontinence. Ultrasound define mass in left adrenal gland hypoechoic, homogeneous and well-defined contours, non calcifications of $4.6\times4.7\times4.2$ cm.
Abdominal MRI was requested later to define a left adrenal mass of 6×5.3 cm, heterogeneous, contours defined: differential diagnosis between atypical adenomas (on MRI if it becomes apparent signal loss in "out of phase"), pheochromocytoma (that is hyperintense on T2) and adrenal carcinoma (for size and heterogeneity presented).
The study of functionality intervention was normal functionality. It was operated by the imagining radiological characteristics of suspected neoplasia and being larger than 4 cm.
After laparoscopic left adrenalectomy was made, study concludes that it was pseudoglandular myxoid adrenal adenoma.
Currently has good clinical and laboratory evolution.
Conclusions
Pseudoglandular myxoid adrenal gland adenoma is a rare variant of myxoid adenomas. The radiological characteristics are variables. The definitive diagnosis is provided by pathologic examination. The evolution of myxoid benign adenomas is similar that conventional ones.

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EP655

Von Hippel-Lindau syndrome with musculoskeletal manifestations. report of a case

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Introduction
Von Hippel-Lindau (VHL) syndrome is an inherited disorder characterized by the formation of tumors and cysts in diverse organ systems. Tumors may be

malignant or benign and they tend to appear during young adulthood. Hemangioblastomas are characteristic of VHL syndrome.
Aim
The aim was to describe the case of a patient with VHL syndrome presenting with musculoskeletal manifestations and multiple tumors.
Case report
A patient female, aged 51 years, presented with painful 1st and 3rd MCP and proximal PP joints. The patient complained of dry mouth and dry eyes. Laboratory investigations revealed positive RF test. The patient had a 10-year history of insulin treated diabetes mellitus type 2 on insulin and antidiabetic drugs. At the age of 27 the patient developed loss of balance, headaches and vision problems. An MRI performed revealed a hemangioblastoma of the cerebellum. The diagnosis of VHL syndrome was made. At the age of 49 she presented with multiple hemangioblastomas of the cerebellum and the spinal cord. There were multiple cases of VHL syndrome within the family. Her mother was diagnosed with VHL at the age of 57, had multiple hemangioblastomas in the CNS and died from clear cell renal carcinoma aged 73. Her sister has also multiple hemangioblastomas and has been diagnosed with clear cell renal carcinoma and has also VHL. Her first son was diagnosed with VHL at the age of 12, developed multiple hemangioblastomas in the CNS causing tetraplegia and died aged 25. Her second son has multiple hemangioblastomas in the cerebellum, a pancreatic serous cystadenoma and had a retinal angioma in the right eye with subsequent loss of vision. Her 2 nephews also suffer from multiple hemangioblastomas in the CNS, one of them having a retinal angioma.
Conclusion
The extremely rare case of a patient with VHL syndrome and diabetes mellitus type 2 is described. The syndrome is inherited in an autosomal dominant pattern, thus patients present with multiple cases within the family.

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EP656

Insulinoma misdiagnosed as neurologic disease

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Introduction
Insulinoma is a rare pancreatic endocrine tumor derived from ß cells that secret insulin, which results in hypoglycemia. Most are benign and solitary. The median age at diagnosis is about 47 years. The age range for peak incidence is between 30 and 60 years and it is more prevalent in women. Diagnosis relies on clinical features along with laboratory tests and imaging. However, the nonspecific symptoms and small size of these tumors can lead to difficulties of diagnosis and localization.
Case report
An 84 years old man was admitted to the emergency department with seizures and severe hypoglycemia (44 mg/dl). The patient have had a previous history of fatigue, dizziness and tremors since the past two years, diagnosed as Parkinson's disease. 72 hour fast test showed increased levels of insulin (7.1 mUI/ml), C-peptide (2.21 ng/ml) and pro-insulin (51.7 pmol/l). Screening for sulfonylurea, anti-insulin antibodies and anti-insulin receptor antibodies was negative.
MEN 1 syndrome was excluded. The abdominal CT scan revealed a 12 mm nodule in the uncinate process of the pancreas. Endoscopic ultrasonography was performed and biopsy was suggestive of a neuroendocrine tumor.
The patient was discharged in euglycemia, under diazoxide and poli-fractionated diet, pending surgical decision.
Surgical resection was performed and histopathology was consistent with the diagnosis of benign insulinoma. The clinical course was favourable, with regression of symptoms without diazoxide.
Conclusion
Insulinoma remains a diagnostic challenge since symptoms are nonspecific and may lead to incorrect diagnosis. As in this clinical case, a neurologic disease might be considered the culprit.
We discuss the importance of considering the diagnosis, since it is easily confirmed by standard endocrine tests and can be potentially curable through surgical resection. On the other hand severe and sustained hypoglycemia can lead to disability and death.

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Female Reproduction

EP657

Immunity to Haemophilus influenzae B and Peumococcal vaccination among adult women with Turner Syndrome

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Introduction
Turner Syndrome (TS) is associated with a higher overall morbidity and mortality than the general population, with respiratory diseases as one of the major causes. Haemophilus influenza type B (HiB) and pneumococcal (PC) vaccination can reduce morbidity and mortality, by alleviating the risk of respiratory diseases. All patients in the Newcastle Adult Turner Syndrome clinic who lack immunity to either HiB or PC at baseline receive vaccination in our TS clinic. However, the response rate following vaccination has not hitherto been examined.
Methods
We prospectively examined the response rate to HiB and PC vaccination among a cohort of 100 consecutive adult women with TS. In our laboratory, the antibody titres at the protective range were 1–20 and 20–200 mg/L, for HiB and PC antigens, respectively. Patients with titres below these lower limits were considered to have inadequate immunity and vaccination was administered in primary care (Pneumovax or Menitorix).
Results
A total of 96 eligible TS patients aged $\geq$18 years were reported. The median age and BMI were 31.5 (24.8–45.0) years and 26.1 (23.2–30.7) kg/m^2, respectively. At baseline, 54.2% (52/96) and 18.8% (18/96) of patients had inadequate antibody response to HiB and PC vaccines, respectively. Intriguingly, 27.5% (14/51) patients in the former and 38.9% (7/18) in the latter, also had a low IgM level ($<$0.71). Furthermore, 7.8% (4/51) and 16.7% (3/18) had a low IgG level ($<$5.8), respectively.
Conclusions
The prevalence of protective antibodies to HiB and PC among adult women with TS were low in this cohort, underpinning the importance of screening and vaccination to achieve protective titres, thereby potentially reducing related morbidity and mortality.

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EP658

Sex hormone and steroid precursor measurement by simple and rapid liquid chromatography-tandem mass spectrometry (Lc-Ms/Ms) method: comparison with current routine immunoassays

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Though LC-MS/MS is replacing immunoassays for major glucocorticoids and androgens routine assessment, the measurement of other sex steroids and precursors is still challenging and available only in experienced research laboratories. Our aim was to develop a simple-prep and rapid 2D-LC-MS/MS method for the simultaneous measurement of estrone (E1), estradiol (E2), dihydrotestosterone (DHT) and 17OHpregnenolone.
Serum volumes of 300ul were spiked with internal standards and processed by single-step liquid-liquid-extraction. Extracts were injected onto Prominence HPLC - LCMS-8050 triple-quadrupole platform (Shimadzu). Analytes were purified by perfusion column, separated on a Gemini C6-phenyl (100$\times$2 mm, 5 um) column (Phenomenex), ionized by electrospray and detected by specific multiple reaction monitoring transition in 11min run. The method showed high functional sensitivity (E2 and DHT: 9.8 pg/ml, E1: 4.9 pg/ml, 17OHpregnenolone: 39.1 pg/ml), proper accuracy (86.4–102.1%) and intra- (0.9–4.9%) and inter-assay (2.1–11.6%) imprecision. Sex and age specific reference intervals were estimated. The LC-MS/MS method was compared with routine E1 and E2 immunoassays. The Passing&Bablok analysis revealed high correlation between Roche-Modular III ECLIA and LC-MS/MS for E2 measurement both at all values (n=82; r:0.991) and at E2 levels $<$100 pg/ml (n=28; r:0.960), with respectively slight or absent proportional (slope (90CI): 1.06 (1.02–1.09) and 096 (0.85–1.11)) and systematic (intercept (90CI): $-$5.50 ($-$10.4–$-$1.68) and $-$0.78 ($-$6.94–4.96)) bias. DSL8700 direct RIA for E1 measurement showed poor correlation with LC-MS/MS (n=42; r:0.872), with relevant proportional (slope (90CI): 076 (063–0.94)) and systematic (intercept (90CI): 18.4 (9.4–22.9)) bias.

The LC-MS/MS assay showed optimal performance to sensitively and accurately determine routinely-assayed estrogens, confirming the reliability of new-generation ECLIA for E2, and highlighting direct RIA unreliability in determining E1. The assay further allowed the determination of important though not-routinely assayed DHT and 17OHpregnenolone. The bench- and run-time required by the LC-MS/MS method allow the integration of steroid profiling capability both in research and clinical settings.

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EP659

Association between prolonged breastfeeding and bone mineral density and osteoporosis in postmenopausal women: KNHANES 2010–2011

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Abstract withdrawn.

EP660

Increased adipsin is associated with carotid intima media thickness and metabolic disturbances in polycystic ovary syndrome

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Context
Adipsin, a protein secreted mainly from the adipose tissue, is a structural homologous of complement factor D, a rate-limiting enzyme of the alternative complement system. Growing evidence suggests that the alternative complement system plays a role both in the regulation of energy homeostasis and the atherosclerotic process. Polycystic ovary syndrome (PCOS) is an inflammatory based-metabolic disease.
Objective
To ascertain whether circulating adipsin levels are altered in women with PCOS, and whether there is association between adipsin and metabolic parameters or carotid intima media thickness (CIMT).
Participants
Hundred and forty four women with PCOS and 144 age- and BMI-matched controls without PCOS were recruited for this cross-sectional study.
Main Outcome Measures
Circulating adipsin levels were measured using ELISA. Metabolic, hormonal parameters and CIMT were also determined.
Results
Circulating adipsin levels were significantly elevated in women with PCOS compared with controls (91.52 ± 14.11 vs 60.31 ± 9.71 ng/ml, $P < 0.001$). Adipsin levels positively correlated with BMI, homeostasis model assessment of insulin resistance (HOMA-IR), total & free-testosterone, high sensitivity C-reactive protein (hs-CRP), triglycerides and CIMT. Multivariate logistic regression analyses revealed that the odds ratio for PCOS was 3.25 for patients in the highest quartile of adipsin compared with those in the lowest quartile (OR = 3.25, 95% CI = 2.64–4.00, $P = 0.016$). Our findings further indicate that BMI, HOMA-IR, hs-CRP and free-testosterone are independent factors influencing serum adipsin levels and that adipsin is an independent predictor for CIMT.
Conclusion
Adipsin might contribute to the development PCOS as well as the cardiovascular risks and metabolic disturbances associated with the disease.

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EP661

Follicular fluid Bisphenol A levels are higher and correlate negatively with the number of oocytes in women with tubal factor infertility compared to women with polycystic ovary syndrome

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Introduction
Bisphenol A (BPA) is a chemical compound found in a variety of everyday products. Exposure to BPA impacts negatively ovarian response, number of fertilized oocytes and implantation in women undergoing *in vitro* fertilization (IVF). The aim of the study was to determine BPA levels in women with polycystic ovary syndrome (PCOS) in comparison to women with tubal factor (TF) infertility who underwent IVF as well as to investigate their effect in critical endpoints of IVF such as number of oocytes and IVF outcome.
Material and Methods
Eighty two women in reproductive age (41 with PCOS and 41 normo-ovulatory with TF infertility) who underwent IVF were included in a prospective controlled study. A novel gas chromatography-mass spectrometry method was developed to determine BPA levels in serum, urine and follicular fluid (FF). Anthropometric, metabolic, and hormonal parameters were assessed.
Results
Higher BPA levels were detected in serum (0.780 ng/ml vs 0.580 ng/ml, *NS*) and FF (1.128 ng/ml vs 0.505 ng/ml, $P < 0.05$) but lower in urine (0.985 ng/ml vs 1.500 ng/ml, $P < 0.05$) of women with TF infertility compared to PCOS. There was a trend towards higher follicular BPA levels in TF women compared to PCOS women after BMI stratification. After adjustment for age, BMI and exogenous FSH administration, follicular BPA levels correlated negatively with number of oocytes collected during oocyte retrieval in TF ($P < 0.05$) but not in PCOS women. Nevertheless, follicular BPA levels had no significant effect on fertilized oocytes fertilized and pregnancy rates in both groups.
Conclusion
The present study showed that there was a trend for higher BPA levels in FF of TF as compared to PCOS women. In TF women BPA FF levels correlated negatively with the number of oocytes collected during oocyte retrieval. However, no effect of FF BPA levels was observed on fertilized oocytes and pregnancy rates in both groups.

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EP662

The relation of liver enzymes and insulin resistance in women with polycystic ovary syndrome (PCOS)

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Introduction
A link between polycystic ovary syndrome (PCOS) and nonalcoholic fatty liver disease (NAFLD) has been recently demonstrated. The pathogenesis of NAFLD is multifactorial, but obesity and insulin resistance (IR) appear to be important contributing factors. The aim of this study was to analyze level of transaminazes in PCOS women, and its relation to the indices of IR.
Methods
We analyzed 600 women with PCOS diagnosed using ESHRE/ASRM criteria (age 25.6±5.9 years, BMI 30.6±6.9 kg/m^2), and 125 body mass index (BMI)-matched healthy controls (age 31.4±5.3 years, BMI 29.6±6.8 kg/m^2). IR was evaluated using homeostatic model (HOMA-IR) with the cut-off of 2.5. Using cut-off, both PCOS and controls were divided into: PCOS-IR (N=384), PCOS-nonIR (N=216), Controls-IR (N=53) and Controls-nonIR (N=72). Serum liver enzymes, glucose, insulin, total testosterone and sex hormone binding globulin were determined and free androgen index (FAI) was calculated. Differences between groups were age and BMI adjusted.
Results
The highest AST was found in PCOS-IR and significantly differed in comparison to PCOS-nonIR (20.75±8.31 vs 17.99±5.04U/L, respectively, $P<0.05$). There was no difference in AST level between Controls-IR and Controls-nonIR (18.96±6.66 vs 18.38±5.63U/L, respectively, $P>0.05$). ALT was highest in PCOS-IR and significantly differed from PCOS-nonIR (25.36±16.21 vs. 18.59±10.08 U/l, respectively, $P<0.05$), while ALT levels were the same in Controls-IR compared to Controls-nonIR (24.60±12.97 vs. 19.97±10.94 U/l, respectively, $P>0.05$). In PCOS HOMA-IR correlated with both AST ($\rho=0.202$, $P<0.001$) and ALT ($\rho=0.315$, $P<0.001$) while in Controls only with ALT ($\rho=0.254$, $P=0.004$).
Conclusions
Although our PCOS women had normal values of liver enzymes, they were higher in comparison to controls. It seems that IR could additionally contribute to the disturbance of liver enzymes in PCOS.
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EP663

Pre-pregnancy risk assessment and combined multidisciplinary care improves pregnancy outcomes in women with Turner's syndrome
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Aims
Women with Turner's syndrome (TS) are increasingly undertaking pregnancies, either via natural conception (mosaic TS) or assisted conception (AC). Increased TS pregnancies have led to reports suggesting high risk of pregnancy associated aortic dissection (AOD) 2%, and maternal mortality 2% due to underlying aortic valve abnormalities and aortopathies. However, the literature is limited to small case series. We report our practice providing risk-assessment and combined specialist TS endocrinology, cardiology and obstetrics services, resulting in low maternal and fetal complications.
Methods
Data were retrospectively analysed for patients with spontaneous pregnancy or AC with multidisciplinary risk-assessment and care during pregnancy and peurperium, and follow-up in a specialist TS clinic between 2009 and 2016.
Results
Of 87 TS patients, thirteen (15%) had spontaneous pregnancies and six (7%) had AC with three successful pregnancies. Pre-conception risk-assessment and counselling were conducted by a multidisciplinary team comprising TS endocrinologist, obstetrician and cardiologist with echocardiography ± cardiac magnetic resonance imaging. Five patients had pre-existing cardiovascular disease (bicuspid aortic valve [n=5]; dilated aortic root or ascending aorta [n=4]; moderate aortic stenosis [n=1]; hypertension [n=3]; surgery for dilated ascending aorta [n=1]; and for complex congenital heart disease including coarctation [n=1]). During pregnancy, patients underwent regular review by a TS endocrinologist, cardiologist with echocardiography and obstetrician in a high-risk maternity clinic. Fetal cardiologist assessment occurred at 20 weeks gestation. Maternal echocardiography was performed post-partum. There were 16 successful live-births (n=13 spontaneous pregnancies, n=3 AC). One patient developed gestational hypertension which responded to medical therapy. One patient developed mild progression of aortic root dilatation post-partum. There were no cases of moderate or severe aortic dilatation, AOD, pre-eclampsia, maternal deaths or fetal cardiac disease.
Conclusions
Pre-pregnancy risk-assessment and close multidisciplinary care by endocrinology, cardiology and obstetrics services during pregnancy and the peurperium ensures low maternal complications and excellent survival in TS.
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EP664

The first hungarian preimplantational karyomapping In men2a syndrome – case report
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The case
The multiplex endocrine neoplasia 2A (MEN2A) syndrome is a monogenic disease caused by mutation of the RET protooncogene leading to medullary thyroid cancer (MTC), pheochromocytoma and primary hyperparathyroidism. The specific mutations determine the timing of the preventive thyroidectomy. In 2007, in a 26 year old female patient, after detailed endocrine investigation, total thyroidectomy with both sided lateral neck lymph node dissection was performed because of suspicion of medullary thyroid cancer. The final histology proved the diagnosis. Three years later hypertensive peaks occured, pheochromocytoma was found and removed by laparoscopic adrenalectomy. The family was screened for MEN2A. The mutation TGC634TTC(Cys634Phe) of the codon 634 was found in the patient, in her father and one brother. After spontaneous conception and normal pregnancy in October 2012 she gave birth to a boy. The son was screened for MTC with calcitonin with the age of 11 and 13 months (15.6–18 pg/ml) and was proven to be RET positive. Preventive total thyroidectomy and partial parathyroidectomy was done with the age of 18 months. The final histology found no sign of medullary thyroid cancer or primary hyperparathyroidism. As the patient did not want to have another child affected by the disease, application of assisted reproductive technologies were recommended. After ovarian stimulation, 4 embryos were biopsied in trophectoderm stage. Karyomapping (preimplantational genetic screening for chromosomal abormalities and preimplantational genetic diagnostics for the specific mutation) was performed revealing one healthy and three MEN2A affected embryos, two of them with maternal aneuploidy aswell.
Conclusion
For the monogenic disease affected families, it is important to offer the possibility of preimplantation genetic diagnosis to exclude the affected embryos to be transfered. Healthy children don't require lifelong endocrine follow-up and operations, and no psychological support.
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EP665

PCOS in women with type 1 diabetes mellitus is not related to diabetes duration or insulin dose
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Introduction
Polycystic ovary syndrome (PCOS) is highly prevalent in women with type 1 diabetes mellitus (T1DM), possibly due to premenarchal exogenous hyperinsulinism (supraphysiological doses and nonphysiologic route of insulin administration). Our aim was to determine if PCOS was related to daily or basal insulin dose or T1DM duration.
Methods
We examined 47 women with T1DM (mean age 36.02 years, ±6.03) treated with continuous subcutaneous insulin infusion (78.7%) or basal/bolus insulin therapy. Rotterdam criteria were used to diagnose PCOS. Participants reported medical history, underwent clinical examination, endocrine testing and ovarian ultrasound scan.
Results
PCOS was confirmed in 20 women (42.5%). Mean HbA1c in PCOS was 7.36% (±0.81%), mean T1DM duration was 20 years (±7.16); daily insulin dose (DID) 36.11 IU (±10.02), basal insulin dose (BID) was 17.72 IU (±7.13) in PCOS and 7.22% (±0.83%), 23.17 years (±11.74), 35.25 IU (±13.34), 17.28 IU (±7.15) in non-PCOS group respectively. Neither comparison of DID and BID, premenarchal onset and T1DM duration nor multivariable logistic regression revealed statistically significant differences between the groups. No significant correlation between PCO ovarian morphology, DID and/or BID and/or T1DM duration was found. Statistically significant correlations in our sample were: correlation of DID to weight ($P<0.001$) and BMI ($P<0.001$), BID to BMI ($P=0.001$), DID to free testosterone concentration ($P=0.001$), BID to free testosterone concentration ($P=0.014$) and T1DM duration to BMI ($P=0.022$).
Conclusion
We confirmed high prevalence of PCOS in our population with long duration and good metabolic control of T1DM. However, no difference was observed in DID or BID and T1DM duration and premenarchal onset of T1DM between PCOS and non-PCOS group. Curiously, a correlation between DID and BID to free testosterone concentration was observed in the study population. Factors other than exogenous hyperinsulinemia, possibly genetics and epigenetics, might be important in pathogenesis of PCOS in women with T1DM.

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EP666

Polycystic ovary syndrome phenotype does not increase prevalence of coronary artery disease in postmenopausal women

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Abstract withdrawn.

EP667

Glucose level after standard oral glucose tolerance test as a potential marker for the development of type 2 diabetes in women with polycystic ovary syndrome (PCOS)

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Introduction
It has been shown that subjects with normal fasting glucose (NFG) and normal glucose tolerance (NGT), whose plasma glucose concentration does not return to their fasting plasma glucose (FPG) level within 2 h following standard oral glucose tolerance test (OGTT), have higher risk of progression into type 2 diabetes (T2D) than NFG/NGT subjects whose glucose returns to FPG level after OGTT. Although the development of T2D during the life of woman with polycystic ovary syndrome (PCOS) is nowadays assumed to be higher than previously thought, the exact reason for that is still unknown.
Methods
We evaluated 193 non-obese PCOS women (body mass index, BMI: 22.47±3.33 kg/m^2; age: 24.93±4.59 years) diagnosed using ESHRE/ASRM criteria and 53 healthy non-obese women in control group (BMI: 24.05±3.29 kg/m^2; age: 30.21±5.57 years). In follicular phase of menstrual cycle 2-h OGTT with 75 g of glucose was performed in all subjects. IFG, IGT and T2D were defined according to International Federation for Diabetes (IFD) criteria. All analysis were adjusted for BMI and age.
Results
None of the PCOS subjects had T2D and none of the controls had either IFG or IGT. In PCOS group, IFG was diagnosed in 3/193 (1.6%) and IGT in 6/193 (3.1%). All PCOS women with IFG had NGT, while all PCOS subjects with IGT had NFG. When only NGT/NFG subjects were analyzed (184 PCOS and 53 Controls), PCOS had higher prevalence of higher postload glucose than FPG in comparison to Controls (67% vs 50%, respectively $P=0.045$).
Conclusion
Higher postload glucose level than fasting plasma glucose level could be a useful marker of risk for the development of T2D in women with PCOS.

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EP668

Serum alanine aminotransferase level as an early indicator of metabolic disturbancies in women with polycystic ovary syndrome (PCOS)

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Introduction
Serum alanine aminotransferase (ALT) level is used to screen patients for unsuspected liver disease. The entire histologic spectrum of nonalcoholic fatty liver disease (NAFLD) can be seen in individuals with normal ALT values. Accordingly, it has been suggested that by using ALT > 19 U/l, early stages of NAFLD could be detected. As it was established a relation of NAFLD and PCOS, the aim of our study was to compare metabolic characteristics of women with polycystic ovary syndrome (PCOS) in relation to ALT levels.
Methods
We evaluated 600 PCOS women diagnosed using ESHRE/ASRM criteria, divided into 2 groups: group A with ALT < 19 IU/l ($N=299$; BMI 28.64±5.86 kg/m^2; age 25.27±5.77 years) and group B with ALT ≥ 19 IU/l ($N=301$; BMI:32.64±7.36 kg/m^2; age 25.93±6.12 years), and 53 healthy non-obese women (Controls: 24.05±3.29 kg/m^2; 30.21±5.57 years). Serum liver enzymes, glucose, insulin, lipids, total testosterone and sex hormone binding globulin were determined. Insulin resistance was evaluated by homeostatic model (HOMA-IR). All analysis were BMI adjusted.
Results
In all examined subjects, liver enzymes were in the reference range. Group B had higher values of aspartate-aminotransferase (AST) (22.75±8.85 vs 16.73±3.60, $P<0.001$), gamma-glutamil-transferase (20.03±10.93 vs 13.40±5.80, $P=0.009$), alkaline phosphatase (78.52±21.36 vs 68.28±20.26, $P<0.001$), insulin (18.46±10.24 vs 13.48±8.83, $P<0.001$), HOMA-IR (4.52±2.78 vs 3.21±2.26, $P<0.001$), total cholesterol (5.15±1.02 vs 4.70±0.94, $P<0.001$), LDL (3.33±0.94 vs 2.97±0.82, $P<0.001$) and triglycerides (1.24±0.60 vs 0.97±0.40, $P<0.001$). There were no difference in fasting glucose, HDL, testosterone and SHBG.
Conclusion
Serum ALT levels greater than 19 IU/l could be an early indicator of metabolic disturbances in women with PCOS.

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EP669

The association between polycystic ovary syndrome and lipid accumalation product index

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Aim
The lipid accumulation product (LAP) index which is associated with abnormal glucose regulation can be easily calculated. Women with polycystic ovary syndrome have more than one risk factor for the development of cardiovascular diseases such as glucose intolerance, insulin resistance and abdominal lipoidosis. In this study, we intend the evaluation of LAP index in women with PCOS.
Method
This study included 35 women patients with PCOS (mean age 22.4±5.2 year) and 33 healthy normoovulatory women in control group who had similar age (mean age 21.0±3.1 year). The plasma lipid profile, glucose and insulin levels of the patients were detected after 12 h fasting and waist circumference was measured. The lipid accumulation product index was calculated with the formula previously defined as (waist circumference (cm) – 58) × triglycerides (mmol/l). HOMA IR glucose was calculated with the formula of (mmol/l)× insulin (μU/ml)/22.5.
Findigs
In this study, the mean of LAP index in the patients and the control group were respectively (38.2±42.6 and 12.0±13.1, $P=0.000$), TG (115.9±67.9 etc. 82.8±46.3 mg/dl, $P=0.004$), HOMA-IR (3.5±2.4 and 2.2±1.3 $P=0.01$), total cholesterol (178.2±35.4 and160.0±27.7 mg/dl $P=0.02$), insulin (16.1±10.1 and 11.0±6.3 μU/ml $P=0.02$), waist circumference (84.3±15.8 and 69.2± 8.05 cm, $P=0.000$), LDL (107.1±31.1 and 88.7±27.1 mg/dl $P=0.01$).
There was a positive correlation between LAP index and bodyweight ($r=0.79$ $P=0.000$), waist circumference ($r=0.81$ $P=0000$) HOMA score ($r=0.35$ $P=0.008$), insulin ($r=0.37$ $P=0.005$), TG ($r=0.79$ $P=0.000$) and LDL levels ($r=0.32$ $P=0.008$).
A positive correlation was detected between BMI and LAP index ($r=0.73$ $P=0.000$), HOMA-IR ($r=0.48$ $P=0.000$), fasting insulin levels ($r=0.46$ $P=0.000$).
Results
High LAP index may help for the evaluation of metabolic risk in women with PCOS.

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EP670

Androgen distribution in different phenotypes of women with polycystic ovary syndrome (PCOS)

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Introduction
Polycystic ovary syndrome (PCOS) phenotypes A and B are considered to be more hyperandrogenic in comparison to phenotypes C and D that are considered to be mostly reproductive. The aim of this study was to analyze distribution of androgens in different phenotypes in our PCOS population.
Methods
We evaluated 365 PCOS women (PCOS:25.05±6.24 kg/m^2; 25.48±5.21 years) diagnosed using ESHRE/ASRM criteria and 125 healthy women (Controls: 25.41±5.16 kg/m^2; 30.35±5.62 years). PCOS group was divided into 4 phenotypes: A [anovulation (ANOV), hyperandrogenism (HA), polycystic ovary morphology (PCOM)], B (ANOV, HA), C (HA, PCOM) and D (ANOV, PCOM). In follicular phase of menstrual cycle total testosterone (TT), SHBG, androstenedione and DHEAS and free androgen index (FAI) were determined in all subjects. All analyses were BMI and age adjusted.
Results
In comparison to Controls, phenotypes A, B and C had higher levels of TT, FAI, and androstenedione; DHEAS was higher in A and C, while SHBG lower in all phenotypes. Only 4% of phenotypes A, B and C had elevated only TT, which was significantly different in comparison to both D and Controls. Prevalence of elevated only DHEAS or androstenedione was the same in all phenotypes. The most common was presence of concomitantly high TT and androstenedione: A 23%, B 24%, C 15% while 0% in both D and Controls ($P<0.05$). A and C had higher prevalence of concomitantly high both TT and DHEAS (13% and 10%, respectively) in comparison to Controls (0%) and phenotype D (0%), ($P<0.05$). The prevalence of concomitantly elevated both androstenedione and DHEAS was the same in all groups.
Conclusion
In our PCOS population the most common hyperandrogenemia pattern is concomitant elevation of both TT and androstenedione. Low SHBG is a common feature in all PCOS phenotypes including phenotype D.

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EP671

Effect of methomyl on the biochemical and reproductive parameters in pregnancy rats: the protective role of Pistacia Lentiscus oil

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Methomyl (MET) is a carbamate insecticide used worldwide to protect a wide variety of crops from insect nuisances. Besides this beneficial role, it is classified as highly toxic compound for humans and animals by the EPA. Pistacia Lentiscus (PL) is a shrub that grows in the Mediterranean region; plant parts and oil have a long history in folk medicine in healing several diseases by their antioxidant, anti-inflammatory, antimicrobial, antifungal, antiatherogenic and anticancer properties. Hence, this study was undertaken to assess the effect of MET on biochemical, histological and reproductive parameters as well as the possible protective role of Pistacia Lentiscus oil (PLO) against MET-induced toxicity in pregnant female rats.
Thirty two pregnant female rats were randomly divided into four equal groups including control, MET group (10 mg/kg/bw), PLO group (0.5 ml/kg/bw) and MET+ PLO group, MET and PLO were administered by oral route. At the eighteenth day of gestation (GD18), the blood samples were taken from retro-orbital sinus to evaluate the biochemical parameters and progesterone level. Then after the parturition, the different reproductive parameters were measured and the ovary and adrenal glands were removed, weighed, fixed and used for histopathological examination.
The results show that MET increased significantly the weight of liver and adrenal gland, the level of cholesterol, glucose, creatinin, urea, ASAT and ALAT, meanwhile the level of total protein was reduced. Likewise, MET induced reproductive toxicity pronounced by a decline in the level of progesterone, an alteration in the reproductive index and an increase in the number of ovary atretic follicles and degenerative corpus luteum. The supplementation of the PLO with MET reverses partially and/or completely all adverse effects noted on the biochemical and reproductive parameters as well as on the histopathological changes by their antioxidant activities. We recommended the use of PLO by oral and/or dermal application as protective agent against several diseases related to reproduction dysfunction.

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EP672

The association between increased circulating irisin levels and inflammatory markers in polycystic ovary syndrome

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Purpose
Irisin is a secreted protein implicated in the regulation of insulin sensitivity and energy metabolism. Polycystic ovary syndrome (PCOS) is an inflammatory-based metabolic disease associated with insulin resistance, dyslipidemia, glucose metabolism dysfunction and obesity. There is also some evidence of a link between irisin and inflammation. Our aim of the study to ascertain whether the association of circulating irisin levels with inflammatory markers in PCOS.
Materials and Methods
A total of 128 women with PCOS and 128 age- and body mass index-matched female controls without PCOS were recruited for this cross-sectional study. Circulating irisin, UCP1, tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) levels were measured using ELISA; metabolic and hormonal parameters were also determined.
Results
Circulating irisin levels were higher in women with PCOS compared with controls (203.49 ± 79.11 vs 169.82 ± 66.05 ng/ml, $P<0.001$), whereas UCP1 levels were lower (31.41 ± 12.57 vs. 38.34 ± 15.29 pg/ml, $P<0.001$). The serum levels of inflammatory markers IL-6, TNF-α and hs-CRP were found to be significantly elevated in women with PCOS. Irisin levels were negatively correlated with UCP1 levels and positively correlated with inflammatory markers high-sensitivity C-reactive protein (hs-CRP), TNF-α, IL-6 and free-testosterone levels. Multiple linear regression analysis revealed that free-testosterone, UCP1, hs-CRP, TNF-α and IL-6 independently predicted irisin levels.
Conclusions
Increased irisin levels were associated with decreased UCP1 levels and elevated free-testosterone and inflammatory markers in PCOS patients, suggesting a possible connection between the irisin signaling pathway and inflammation in PCOS.

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EP673

Improvement of beta-cell function with DPP-4 inhibitor alogliptin vs alogliptin in combination with pioglitazone as a potential treatment target in metformin treated PCOS with persistent high metabolic risk: randomized pilot study

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Introduction
High conversion rates to impaired glucose tolerance (IGT) and diabetes in PCOS indicate that current treatment strategy with lifestyle modification and metformin is insufficient. Preservation of β-cell function remains unaddressed although it is declined by 80% long before IGT is identified. Alogliptin is selective dipeptidyl peptidase-4 inhibitor improving insulin sensitivity (IS) and β-cell function. Pioglitazone predominantly improves insulin resistance (IR) and when given early also preserve β-cell function. The aim of the study was to evaluate whether the addition of alogliptin alone or in combination with pioglitazone improves β-cell function along with IR as measured by static and dynamic glucose homeostasis models in metformin treated PCOS with persistent high metabolic risk.
Design
In 12-week randomized study, alogliptin (ALO) 25 mg QD ($n=15$) or alogliptin 25 mg QD and pioglitazone (PIO) 30 mg QD ($n=15$) was added to metformin (MET) 1000 mg BID in 30 PCOS women (aged 34.4 ± 6.5 years, BMI 39.0 ± 4.9 kg/m^2, HOMA-IR 4.82 ± 2.52, mean $\pm$ S.D.). Fasting and acute glucose and insulin response to 2-h meal tolerance test was determined at baseline and study end. The ability of β-cell function to adapt insulin secretion to ambient IS was assessed by adaptation index (AI).
Results
14 patients on MET-ALO and 14 on MET-ALO-PIO completed the study. MET-ALO and MET-ALO-PIO resulted in significant decrease of HOMA-IR (for -1.56 ± 2.29 ($P=0.039$) vs -2.86 ± 3.34 ($P=0.001$) and increase in IS after meal ingestion (oral glucose IS) for 31.37 ± 97.52 ml min^{-1} m^{-2} ($P=0.007$) vs 39.0 ± 58.11 ($P=0.039$), respectively. AI across the entire group was significantly improved from 329.60 ± 200.63 to 442.51 ± 303.87 ($P=0.048$). Triple combination also led to significant improvement of androgen and lipid profiles.
Conclusion
Alogliptin alone and in particular in combination with pioglitazone improved meal related β-cell function along with IS and IR when added to metformin resistant PCOS.

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EP674

Pregnancy by Treatment for Graves Disease in a Patient with Primary Ovarian Failure

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Introduction
Premature ovarian failure (POF) is a disorder associated with female infertility, and it affects approximately 1% of women under the age of 40 year. It is considered a multifactorial, heterogeneous condition, for which the exact underlying cause remains unclear. Associations with autoimmune diseases, environmental factors and genetic causes have been described. Herein we presented a case with POF who regained fertility after the treatment of Graves disease.
Case
A 29-year-old nulligravida woman with amenorrhea for six years was referred to our clinic for the treatment of hyperthyroidism. She had been followed by gynecology clinics with the diagnosis of POF and received hormone replacement therapy before application to our clinic. Her *follicle stimulating hormone, luteinizing hormone, estradiol checked in her last visit before the referral were; 107.3 mIU/ml, 63.5 mIU/ml and 10.41 pg/ml, respectively. Her karyotype was 46, XX.* New blood test revealed a thyroid stimulating hormone of 0.017 uIU/ml (normal, 2.0–4.4), free thyroxin of 4.29 ng/dL (normal, 0.9–1.7), free *triiodothyronine of 13.66 pg/ml (normal, 0.27–4.2) and thyroid stimulating antibody level of 44.49 u/l (normal, 0-14).* On ultrasound, the thyroid was diffusely enlarged with coarse heterogeneous echogenity. A diagnosis of Graves's disease was made and methimazole was started 15 mg once daily. The dosage was adjusted accordingly and she had used methimazole for 13 months and was euthyroid when the pregnancy was determined.
Conclusion
Numerous case reports and certain observational and interventional studies have reported spontaneous pregnancies and ovulation in POF patients. Some authors suggested the possible effects of immuno-modulating therapy on the resumption of ovarian function and fertility in a selected group of POF patients. Anti- thyroid drugs may have clinically important immunosuppressive effects. To our knowledge, this is the first case in the literature who had POF and Graves disease and got pregnant upon anti-thyroid drug treatment.

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EP675

Baseline and metoclopramide induced plasma prolactin level in lean PCOS women according to their FAI phenotype

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Aim
Aim of our study was to compare: the baseline and metoclopramide induced prolactin plasma level between PCOS women with FAI <5 phenotype (group A) (FAI, total testosterone divided by sex hormone biding globulin, whole multiply by 100) and PCOS women with FAI >5 phenotype (group B).

Patients and methods
The study population consisted of 354 lean women with PCOS. In all the patients the prolactin level at 02:00 h, 08:00 h and during the metoclopramide oral test, were assessed. The free androgen index was calculated to each woman. The population was dived into two group according to the FAI phenotype. The group A contains 250 women with PCOS and FAI >5, the group B contains 104 women with PCOS and FAI <5. The groups did not differ in age (group A: 24.3 ± 5.3 years vs. group B 25.4 ± 5.7 years and BMI (group A: 21.3 ± 2.1 kg/m^2 vs. group B: 20.9 ± 2.1 kg/m^2 at baseline.
Results
The prolactin level was statistically significant higher ($P<0.0001$) in group B at 02:00 h (55.2 uIU/ml vs. 98.7 uIU/ml), at 08:00 h (159.8 uIU/ml vs. 390.2 uIU/ml), at 60-minute of metoclopramide test (690.41 uIU/ml vs. 1853.5 uIU/ml) and at 120-minute of metoclopramide test (606.4 uIU/ml vs. 1328.2 uIU/ml). The prolactin ratio at 120-minute of metoclopramide test to the baseline level was also higher in the group B (11.1 ± 6.5 vs. 14.7 ± 10.2; $P<0.001$).
Conclusion
The results may suggest that prolactin levels are lower in women with PCOS and FAI >5 than in women with PCOS and FAI <5. The prolactin level in PCOS women may be connected with the level of androgenicity in PCOS women.

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EP676

Determinants of the reliable contraceptive use: a nationwide cross-sectional survey in Hungary

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Objective
The purpose of this study was to investigate the contraceptive practice and sociodemographic determinants of employment of contraceptive methods among sexually active women.
Design and methods
A randomly selected representative sample of 4542 women aged 15–49 years from the Hungarian population participated in a prospective web-based and postal questionnaire survey. Women completed self-report questionnaires on socio-demographic characteristics, contraceptive practice and sexual activity between June and July 2015. Factors associated with the use of reliable contraceptives were studied. Multiple logistic regression analysis was applied to evaluate the factors influencing the contraceptive practice of women in reproductive age. Informed consent was obtained by email or written form via post.
Results
The mean age of the women was 29.4 years (±8), and 77% reported urban residents. The rate of use of reliable methods (hormonal contraceptives, intrauterine devices or sterilization) was 43%, while no method was used by 4.7% of the participants. They had stable sexual partnership (91.1%) predominantly and almost one tenth claimed that they had only occasional partner (8.9%).
Logistic regression indicated that high income was favourable for the choice of modern contraceptive methods (adjusted odds ratio (AOR): 1.1), like the increased sexual frequency (AOR:1.1). The number of lifetime partners (AOR:0.99) and sexarche (AOR:0.94) was correlated inversely with the use of reliable contraceptives. Previous abortion (AOR:1.4) or delivery (AOR:1.58) was correlated significantly with an increased chance of reliable method use. Women with future child wish are significantly less prone to the use of reliable methods (AOR:0.70).
Conclusion
To the best of our knowledge, this is the first large scale representative report describing the contraceptive preferences in Hungary as a result of complex interplay between sociodemographic and sexual characteristics.

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EP677

The influence of the body fat distribution on the selected biochemical parameters in a group of women with Polycystic Ovary Syndrome – preliminary report

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Introduction
Polycystic Ovary Syndrome is usually accompanied by metabolic changes such as carbohydrate and lipid metabolism disorders and obesity.
Aim
The aim of the study is to determine the impact of the deployment of body fat on selected biochemical parameters in women with Polycystic Ovarian Syndrome.
Materials and methods
The study included a group of 45 women with diagnosed Polycystic Ovarian Syndrome based on the 2003 Rotterdam criteria. In order to evaluate the distribution of body fat, the WHR (Waist-Hip Ratio) index was used. For the diagnosis of abdominal obesity we adopted the values ≥0.85 and <0.85 for gluteal-femoral obesity. A P value of <0.05 was considered to be significant.
Results
The group of women aged 18-40 years (16.4 ± 5.6) entered the study. Significant differences were found between the group of women with gluteal-femoral obesity and the group of women with abdominal obesity in terms of average values of: HDL cholesterol (mg/dl) (71.08 ± 14.84 vs. 48.95 ± 8.48; $P<0.0001$), TG (mg/dl) (81.80 ± 34.65 vs. 125.58 ± 63.23; $P=0.0054$), HOMA index ($1.97\pm1,64$ vs. 3.07 ± 1.18; $P=0.0186$), SHGB (nmol/l) ($25.69\pm31,53$ vs. 32.44 ± 19.01; $P=0.0008$), free testosterone (pg/ml) (5.74 ± 4.19 vs. 11.81 ± 6.37; $P=0.0004$), and FAI index (4.02 ± 3.31 vs. 8.16 ± 4.00; $P=0.0017$).
Conclusion
Evaluation of body fat distribution seems to be useful in determining the risk of carbohydrate metabolism and lipid metabolism disorders as well as hyperandrogenemia in with Polycystic Ovarian Syndrome patients.

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EP678

The influence of insulin resistance on selected anthropometric and biochemical parameters in women with Polycystic Ovary Syndrome- preliminary report

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Introduction
Polycystic Ovary Syndrome is the most common recognized endocrinopathy in women. The syndrome is often accompanied by obesity and insulin resistance.
Aim
The aim of the study was to assess the differences between the selected anthropometric and biochemical parameters in a group of women with insulin resistance and without insulin resistance.
Materials and methods
The study included a group of 45 women diagnosed with Polycystic Ovary Syndrome based on of the 2003 Rotterdam criteria. Insulin resistance was assess with HOMA-IR index. In accordance with the guidelines of the European Group for the Study of Insulin Resistance, we adopted HOMA-IR <2 as the valid values. Body composition was measured with TANITA BC-420 Analyzer. We assumed a significance level $\alpha=0.05$.
Results
Insulin resistance has been recognized in 57.1% of women. Significant differences were found between the group of women with insulin resistance (average value of HOMA-IR $=3.37\pm1.44$) and the group of women without insulin resistance (average value of HOMA-IR $=1.26\pm0.44$) in terms of average values of: body mass (kg) (83.90 ± 17.06 vs 64.38 ± 14.66; $P=0.0004$), BMI (kg/m^2) (30.62 ± 6.37 vs 24.20 ± 5.57; $P=0.0015$), body fat (%) (39.41 ± 8.15 vs 29.64 ± 8.29; $P=0.005$), visceral fat (6.63 ± 3.21 vs 3.33 ± 2.66; $P=0.0011$), HDL cholesterol (mg/dl) (54.96 ± 13.35 vs 66.72 ± 17.56; $P=0.0193$), SHGB (nmol/l) (36.64 ± 21.09 vs 71.28 ± 33.48; $P=0.0008$), insulin (uU/ml) (14.78 ± 6.06 vs $6.70\pm2,68$; $P<0.0001$) and FAI index (7.53 ± 4.19 vs 3.43 ± 2.85; $P=0.0028$).
Conclusion
In the group of insulin resistant patients, the percentage of body fat and visceral fat were higher. Insulin resistance was also associated with differences in the studied biochemical parameters.

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EP679

Evaluation of serum osteoprotegerin and soluble receptor activator of nuclear factor κB ligand in obese and non-obese patients with polycystic ovary syndrome

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Introduction
Polycystic ovary syndrome (PCOS) is a common endocrinopathy associated with increased cardiovascular risk in reproductive aged women. Circulating osteoprotegerin (OPG) and soluble receptor activator of nuclear factor κB ligand (sRANKL) are associated with subclinical atherosclerosis. Our aim is to evalutate serum OPG and sRANKL levels and their relations with cardiovascular and metabolic markers in paients with obese and non-obese PCOS.
Methods
Overall 25 patients with PCOS (14 obese, 11 non-obese, group 1 and group 2, respectively) and 27 age matched controls (group 3) recruited to the study. Metabolic and hormonal profiles, carotid artery intima-media thickness (CIMT), serum OPG and sRANKL levels were assessed.
Results
Mean OPG and sRANKL levels were similar between three groups ($P>0.05$). Serum HDL levels were similar in group 1 and 2, but significantly different in group 2 and 3, group 1 and 3 ($P=0.4$, $P=0.04$, $P=0.001$ respectively). Serum total testosteron levels were similar in group 1 and 2, group 1 and 3 but significantly different in group 2 and 3 ($P=0.11$, $P=0.31$, $P=0.02$ respectively). Homeostasis model assesment-insulin resistance was similar in group 2 and 3,whereas different in group 1 and 3, group 1 and 2 ($P=0.7$, $P=0.001$, $P=0.001$ respectively). hsCRP levels were significantly higher in group 1 than in group 2 ($P=0.04$). However, CIMT measurements were similar in three groups. Furthermore, no significant correlation between OPG, sRANKL and cardiovascular and metabolic parameters.
Conclusion
PCOS is associated with increased cardiovascular risk particularly in obese patients. Based on the results of this study, OPG and sRANKL had not taken a critical role on the development of preclinical atherosclerosis in PCOS. Further prospective studies are needed in large number of patients on this issue.

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EP680

Validation of the Estradiol III assay (Roche) in the ovulatory phase

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Introduction
Estradiol is an important parameter in the evaluation of female fertility. Moreover, the measurement estradiol is essential in determining the right moment for oocyte retrieval in modified natural cycle IVF (MNC-IVF). Estradiol is measured by an immunochemical method and a change between immunoassays usually comes with a change in reference values due to differences in antibodies used and the lack of harmonization. In our hospital we changed in 2014 from the AutoDELFIA assay (AD) (PerkinELmer) to the Roche method because of continuity. Unfortunately, within a year after the introduction of the Estradiol II assay ($E2^{II}$) (Roche) the manufacturer introduced of the Estradiol III assay ($E2^{III}$), leading to another change in reference values which is disturbing continuity in patient care.
Methods
Estradiol levels related to follicle size from patients followed in the (MNC-IVF) in 2013 (using AD) were compared with levels from patients from 2015 (using $E2^{II}$) by status research. $E2^{III}$ was compared to $E2^{II}$ according to the CLSI EP9 and EP5 protocols. Since the given reference levels between the two assays varied more than the two assays differentiated from each other, especially in the ovulatory phase, the $E2^{III}$ assay was evaluated in 23 patients followed in the MNC-IVF.
Results
The $E2^{II}$ assay results in ~25% higher estradiol levels compared to AD assay. At follicle size 18 mm average estradiol levels were 0,87 nmol/l ($E2^{II}$) vs. 1,06 nmol/l (AD). Passing-Bablok regression from $E2^{II}$ vs. $E2^{III}$ was $E2^{III}=0.02+0.93\times E2^{II}$ over the whole range. In the range used in MNC-IVF patients the comparison was $E2^{III}=0.02+0.85\times E2^{II}$.
Conclusion
The $E2^{III}$ resulted in 15% lower values compared to the $E2^{II}$ in patients in MNC-IVF, but are more comparable to the formerly used AD. However, the median reference value for the ovulatory phase set by the manufacturer was 44% lower, therefore, new reference values should be set.

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EP681

The influence of hormonal disorders on quality of life of women with acne

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Introduction
About 80% of people had acne of some form. This dermatosis manifests at age 12–14, when there is a physiological increase in the level of hormones, and in most cases it regresses at 18–22. However today, the number of women with acne at age 25 and older has significantly increased.
Methodology
Conducted was prospective observational study involving 126 women aged 19 to 37 years with inflammatory form of acne of different severity. All of the women were studied for blood hormonal level in order to detect the syndrome of hyperandrogenism. Quality of Life Cardiff Acne Disability Index (CADI) was used in order to assess the quality of life of patients.
Results
Among the examined 126 women, condition of acne was mild in 42% of cases, moderate in 51%, and severe in 7%. According to the level of hormone concentrations in blood, syndrome of hyperandrogenism was determined in 109 of studied females. Adrenal genesis of hyperandrogenism was established in 44.9% of women, mixed genesis - in 34.9%, and ovarian genesis - in 20.2%. Among the women of this research, the mean score on the CADI responses was 7.8, and 84.1% of them had the CADI score more than 6, indicating a marked impact on quality of life. The mean score of CADI in women with adrenal type of hyperandrogenism was 6.2, with ovarian type - 7.3, and with mixed type - 9.8.
Conclusion
It was found out that 86.5% of adult women with acne had different hormonal disorders that lead to development of acne. It was also found out that the quality of life of women with acne is influenced not only by the severity of the clinical manifestation and localization of skin rashes, but an important role is played by the genesis of hyperandrogenism.

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EP682

Polycystic ovary syndrome (Pcos) in female-to-male (Ftm) transsexual persons

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This study was conducted to evaluate the frequency of PCOS in a group of FTM transsexual persons and its relationship between clinical, hormonal and metabolic characteristics.
Subjects and Methods
We studied 21 FTM cases, aged 17–37 years, BMI 24.6 ± 5.2. No patient reported previous hormonal treatment or sex re-assignment surgery. PCOS was diagnosed according to the Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group, 2004. World Health Organization's criteria for metabolic syndrome (MBS) was used. Insulin resistance was determined using the homeostasis model assessment of insulin resistance (HOMA-IR).
Results
Twelve out of 21 FTM trans participants (57.1%) were diagnosed as PCOS. None of the PCOS patients had MBS. No significant differences in BMI nor plasmatic levels of free and total testosterone, LH, FSH, estradiol, cholesterol and triglycerides were found between PCOS and no PCOS trans patients. PCOS trans patients had higher plasmatic insulin levels and HOMA-IR compared to no-PCOS FTMs (8.6 ± 3.5 vs. 4.5 ± 1.6; $P<0.005$ and 2 ± 0.9 vs. 0.9 ± 0.4; $P<0.05$ respectively).

Conclusions
In our study we found more than half of FTM individuals with PCOS, which was associated with elevated levels of plasmatic insulin and HOMA-IR. Our data suggest that transsexual men should be screened for PCOS and parameters of insulin resistance, as PCOS and cross sex androgen treatment have been reported as predisposing factors for the development of diabetes. A larger study is ongoing in order to confirm these preliminary results.

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EP683

Increased level of serum irisin concentration and its regulation by hyperinsulinemia in women with polycystic ovary syndrome

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Background
Irisin is an adipokine/myokine which could be connected with insulin sensitivity. Polycystic ovary syndrome (PCOS) is characterized by oligo- or anovulation, polycystic ovary, hyperandrogenism and insulin resistance.
Objective
The aim of the present study was to determine the relationship between serum irisin concentration and insulin sensitivity (M_{ffm}) as well as the effect of insulin infusion on circulating irisin levels in PCOS women as compared with healthy controls.
Subjects and methods
Seventy seven women were enrolled in the study - 57 with PCOS and 20 healthy controls matched for BMI and age. Hyperinsulinemic euglycemic clamps were performed in all of the study participants. The serum concentrations of irisin at baseline and after the clamp, as well as changes of serum irisin concentration in response to insulin supplied during the clamp (Δ irisin), were estimated.
Results
The mean serum concentrations of irisin achieved at baseline and after hyperinsulinemia were higher in PCOS women in comparison to the control group ($P=0.01$; $P=0.006$, respectively). Insulin infusion resulted in a decrease of serum irisin concentration only in the PCOS group ($P=0.007$). In the control group, Δ irisin positively correlated with M_{ffm} ($r=0.56$, $P=0.009$). In the entire group, multiple regression analysis showed that Δ irisin ($\beta=0.70$, $P=0.0002$), FFAs 60' during the clamp study ($\beta=-0.22$, $P=0.01$), SHBG ($\beta=0.54$, $P<0.0001$) and the interaction between Δ irisin and PCOS ($\beta=-0.67$, $P=0.0004$) were significantly associated with M_{ffm}.
Conclusion
An increase in serum irisin concentration at baseline and an inappropriate change in response to insulin infusion might be secondary to insulin resistant conditions in PCOS women.

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EP684

Usefulness of dynamic Tsh evaluation for diagnosis of subclinical hypothyroidism in luteal deficiency

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Introduction
It is known that thyroid disorders can influence menstrual cycle, but subclinical hypothyroidism (SH), as cause of ovulation disorders and luteal deficiency (LD) in particular,is underestimated. Monitoring women's cycles, according to the Billings Ovulation Method (BOM), can allow a precise timing for hormonal evaluation and diagnose LD. Usually, a basal TSH value of 2.5 mg/ml is considered as cut-off for a good luteal function, but alone cannot identify all cases of SH. In order to verify the sensitivity of TSH dynamics, we have performed TRH test (200 mg iv) in patients with LD, stratifying women according to different ranges of basal TSH values.
Methods
We enrolled 65 women, 20–45 ys, consulting our Centre aimed to learn the BOM for achieving or spacing pregnancy. 40 exhibited an history of infertility. LD was diagnosed by a shortened post-Peak phase length (<11 days) and/or low progesterone (P) levels on the 6th or 7th days after the "mucus peak". SH was diagnosed with TSH peak >15 mcU/ml after TRH administration (normal basal TSH range: 0.4–3.2 mg/ml, by ECLIA). RESULTS: According to basal TSH levels, patients were divided in 3 groups: group A ($n=17$, 0.8–1.4 mg/ml), group B ($n=20$, 1.5–2.4), group C ($n=28$, 2.5–6.5). An increased TSH response was observed in 3/17 patients of group A, 14/20 of group B, 27/28 patients of group C. In the overall group, the evidence of thyroid autoantibodies was 23% and therefore we escluded auto-immune mechanism as cause of ovarian dysfunction. Mean progesterone levels were in the low-normal range in all groups (mean ± S.E.M: 6.8 ± 1.7 in group A, 10.5 ± 2.3 in group B, 8.5 ± 0.1 in group C).
Conclusion
These data suggest that SH has an important impact on luteal function; BOM can be effective for screening these situations and give rise a useful tool in diagnostic and therapeutic options in subfertile couples. Dynamic TSH evaluation can allow to diagnose SH,even in presence of normal TSH basal levels.

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EP685

Subclinical hypothyroidism and polycystic ovary syndrome

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Introduction
The correlation of subclinical hypothyroidism (SH) and polycystic ovary syndrome (PCOS) is a still insufficiently explored entity. It is known that the patients with PCOS are at the greatest risk of infertility as well as cardiovascular morbidity and mortality. The aim of this study was to determine the existence of correlation between SH and PCOS. We also aimed to investigate the impact of SH on the metabolic and endocrine parameters in women with PCOS.
Methods
The study included a total of one hundred and ninety-eight women of reproductive age with PCOS, divided into two groups: group I (83 patients with PCOS and SH) and group II (115 PCOS patients with normal thyroid function). Endocrine and metabolic parameters were measured in all patients and compared between women with and without elevated thyroid-stimulating hormone (TSH) levels. Laboratory tests were included lipid profile, glucose and insulin levels during oral glucose tolerance test, levels of C-reactive protein (CRP), steroids, prolactin and TSH. We also analysed insulin resistance index (HOMA-IR) and body mass index (BMI).
Results
PCOS women with SH showed higher values of total cholesterol ($P=0.01$), CRP ($P=0.001$), HOMA-IR ($P=0.001$), androgens and BMI ($P=0.01$) compared to PCOS women with normal thyroid function. Furthermore, there was a significant correlation between subclinical hypothyroidism and metabolic, hormonal and clinical parameters in women with PCOS. SH is significantly correlated with: BMI ($P=0.01$), HOMA-IR ($P=0.001$), CRP ($P=0.001$), cholesterol ($P=0.01$) and with androgens ($P=0.001$). SH is negatively correlated with SHBG ($P=0.001$).
Conclusion
Subclinical hypothyroidism significantly correlated with polycystic ovary syndrome. Subclinical hypothyroidism has a significant impact on clinical, metabolic and hormonal characteristics in patients with PCOS. Therefore, women with diagnosed PCOS should be screened for thyroid dysfunction.

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EP686

Cigarette smoke exposure disturbed maturation of ovarian follicle and induced abnormal growth of uterus inner wall of female rats

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Cigarette smoke (CS) is well known to be very harmful to human body functions such as fertility, reproduction, and development. To elucidate the effect of CS on women's fertility more definitely, we examined the histophaological characteristics of the uterus and ovary samples received from Korean Conformity Laboratories (KCL), which were obtained from the female rats exposed to the different amounts (low, medium, and high concentrations) of smoke of the standard cigarette (3R4F) for 2 h/day and 5 days/week for 28 days according to the OECD guidelines. The animals used for the present study were the spontaneously hypertensive female Wistar Kyoto (WK) rats. We manufactured tissue slides from uterus and ovary samples and evaluated maturation of follicle of ovary and uterus development through H&E and immunohistochemistry (IHC). As a result, we confirmed decreased maturation of follicle and abnormal uterus development by CS exposure. In IHC analysis on ovary tissues, the expression of PCNA was decreased, but the expression of Bax, a pro-apoptotic protein, and C/EBP homologous protein (CHOP), an endoplasmic reticulum (ER)-stress marker, was increased by exposure to CS compared to the control (ovary tissues from non-exposed rats). For uterus, the thickness of inner wall of uterus was decreased by the exposure to CS at low and medium concentrations. In accordance with this result, the expression of PCNA was decreased, but the expression of Bax and CHOP was increased by exposure to CS at low and medium concentrations. However, acute exposure to CS at high level induced the abnormal over-growth of uterus wall. Taken together, the exposure of CS may have a harmful effect on women's fertility and pregnancy by inducing decreased maturation of ovarian follicle and abnormal growth of uterus inner wall.

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EP687

Would thyroid binding globulin compensate for albumin loss during pregnancy?

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Introduction
Normal thyroid function is necessary for normal body function. During pregnancy if the thyroid hormone deficiency, it will induce maternal and fetal hypothyroxinemia. And the vulnerable fetuses and neonates will suffer from irreversible deficit in the neuro-psycointellectual development including mental retardation. It is being established that albumin level decreases during pregnancy with recorded increase in urine microalbumin, An elevation in both thyroid stimulating hormone (TSH) and TBG levels was also described during pregnancy. Therefore, the aim of this study was to investigate the relation between TSH and TBG changes and its correlation to reduced albumin during the three trimesters of pregnancy.
Method
Blood samples were collected from 20 healthy nonpregnant (control) and pregnant females at their first ($n=32$), second ($n=29$) and third trimesters ($n=30$). Serum albumin, thyroid stimulating hormone (TSH) and thyroid binding globulin (TBG) were measured as well as urine microalbumin.
Results
Albumin levels were a significantly reduced $P<0.01$, by the third trimester compared to control subjects. A small increase in urine microalbumin was noted with progression of pregnancy, however, not significant. Measurements of TBG and TSH showed a statistically significant increase in both parameters with the progression of pregnancy, and the changes in TBG levels were negatively correlated ($r=-.08$) with a similar percent of change noticed in albumin levels. This was manifested by the 43%, 52% and 56% increase in the TBG levels in the first, second and third trimesters compared to control respectively.
Conclusion
The albumin reduction during pregnancy is known to be resulting from the increased glomerular filtration rate. Albumin is also known as a minor carrier protein for thyroid hormones, therefore, we propose increased TBG levels is a response and compensatory to the reduction in albumin to meet the high demand for the fetus for the thyroid hormones.

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EP688

Endocan as a novel biomarker to evaluate cardiovascular risks in Polycystic Ovary Syndrome

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İntroduction
Polycystic ovary syndrome (PCOS) is associated with risk of cardiovascular disease (CVD). Endocan is potential immunoinflammatory and endothelial dysfunction marker that may be linked to CVD. This study aimed to evaluate the risk of CVD in PCOS patients and to identify the novel biomarker for CVD risk.
Material and methods
We analyzed 52 premenopausal women with PCOS and 59 healthy controls. Clinical, biochemical parameters and endocan were analysed.
Result
Ferriman Gallwey score, BMI, waist-hip ratio, HOMA-IR, total testosteron were significantly higher in PCOS than controls. Serum endocan levels were significantly higher in the PCOS compared with the controls (457.19±239.32 vs 356.85±183.48 ng/ml, $P=0.015$, respectively) (Table 1).

Table 1 The clinical, biochemical analyses of PCOS and controls.

	Controls	PCOS	*P*
Age (years)	25.93±5.22	23.46±5.31	**0.015**
BMI (kg/m2)	22.56±3.23	26.90±5.69	**0.001**
Waist-hip ratio	0.77±0.66	0.85±0.54	**0.012**
Ferriman Gallwey Score	6.89±0.97	15.11±5.60	**0.001**
Glucose (mg/dl)	78.44±8.57	81.37±7.71	0.652
HOMA-IR	1.80±0.93	3.53±2.61	**0.001**
Total testosteron (pg/ml)	29.96±9.26	66.45±27.26	**0.001**
Endocan (ng/ml)	356.85±183.48	457.19±239.32	**0.015**

Conclusion
Endocan is a potential inflammatory and CVD biomarker in PCOS. Further studies are needed to assess the relevance of endocan in CVD risk of PCOS.

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EP689

Body composition in lean women with polycystic ovary syndrome (PCOS) in relation to lipids and insulin resistance

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Introduction
PCOS women appear to have an adverse body composition (BC). The aim of this study was to compare BC in lean PCOS in comparison to controls and to assess possible metabolic consequences.
Methods
We evaluated 150 lean PCOS women (BMI: 20.96±2.06 kg/m^2; age: 25.50±4.52 years) diagnosed using ESHRE/ASRM criteria, and 39 lean BMI-matched healthy women (BMI: 20.33±2.16 kg/m^2; age: 27.67±5.39 years). BC was evaluated using bioelectrical impedance (Tanita) and waist circumference (WC) was measured. In follicular phase of menstrual cycle lipids, glucose, and insulin were determined. Insulin resistance was determined by homeostasis model assessment (HOMA-IR) and lipid ratios were calculated. All analyzes were age adjusted.
Results
There were no difference between groups in WC ($P=0.066$), whole body (WB) fat mass (FM, $P=0.063$), and WB fat free mass (FFM, $P=0.763$), abdominal FM

(AFM, $P=0.079$) and abdominal FFM (AFM, $P=0.520$), HDL ($P=0.777$), LDL ($P=0.065$), LDL/HDL ($P=0.059$), triglycerides/HDL ($P=0.086$) and HOMA-IR ($P=0.115$). PCOS women in comparison to controls had higher FM/FFM ratio (0.35 ± 0.01 vs. 0.31 ± 0.02, respectively, $P=0.044$), total cholesterol (TC) (5.05 ± 0.09 vs. 4.65 ± 0.17, respectively, $P=0.037$), triglycerides (0.92 ± 0.03 vs. 0.78 ± 0.06, respectively, $P=0.048$), non-HDL (3.57 ± 1.08 vs. 3.27 ± 0.80 mmol/l, respectively, $P=0.037$), TC/HDL (3.51 ± 0.07 vs. 3.18 ± 0.13, respectively, $P=0.029$). In PCOS group FM/FFM correlated with WC ($\rho=0.561$, $P<0.001$), non-HDL ($\rho=0.176$, $P=0.032$), TC/HDL ($\rho=0.228$, $P=0.005$) and LDL/HDL ratio ($\rho=0.196$, $P=0.016$).

Conclusion

Our lean PCOS women had the same BC as lean controls although with disproportional FM to FFM, and that suggested its possible involvement in the pathogenesis of dyslipidemia in PCOS. As HOMA-IR index predominantly assess hepatic insulin resistance, it could possibly explain lack of correlation between FM/FFM and HOMA-IR.

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EP690

Turner syndrome and reproductive counseling

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Introduction

Spontaneous fertility in Turner syndrome (TS) is rare, due to low or absent ovarian reserve. A greater number of ovarian follicules is present in the cases of gonadal mosaicism, although the accelerated pace of apoptosis remains. Thus, the early referral to reproductive counseling is advisable, ideally soon after diagnosis. The criopreservation of oocytes is one of the options for fertility preservation. The authors present a series of 7 patients with TS admitted in Reproductive Medicine Department between 2012 and 2015.

Case reports

Case 1: 33-years-old, karyotype 45,X, admitted with primary infertility. Because of low ovarian reserve, she was advised about oocyte donation and cardiovascular risks of pregnancy were explained. Case 2: 37-years-old, karyotype 45,X, admitted for fertility preservation. After the second ovarian stimulation cycle (OSC), she has 1 oocyte criopreserved. Case 3: 37-years-old, karyotype 45,X/46,XX. Admitted with secondary infertility (one previous pregnancy three years ago after *in vitro* fertilization). The two OSC were unsuccessful. Case 4: 16-years-old, karyotype 45,X/46,XX and admitted for fertility preservation. After the first OSC, she has 11 criopreserved oocytes. Case 5: 33-years-old, admitted with primary infertility, karyotype 45,X/46,XX. After the first OSC, three oocytes were retrieved, originating 2 embryos, which were not transfered because of bad development. Case 6: 24-years-old, karyotype 45,X. She was informed that pregnancy is contraindicated because of cardiovascular disease (bicuspid aortic valve with mild regurgitation). Case 7: 33-years-old, karyotype 45,X. Admitted with primary infertility. The patient has a mild aortic aneurisma. She was referred for oocyte donation because of poor ovarian reserve and will to conceive, despite the risks.

Conclusion

These 7 cases illustrate the complexity of reproductive counseling in these patients. Early referral increases the probability of success in oocyte preservation. The ovarian reserve, structural cardiovascular disease and ethical problems condition the therapeutic options.

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EP691

Flutamide treatment in severe acne in women-still controversial

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Guidelines recommend hormonal treatment in severe acne, in forms of acne with no response to standard therapeutical options, in women with proved hyperandrogenism. Hormonal therapy for acne includes oral contraceptives; anti-androgens, such as cyproterone acetate, spironolactone and flutamide; low-dose glucocorticoids and gonadotropin-releasing hormone agonists.

In daily practice there are many cases with moderate to severe forms of acne, in young women without any clinical or hormonal abnormalities, who do not respond to systemic antibiotics, associated with topical antibiotics, azelaic acid, tretinoin, benzoyl peroxide or combinations.

We performed a study on 44 young women, with age ranging from 17 to 37 years, with non-responding severe forms of acne after 6 months of therapy.

Endocrine examination was done at the beginning of the study measuring: testosterone levels, BMI, calculating Ferriman hirsutism score and evaluating liver function.

Out of 44 patients only 6 patients (13.4%) had high levels of testosterone and no other lab abnormal parameters. We presumed a high affinity of androgen receptors to normal level of testosterone and antiandrogen treatment was started. Hormonal therapy was performed for 6 consecutive months using different schemas such as: only flutamide 125 mg/day in 27 cases; flutamide 125 mg/day associated with spironolactone 100 mg/day and metforfin 500 mg/day in 3 cases; flutamide 125 mg/day plus utrogestan 100 mg/day and metformin 500 mg/day in 1 case; flutamide 125 mg/day and spirolonactone 50 mg/day in 6 cases; flutamide 125 mg/day and metformin 500 mg/day in 7 cases. The same topical anti acne treatment was associated in each case: azelaic acid and erythromycin plus tretinoin applied daily.

Good tolerability and no side effects have been declared.

Despite different association of hormonal therapy clearing of acne was achieved at the end of 6 months of treatment with no difference, but in all cases rebounds were observed after withdraw the hormonal therapy, despite the maintenance of the topical treatment.

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EP692

Resistant macroprolactinoma and infertility: a difficult challenge

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Introduction

Dopamine agonist resistance is rare in prolactinoma (10%). Doses of cabergoline of up to 2.0 mg/week are usually effective in controlling prolactin (PRL) secretion and reducing tumor size. Surgical treatment is rarely indicated.

Case report

An 18-year-old female presented in 2002 with a 2-year history of amenorrhea and galactorrhea. Hormonal investigation showed a hyperprolactinemia (4800 mUI/l) with integrity of the other pituitary axis. The acromegaly was excluded. The magnetic resonance imaging (MRI) revealed a 2 cm pituitary adenoma with suprasellar extension. The visual field showed central bilateral scotoma.

The patient was initiated on bromocriptine, which was titrated to a daily dose of 15 mg. Subsequent MRI showed a decrease in the pituitary mass to 11 mm but PRL never normalized during 6 years of bromocriptine and ranged from 1677 to 3074 mUI/l.

In 2010, she switched to cabergoline, which was titrated to a weekly dose of 2.5 mg. Subsequent MRI showed no amelioration, prolactin never normalized and the patient was always in amenorrhea, despite compliance to cabergoline and increasing to a weekly dose of 6 mg.

Finally, she was referred to neurosurgery and she underwent a transsphenoidal endoscopic resection of the pituitary adenoma. The immunohistochemical analysis demonstrated positive staining for PRL (+++) and LH(+). Ki-67 nuclear labeling was estimated at 1%.

The patient had no postoperative complications, with integrity of corticotrope and thyretrope axis. But 3 months after the surgery, she had no resumption of menses and the hormonal exploration showed a hyperprolactinemia (2668 mUI/l). The serum HCG level was elevated. A spontaneous pregnancy of 13 weeks of amenorrhea was diagnosed.

Conclusion

Although rarely indicated, the surgical treatment is interesting in resistant prolactinoma, especially in young woman with infertility.

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EP693

A 12-year-old virilized girl

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Introduction
Hyperthecosis ovarian is a type of hyperandrogenism and severe insulin resistance, usually found in postmenopausal women.
Case Report
This case is about a 12 year-old girl who came to our hospital because of a rapidly progressive virilization. She had no medical history. For the previous 10 months, she had felt progressive growth of terminal hair in androgen-dependent areas, abundant hair loss, facial acne and voice changes. Axilarche and pubarche had occurred when she was 10 years old. She had not had menarche. She was not in contact with exogenous testosterone preparations. Physical examination revealed a score of 28 on the Ferriman Gallway scale, mild cervical acanthosis nigricans, clitoris hypertrophy and Tanner stage 2 breast development. Laboratory tests showed: glucose 78 mg/dl, HbA1c 4.8%, FSH 7.47 (follicular phase 3.6–12.5 mU/ml), LH 10.33 (follicular phase 1.7–12.5), 21.47 prolactin (6–30 ng/ml), 17 OH-PG 2.8 (0.1–1.4 ng/ml), DHEAS 96.3 (33.9–280 mcg/dl) androstenedione 3.1 (0.5–4.7 ng/ml), total testosterone 4.23 (0.06–0.82 ng/ml), free testosterone 6.2 (0.2–3.2 pg/ml), SHBG 7 (20–140 nmol/l), basal cortisol 28 (6.2–19.4 mcg/dl), insulin 100.9 mIU/ml (2.6–24.9). Hypercortisolism and 21-hydroxylase deficiency tests were negative. The pelvic MRI showed enlarged ovaries with oval morphology of $50\times17\times18$ mm (right) and $48\times19\times18$ mm (left). The patient underwent a laparoscopic bilateral ovarian wedge resection. The pathology showed ovarian hyperthecosis with androgen-positive receptors. After the surgery, the total testosterone levels were 4.12 ng/ml. Treatment was initiated with flutamide 250 mg/day and metformin 2000 mg/day. The patient experimented the menarche two months after starting treatment. Currently it is being considered to start GnRH analogues and hormone replacement therapy with metformin.
Conclusions
The clinical interest of this case lies in the severity of the disease, early age of onset and the difficult therapeutic management of the disease in premenopausal women, with very little bibliography available.

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EP694

Correlation between dehydroepiandrosterone-sulfate levels and markers of bone turnover in hypothalamic amenorrhea

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It is known that functional hypothalamic amenorrhea is associated with low bone turnover due to low gonadal homone levels. Estrogens are critical for activation of bone remodelling units, suppression of bone reabsorption, increase of 1-25(OH)Vitamin D receptors expression. Other mechanisms could be operative, including improper diet and unbalanced exercise; however the physiopathology of such a condition is not entirely known. In order to evaluate the correlation between pituitary, gonadal and adrenal hormones with markers of bone metabolism, we have studied a group of 21 female patients with a history of secondary amenorrhea, lasting at least six months.
They were aged 19–35 ys, with a BMI range 17.5–19.5 kg/mq. Bone mineral density (BMD) was determined by DXA scan at lumbar spine and neck of the right hip femur. The following parameters were evaluated in a blood morning sample: FSH, LH, estradiol, ACTH, DHEAS, osteocalcin, bone alkaline phosphatase, beta-crosslaps, Vitamin D and PTH. Hormones were assayed by CMIA or CLIA method; osteocalcin and beta-crosslaps by electrochemiluminesce.
DXA evaluation showed a significant reduction in BMD (osteopenia or osteoporosis) in 8 patients (T score at lumbar spine from -1.1 to -2.9). Mean $\pm$ SD FSH and LH levels were respectively 5.5 ± 1.28 mUI/ml and 3.52 ± 3.13 mUI/ml; Estradiol levels were 31.1 ± 7.7 pg/ml and 25(OH)-Vitamin D 28.8 ± 7.2 ng/ml (with 13 patients with values in the range of Vit.D deficiency); DHEAS, on the contrary, were in the normal range (2460.4 ± 615.1 ng/ml) and showed a significant direct correlation with osteocalcin ($P<0.05$).
These preliminary data suggest that, in presence of low estradiol levels, the main regulation of bone formation could be represented by DHEAS. Further studies can show the possible therapeutic implication of these data.

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EP695

High testosterone level in Chronic Liver Disease

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A 26 year old lady under investigation for infertility was referred to our endocrine clinic for raised testosterone levels at 6.6 nmol/l (0.5–2.8).she had regular period with no features of hirsutism. Her past medical history included common acute lymphoblastic leukaemia on chemotherapy, liver cirrhosis with portal hypertension secondary to chemotherapy, Trans jugular intrahepatic portosystemic shunt (TIPS) insertion for bleeding gastric varices.
Clinical examination she has no features of hirsutism.
Endocrine Investigations: Plasma Testosterone- 6.6 nmol/l, SHBG 139 nmol/l, Androstenedione 35 nmol/l were high. DHEAS, Dihydrotestosterone, TSH, Prolactin, gonadotropins and oestrdiol were within reference range. Baseline and post synacthen 17-hydroxypregestrone were normal. The repeat short synacthen test showed normal cortisol response and follicular phase 17 OHP was not raised making congenital adrenal hyperplasia unlikely. Low dose dexamethasone suppression test showed supressed cortisol, testosterone, androstadiene and DHEA which excludes adrenal/ovarian androgen producing tumours.
Her day 21 progesterone was reasonable but still she was unable to conceive. A urine steroid profile showed low virilising androgen metabolites but increased androstenetriol and normal a-cortlone levels. CT adrenals excluded ovarian and adrenal pathology.
Discussion The high testosterone level in this patient was likely to be due to portal hypertension secondary to liver cirrhosis. The majority of patients with liver cirrhosis have raised SHBG concentrations which in fact will protect them from virilising symptoms. This accounts for the less free plasma testosterone concentrations. As per our literature search we could find only one another case with similar condition. We do not believe her high testosterone is contributing to her infertility especially when she does not have any signs of androgenisation and we suspect virilisation risk of the foetus is extremely low if she conceives. However foetus is completely protected by placental aromatase which inactivates maternal androgens.

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EP696

Increased uric acid levels and clinical relationship in polycystic ovary syndrome

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Introduction
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder that affects women of reproductive age. Clinical and biochemical characteristics are similar to metabolic syndrome. Insulin resistance in patients with metabolic syndrome, is associated with serum uric acid levels. In our study, we aimed to investigate the relationship between serum uric acid levels and clinical and laboratory in PCOS patients.
Materials and Method
PCOS patients and 34 age and body mass index (BMI) matched control, a total of 206 cases attending at endocrinology outpatients clinic included in the study. Early follicular phase, blood samples were taken after 12-hour fasting. Basal serum hormone levels were measured by immunoassay.

Results
Uric acid levels was statistically significantly higher in PCOS than control group (4.25 ± 1.07 PCOS control 3.7 ± 0.79, $P = 0.048$). Uric acid levels were positively correlated with BMI, total cholesterol, insulin, cycle time, Feriman Gallwey score and negatively correlated with HDL cholesterol levels. Uric acid levels were higher than 2 times in PCOS group independently age and BMI with multivariate logistic regression.
Conclusion
Uric acid levels in study group was significantly higher independent of age and BMI. Cardiovascular risk factors; LDL, insulin, triglycerides, BMI was positively correlated with uric acid in PCOS group. Clinical indicators; Feriman Gallwey score and cycle time was also positively correlated. Elevated uric acid levels in PCOS patients may be a risk factor for cardiovascular disease, may show negative results in the clinic.

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EP697

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Introduction
Polycystic ovary syndrome (PCOS) is a common endocrinopathy affecting 6–10% of reproductive aged women. This syndrome is associated with obesity, menstrual irregularity, infertility, hirsutism and insulin resistance. It has been reported that PCOS is frequently associated with hyperprolactinemia with ranges from 17 to 50%. So for many researchers the difficulty is to differentiate between real PCOS associated with hyperprolactinemia or hyperprolactinemia with PCOS aspect (chronic anovulation and polycystic ovaries.
Objective
This study aims to to identify the cause of hyperprolactinemia in patients with PCOS.
Materials
A prospective study was performed (since 2010–2015) on 100 PCOS.The consensus of Rotterdam was used to make the diagnosis of PCOS. All patients were screened for clinical exam, anovulation, prolactinemia, hypophysis MRI and pelvic ultrasound. The hyperprolactinemic patients were first treated with dopaminergic agonist.
Results
The mean BMI was 27.2 kg/m2 and the mean age 24.5 years. The mean prolactinemia was 65 ng/ml Twelve ($n = 12$) of our patients had hyperprolactinemia (12%). Among them 9 (75%) had micro-prolactinoma, one used neuroleptics and 2 were idiopatic (as no causes was found). All of them were treated with dopaminergic agonist without improvement of the symptomatology.
Discussion
In our study hyperprolactinemia is quite frequent (12%) in PCOS women. In all cases the diagnosis of hyperprolactinemia was made. In order to distinguish PCOS with hyperprolactinemia from hyperprolactinemia with PCOS aspect, agonist dopaminergic were used. The absence of improvement confirm the fact that PCOS and hyperprolactinemia are distinct, in fact patients with PCOS do not respond to bromocriptine treatment because they do not have alterations in hypothalamic dopamine secretion.
Conclusion
It's important to make a systematic investigation on the origin of hyperprolactinemia in women with chronic anovulation in order to distinguish it from PCOS. In all of our patient a well-defined cause for the high PRL level was identified.

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EP698

Can weight loss reverse polycystic ovary syndrome?

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Introduction
Weight loss is a mainstay in the treatment of polycystic ovary syndrome (PCOS). While the cause of this complex endocrine disorder remains unknown, it's approved that weight loss improves symptoms of PCOS. We report a case of a patient with PCOS. Her symptoms disappeared totally after losing 50kg
Case report
In 2005, a 16-year-old girl presented for evaluation of spaniomenorrhoea and obesity. Physical examination showed a weight of 88 kg, a body mass index (BMI) of 37.5 kg/m^2, a waist circumference of 85 cm and a normal blood pressure (110/80 cmHg). The patient had no clinical signs of hyperandrogenism. Serum testosterone and luteinizing hormone levels were elevated, while follicle-stimulating hormone, prolactin and 17-OH progesterone levels were normal. Fasting blood glucose, oral glucosetolerance test and serum lipid profile were normal. Pelvic ultrasound showed bilateral polycystic ovaries. There were no clinical signs of Cushing syndrome. The diagnosis of PCOS was established. She was evaluated by a nutritional therapist and given lifestyle advice to reduce weight and increase physical activity. Metformin 1.7 g/day (850 mg*2) was started in order to improve insulin sensitivity.
Within 2 years, there was a 20 kg weight reduction and her BMI decreased to 27.9 kg/m^2. Menses were normal without progesterone medication during 3 years. But thereafter the patient no longer followed life style rules, she gained weight to 102 kg in 3 years (BMI:42.3 Kg/m^2). She presented for obesity and secondary amenorrhea (since 6 months). Lifestyle changes and metformin therapy were reapplied.
Now, 2 years after lifestyle changes and metformin therapy, the patient weights 52 kg (BMI: 24.3 kg/m^2). She has normal ovulatory cycles and normal testosterone.
Conclusions
Our case illustrates the close relationship between overweight and PCOS. Therefore, lifestyle changes should be the first-line intervention in these patients, especially in presence of obesity.

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Growth hormone IGF axis – basic

EP699

A placebo-controlled study of repeated subcutaneous doses of COR-005 alone or with octreotide on GHRH-stimulated GH and pharmacokinetics in healthy male subjects

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Octreotide is first-line medical therapy for patients with acromegaly. Up to 80% of patients are not satisfactorily controlled on octreotide alone and up to 20% have no response. COR-005 (previously DG3173) is a novel somatostatin analogue under investigation for treatment of acromegaly. COR-005 has high affinity for human somatostatin receptor subtypes 2, 4 and 5.
The study was designed to assess pharmacokinetics of escalating doses COR-005 sc tid and compare the pharmacodynamics of COR-005 alone or in combination with octreotide 300 μg sc tid for 6.3 days versus octreotide 300 μg sc tid alone and placebo on GHRH-stimulated GH profiles.
A total of 42 subjects (6 total per group) received placebo (P, $N = 1$/gp), octreotide 300 μg tid (O, $N = 1$/gp) or COR-005 alone (C, $N = 4$/gp) as 100 μg, 300 μg, 900 μg, or 1800 μg C tid or as 100 μg or 300 μg or 900 μg C in combination with O. GHRH stimulation was performed before first and after four treatments.
Maximal inhibition of GHRH-stimulated GH by COR-005 or octreotide alone was ranked as follows: $P <$ (100 μg C or 300 μg C) $<$ (900 μg C or O) $<$1800 μg C. GH inhibition with combinations of COR-005 and O were in the order of: O $<$ (O + 100 μg C and O + 300 μg C) $<$ O + 900 μg C. COR-005 T_{max} was $\leq$1 hour and $t_{1/2}$ was $\sim$2 h after first and last injections. C_{max} and $AUC_{0\text{-}8}$ increased dose-linearly. Co-administration of COR-005 with O did not affect C PK below 900 μg, greater variability in C $AUC_{0\text{-}8}$ was noted at 900 μg.
COR-005 inhibits dose-dependently GHRH-stimulated GH with less potency but similar maximal efficacy as maximally dosed octreotide.

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EP700

Quality of Life (QoL) and IGF-I Status in Adults with Severe GHD

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Introduction
In adult patients with pituitary disease no relationship has been established between the biochemical severity of GHD and the degree of QoL impairment. Reasons may include heterogeneity of underlying pathologies, and the type of therapies received by GHD patients.
Methods
The KIMS (Pfizer International Metabolic Database) database was used to focus solely on patients with non-functioning pituitary adenomas and prolactinomas treated by surgery alone. Entry criteria include peak GH of less than 3 ng/ml to an ITT and at least 2 other pituitary hormone deficits. IGF-I was measured centrally and IGF-I SDS calculated using normal range for age and gender. Health-related QoL was measured using QoL-AGHDA, a disease-specific validated questionnaire for which higher scores (0-25) indicate worse QoL. In the UK, QoL-AGHDA scores alone are used to determine treatment eligibility.
Results
The analysis was performed separately for UK data versus the collective other European countries (Belgium, Germany, Sweden, France, Holland, Spain) data. Median AGHDA score at baseline for UK ($n=68$) was 15.5 and for Europe ($n=299$) 7.0 ($P<0.0001$) whilst median IGF-I SDS for UK ($n=54$) was -0.87 and for Europe ($n=178$) -1.53 ($P=0.0042$). The UK cohort have much greater impairment of QoL but are less severely GHD than the Europe cohort, implying a significant component of impaired QoL in the UK cohort is unrelated exclusively to their GH status.
Conclusions
The literature indicates that QoL improves significantly in UK GHD adults in response to GH replacement, however our results question a treatment strategy focused on QoL alone, a medical endpoint not shown to be related to the degree of GHD, and affected by multiple factors; for all other endocrine deficits the classical approach is to treat those with biochemical evidence of the severest deficit first.

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EP701

Batch-to-batch consistency of a highly o-glycosylated long-acting human growth hormone (MOD-4023)

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Background
OPKO Biologics is a clinical-stage public company developing long-acting therapeutic proteins utilizing CTP technology. The technology involves fusion of the C-terminal peptide of human chorionic gonadotropin (hCG), which is highly O-glycosylated, to the target protein. CTP enabled the production of a long-acting human growth hormone (hGH) (MOD-4023), which supports a single weekly injection in growth hormone-deficient patients. MOD-4023 is manufactured as a non-viscous liquid formulation.
Aims
The objective of the study was to develop a highly O-glycosylated drug product with respect to protein quality attributes, process reproducibility, and batch-to-batch consistency.
Methods
The consistency of MOD-4023 glycosylation was tested by applying various analytical methods, including O-glycan and sialic acid analysis by HPLC, capillary zone electrophoresis (CZE), and isoelectric focusing (IEF). MOD-4023 potency was assessed *in vitro* by a cell-based assay (CBA), utilizing cells that stably express the human growth hormone receptor (GHR).
Results
Similar O-glycan and sialic acid contents were obtained in different of MOD-4023 batches, supporting the consistency of the drug substance glycosylation profile for each batch. Comparable results for different batches were also obtained using both CZE and IEF analysis. Several batches of MOD-4023 had shown similar levels of binding and activation of the human GHR.
Conclusions
A robust manufacturing process was developed for the production of MOD-4023 DS, producing a highly reproducible O-glycosylated product.

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EP702

Macronutrient composition has sex specific effects on the GH-IGF-I axis

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Metabolic diseases are among the most important diseases in western societies and usually related to obesity. Dietary interventions are recommended for treatment and include both strategies with reduced caloric intake and alterations in macronutrient composition. Metabolism must be assumed to be regulated differently in females and males. In previous studies we demonstrated that low carbohydrate high fat (LCHF) diets affect GH/IGF-I axis in male rats. We know investigated whether the same effects can be seen in females, and also included a high carbohydrate, high fat diet (HCHF) in our study. Purified diets (% of metabolizable energy, fat/protein/carbohydrate: Chow (CH, 16.7/19.0/64.3), protein matched LCHF-1 (78.7/19.1/2.2), ketogenic LCHF-2 (92.8/5.5/1.7) and HCHF (61.9/18.7/19.4)) were pair-fed isoenergetically for 4 weeks to male and female Wistar rats (12 weeks at start, $n=7$/group). GH secretion profiles were collected (10 samples/5 hours) after 3 weeks. At study end (6 hours fasting, dark phase), blood samples and organs were collected. Pituitary GHRHR and GH as well as liver GHR and IGF-I mRNA were analyzed. Serum GH secretion showed higher nadirs and lower peaks in females. On the ketogenic LCHF-2, GH tended to be lower in both sexes, while GH was increased on HCHF only in females. In males, IGF-I (ng/mL) was significantly reduced on all HF diets (CH: 1441 ± 79.13, LCHF-1: $961.9^{***}\pm31.48$, LCHF-2: $940.2^{***}\pm39.87$, HCHF: $993.6^{***}\pm14.78$), but only on the ketogenic LCHF-2 diet in females (CH: 713.3 ± 49.0, LCHF-1: 588.0 ± 48.15, LCHF-2: $463.3^{***}\pm34.58$, HCHF: 574.4 ± 26.4). Pituitary GH mRNA was generally higher in females, and lowest in rats of both sexes fed LCHF-2. In both sexes, GHRHR mRNA was reduced on all HF diets (males: CH: 0.07 ± 0.01, LCHF-1: 0.04 ± 0.01, LCHF-2: 0.04 ± 0.01, HCHF: 0.03 ± 0.01*; females: CH: 0.08 ± 0.01, LCHF-1: 0.03 ± 0.02, LCHF-2: 0.03 ± 0.01*, HCHF: 0.04 ± 0.01). Liver GHR mRNA tended to be lower on LCHF-1 and LCHF-2 in both sexes and increased on HCHF in females. Our data demonstrate that HF diets lead to a more pronounced deterioration of the GH/IGF-I axis in males. Whether hypothalamic or pituitary mechanisms regulating GH secretion or peripheral mechanisms regulating GH sensitivity cause the sex difference is currently studied.

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EP703

High normal TSH – risk factor for subclinical hypothyroidism in GH treatement for pituitary dwarfism?

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Background
Normal thyroid function is necessary for the optimal effect of recombinant growth hormone (rhGH) on growth rate. GH therapy in children with GH deficiency (GHD) has yielded conflicting results concerning its impact on thyroid function. Data about patients developing subclinical hypothyroidism (SH) are scanty, but it is thought to be associated with impairment of metabolic profile and lower growth response.
Objective
To evaluate the effect of rhGH administration on TSH tertiles and FT_4, the frequency of SH, as well as to assess its influence on therapy effectiveness.
Method
We reviewed the cases of 75 children (59 boys, 16 girls, aged $4-14$) with pituitary dwarfism. Clinical and hormonal data, as well as radiographic bone assessments were documented at the beginning, 6 months and after first year of treatment.
Results
At therapy onset, all patients had the height below -2.5 SD (mean -3.2), delayed bone age, decreased or low normal IGF1 and normal thyroid function. After one year of therapy, SH was the only impairment in thyroid function in 12 patients (16%). The risk of SH was increased among subjects with the highest tertile TSH as compared with subjects with the lowest tertile ($P<0.05$). Despite similar IGF1 secretion increase, the improvement of height velocity was significantly lower in children with SH (0.65 cm/month) than in those who remained euthyroid (0.88 cm/month, $P<0.05$). An increase in IGF1 levels was

associated with increasing levels of TSH in SH patients and led in four cases to administration of $L-T_4$ substitution.
Conclusion
The incidence of SH during the first year of rhGH treatment in children with GHD and the influence on the growth rate should be taken into account, as it may worsen the growth response. Our findings suggest that suboptimal thyroid function increases vulnerability to the occurrence of SH in children treated with rhGH, needing a closer monitoring.

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EP704

Concomitant medication in growth hormone (GH)-treated patients with adult GH deficiency (AGHD): an analysis from NordiNet® International Outcome Study (IOS)

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Introduction
Patients with AGHD receiving GH often have comorbidities requiring concomitant treatment. We evaluated patterns of concomitant medication use relative to GH therapy initiation in patients with AGHD.
Methods
Patients with AGHD with data on concomitant medications enrolled in NordiNet® IOS (NCT00960128), an international, non-interventional study, receiving GH (Norditropin®, Novo Nordisk A/S, Denmark) therapy were included. Concomitant medications were grouped by main therapeutic properties/target body system into nine treatment clusters. Start of concomitant medication in each cluster was analysed relative to GH therapy initiation (before/at[$\pm$2 months]/after). The association between concomitant medication start and GH initiation (after versus before) was analysed by chi-square test.
Results
Overall, 14,412 prescriptions of concomitant medications were recorded for 986 patients (female, 42%; adult-onset AGHD, 88%), representing 42% of all patients with AGHD in NordiNet® IOS. The most frequent treatment clusters and numbers of patients (% patients with first prescription before/at/after GH initiation) receiving at least one treatment in each cluster were: hormone (other pituitary/sex hormones) replacement, 952 (60%/20%/20%); cardiovascular system therapies, 169 (43%/17%/41%); nutrition and supplements, 97 (28%/23%/49%); diabetes treatment, 61 (33%/25%/43%); osteoporosis treatment, 53 (32%/23%/45%); nervous system treatment, 44 (34%/30%/36%); pain relievers, 46 (52%/17%/30%); prolactin suppression therapy, 44 (50%/18%/32%); fertility treatment, 14 (57%/0%/43%); miscellaneous, 90 (41%/23%/36%). Except for hormone replacement therapy, and nutrition and supplements ($P<0.05$ for both), no significant differences were shown in the proportions of patients receiving their first concomitant medication prescription after versus before GH initiation within treatment clusters.
Conclusions
Hormone replacement and cardiovascular system treatments were the most frequently prescribed concomitant medications. There was no change in the proportion of first prescriptions for cardiovascular system, diabetes or osteoporosis treatments after versus before GH therapy initiation. The high proportion of prescriptions for other hormone replacement therapy before GH initiation indicates GH might often be the last pituitary hormone to be substituted.

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EP705

Shipment associated effects on the somatotropic axis in pigs - a pilot study

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Transport of farm animals is considered as a key stress factor including multiple stressors as handling or fasting. In humans, compounds for the IGF-system are affected by acute or critical illness or stress. We have asked, if compounds from the IGF-system also may have biomarker potential in farm animals. A total of 80 pigs were transported for 2 h from a commercial finishing farm to the slaughterhouse. Blood samples from 40 pigs were taken before (basal levels) and after shipment and after lairage and slaughter. A control group of 40 pigs without blood collection before slaughtering was investigated to determine potential effects of blood sampling on parameters in slaughter blood. In plasma, IGF-1 and IGF-binding proteins (IGFBPs) were analyzed using ELISA and quantitative Western Ligand Blotting. The ratio of IGF-1 to the total amount IGFBPs was calculated to examine the IGF-1 bioavailability. Shipment severely reduced plasma IGF-1 ($P<0.01$) in pigs if compared to pre-shipment conditions. IGFBP-3 and -2 concentrations decreased with prolonged time leading to reduced ($P<0.01$) concentrations in slaughter blood compared to basal levels. In contrast, IGFBP-5 was increased ($P<0.001$) after shipment but normalized after lairage and slaughter. The ratio of IGF-1/IGFBPs, and thus IGF-1 bioavailability was reduced ($P<0.01$) after shipment but not after lairage or slaughter. Repeated blood sampling increased concentrations of IGFBP-3 and IGF-1 compared to controls. The results indicate that acute stress factors during shipment or repeated blood sampling induces changes in somatotropic axis. Our findings indicate that the somatotropic axis may have biomarker potential for defined conditions of stress, which may be useful in order to improve animal health and welfare in pigs.

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EP706

The association between neutrophil and lymphocyte ratio in patients diagnosed with acromegaly

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Aim
İmpaired glucose tolerance and hyperinsulinism/insulin resistance frequently accompany by acromegaly. NLO (Neutrophile lymphocyte ratio) is demonstrated as a simple indicator of systemic inflammation and it is also known that NLO is associated with atherosclerosis progression in coronary artery and a risk factor in coroner artery disease. In this study, we intend to search the association between both coronary atherosclerosis seen frequently in patients diagnosed with acromegaly and glucose metabolism disorders occurring based on hyperinsulinism as the result of excessive GH release and NLO ratio.
Method
This study included 106 persons which 59 of them were patients with acromegaly and 47 of them who were healthy and no significantly different statistically in terms of age were in control group. The mean age of patients was 44.1 ± 13.8 years and the mean age of control group was 38.8 ± 15.4 years. There was no a significant difference statistically between them ($P=0.06$).
Result
In our results, we statistically detected a significant difference in NLO level (mean NLO levels 2.1 ± 1.0 in acromegaly group vs. 1.5 ± 0.6 in control group, respectively, $P=0.002$) CRP level (mean CRP level 3.5 ± 3.3 mg/dl in acromegaly group vs. 1.3 ± 1.2 mg/dl control group, respectively, $P=0.004$). There was a significant difference statistically between the patients and control groups, respectively in terms of neutrophile (4.9 ± 1.9 and 3.9 ± 1.2 $P=0.01$), fasting blood glucose (111.6 ± 37.1 and 88.2 ± 6.8 $P=0.0001$) and fasting insulin levels (20.1 ± 19.3 and 8.4 ± 6.7 $P=0.03$). It was determined a positive correlation between NLO and neutrophile ($r=0.58$, $P=0.0001$), between CRP and HOMA score ($r=0.61$, $P=0.003$) in the patients with acromegaly.
Discussion
Based on the outcomes provided by this study, it was found that excessive growth hormone release formed an inflammatory environment by effecting glucose mechanism and also increasing coroner atherosclerosis

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EP707

Robust viral clearance capacity of CTP-modified long-acting growth hormone (MOD-4023) downstream production process

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Background
OPKO Biologics is a clinical-stage public company developing long-acting therapeutic proteins utilizing CTP technology. The technology involves fusion of

the C-terminus peptide of human chorionic gonadotropin (hCG), a highly O-glycosylated peptide, to the target protein. CTP enabled the production of a long-acting human growth hormone (hGH) (MOD-4023) that supports a single-weekly injection in growth hormone-deficient patients. MOD-4023 is manufactured as a non-viscous liquid formulation.
Objective
Effective inactivation and/or removal of viruses in the downstream manufacturing process of MOD-4023 was validated as part of the regulatory requirement to demonstrate the safety of pharmaceutical products derived from a biological source.
Design and methods
The overall study design consists of a detergent-based virus inactivation step, a virus filtration step, and three chromatographic steps (anion exchange chromatography, mixed-mode chromatography, and cation exchange chromatography). Chromatography-based removal of four different viruses with distinct characteristics was evaluated with fresh resins and with used resins at the end of column lifetime. In addition, carry-over runs were conducted, in which the effectiveness of the regeneration/sanitization procedures was evaluated. In these studies, the removal of residual viruses potentially left on the column was demonstrated using non-virus-spiked runs.
Results
The viral validation study had demonstrated that the manufacturing process of MOD-4023 provides a total clearance of >20 log for lipid-enveloped viruses and >9 log for chemically resistant, non-enveloped small viruses. Moreover, the process consists of 2 to 5 robust removal steps for each of the viruses.
Conclusions
The manufacturing process of MOD-4023 provides a robust removal of viruses, with high virus reduction capabilities and high safety margins (>14 log). The study demonstrates a safe production process, in accordance with FDA and EMA requirements.

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EP708

Acromegaly and Dyslipidemia

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Aim
The risk of cardiovascular mortality is high in patients with acromegaly. In this study, we intent to evaluate serum lipid profile in patients newly diagnosed with acromegaly and determine its association with increased growth hormone (gh) and insulin like growth factor-1 (igf-1) levels.
Material and method
This study includes 57 patients newly diagnosed with acromegaly in our hospital (mean age 44.1 ± 13.8 years; mean bmi 29.6 ± 5.4 kg/m^2) and 31 persons in control group who have similar age and bmi (mean age 38.8 ± 15.4 years; mean bmi 26.9 ± 7.3 kg/m^2). None of the patients were on antilipemic drug. All venous blood sampling were taken for gh, igf-1, triglycerides (tg) and hdl-c, ldl-c were taken in 12 hours fasting state.
Findings
In our results, we statistically detected a significant difference in ldl level (mean ldl-c levels 140.2 ± 61.3 mg/dl in acromegaly group vs. 115.6 ± 30.4 mg/dl in control group, respectively, $P=0.029$), triglyceride level (mean tg levels 137.6 ± 84.0 mg/dl in acromegaly group vs. 102.9 ± 43.0 mg/dl control group, respectively, $P=0.027$) and hdl level (mean hdl levels 41.5 ± 10.5 mg/dl in acromegaly group vs. 50.5 ± 10.6 mg/dl in control group, respectively, $P=0.001$) between the patients with acromegaly and the control group. It was found a positive correlation between gh and ldl-c ($r=0.375$, $P=0.02$) and tg ($r=0.302$, $P=0.01$). There was also a significant positive correlation between igf-1, ldl-c ($r=0.295$, $P=0.01$) and tg ($r=0.476$, $P=0.0001$). Additionally, it was determined a significant negative correlation between gh - hdl ($r=-0.399$, $P=0.001$) and igf-1 - hdl ($r=-0.310$, $P=0.01$).
Results
In conclusion, growth hormone and igf-1 increase may be establishing a ground for atherosclerotic heart diseases by leading to proatherogenic lipid profile in patients with acromegaly. Therefore, it might be important to follow closely lipid levels in acromegaly monitorization.

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EP709

The frequency of growth hormone deficiency in patients with nonfunctional pituitary tumors

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Aim
To study the frequency of growth hormone deficiency (GHD) in patients with nonfunctional pituitary tumors (NFPA).
Materials and methods
Over a period of 1.0 year, we studied in our department retrospective data of 33 patients with pituitary tumors in terms of CT/MRI imaging and detailed hormonal functional assessment – STH, IGF-1, LH, FSH, ACTH, prolactin, TSH, cortisol, thyroxine. From the patients are 11 – men and 12 women, mean age of patients 38.5 years.
Results
Microadenomas (<10 mm) were found in 11 patients, mesoadenomas (11–20 mm) in 11, macroadenomas (20–30 mm) in 11 patients.
Panhypopituitarism (PH) was noted in six persons (18.3%), PH with diabetes insipidus in 5 (15.2%), isolated GHD in 7 (21.2%), GHD and LH deficiency in 2 (6.0%), GHD and LH, FSH deficiency – in 11 patients (33.3%), GHD and LH, FSH, TSH deficiency in 2 (6.0%) Hypopituitarsin, that is, reduction in the levels of pituitary tropic hormones, such as, STH, LH and FSH was found in 75% (25 patients) large pituitary tumors with supra-, para- and infrasellar growth being registered in the patients.
Conclusions
The distribution of GHD in patients with NFPA has a lot of various disorders with combined deficiency of pituitary hormones levels.

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EP709B

Weight loss after pregnancy is associated with reduced IGFBP-3 and increased cGP/IGF-1 ratio

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Background
Impaired Insulin-like growth factor-1 (IGF-1) function is associated with obesity and hypertension, but the correlation of circulating IGF-1 with these conditions is weak. As a metabolite of IGF-1, the ratio of cGP/IGF-1 regulates IGF-1 bioavailability and may be a more accurate biomarker of IGF-1 function in obesity and hypertension.
Methods
Using ELISA and HPLCms methodologies, we analysed plasma concentration of IGF-1, cGP and IGFBP-3 in 40 women that grouped as non-obese + normotensive, obese + normotensive; non-obese + hypotensive and obese + hypertensive at both 15 weeks gestation and 6 years post-partum of first pregnancy. Only post-partum samples were analysed in hypotensive women. We also analysed the samples from a further 20 women that either were obese during first pregnancy or became non-obese 6 years post-partum or vice versa.
Results
At 6 years post-partum: plasma IGF-1 levels were lower among obese ($P=0.001$) groups; cGP ($P=0.043$) and IGFBP-3 ($P=0.046$) was lower among hypertensive groups; cGP/IGF-1 ratio was no difference among hypotension groups but higher among obese ($P=0.005$) groups. In the paired samples at 15 weeks gestation and 6 years post-partum: the change in plasma IGF-1 was lower in the groups that changed from being obese to normal ($P=0.004$) and that remained to be obese ($P=0.018$) compared to non-obese controls. Compared to normal control group,

group with weight loss after pregnancy had an increase in cGP/IGF-1 ratio ($P=0.01$) and a decrease in IGFBP-3 ($P=0.0001$); the group that gained weight had a decrease in IGFBP-3 ($P=0.03$), but no change in cGP/IGF-1 ratio and the group remained to be obese had an increase in cGP/IGF-1 ratio ($P=0.006$), but no changes in IGFBP-3.

Conclusions

Increase in cGP/IGF-1 ratio is observed in obesity but not hypertension. The collective responses of reduced IGFBP-3 and increased cGP/IGF-1 ratio may be essential to weight loss.

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EP710

Androgen profiling in males of two high-fertility mouse models does not reveal a distinct phenotype but provides new reference values for androgens in mice

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Animal models are valuable tools in fertility research. Worldwide, there are more than 1000 transgenic or knockout mouse models available showing a reproductive phenotype; almost all of them exhibit an infertile or at least subfertile phenotype. By contrast, animal models revealing an improved fertility phenotype are barely described. We developed two outbred mouse models exhibiting a 'high-fertility' phenotype. These mouse lines were generated via selection over a time period of more than 40 years and 170 generations. By now both mouse lines doubled the number of offspring as well as the total birth weight per litter.

We performed a two-factorial experiment by mating males and females of the three different genotypes (fertility line #1 (FL1), fertility line #2 (FL2) and control line (ctrl)) in all 9 possible combinations. We observed that increased fertility performance almost completely depended on the genotype of the females. Though not significant, the largest effect has been observed for males of the FL2 line. We noticed that the two independent fertility lines warranted the phenotype 'high fertility' using different physiological strategies.

In order to test whether this is reflected by different endocrine concentrations, we measured androgen concentrations in serum of males of the three lines (FL1, FL2, ctrl) using a gas chromatography-mass spectrometer (GC-MS) method. We measured testosterone concentrations between 5.0 and 6.4 ng/ml with no difference between the lines. We also measured other androgens (4–androstenedione: not detectable (nd) −0.06 ng/ml; dehydroepiandrosterone: nd −0.31 ng/ml; androstenediol: 0.14 to 0.39 ng/ml; dihydrotestosterone: 0.08 to 0.19 ng/ml). These androgen concentrations are at least 10-fold lower compared to testosterone. Since androgen concentrations in the mouse, measured by the "gold standard" GC-MS, are barely described in the literature we have to consider these concentrations as reference values in mice.

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EP711

Altered testicular vascularization and impaired blood supply in the 41,XX^{Y*} mouse model for Klinefelter syndrome

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Intratesticular testosterone levels in Klinefelter syndrome (KS) are comparable to controls and Leydig cell function was proven to be normal at least *in vitro*, testicular vascularization changes came into focus as a potential factor contributing to hypogonadism. We performed enhanced ultrasound based analysis of the testicular blood support in our 41,XX^{Y*} mice. Adult male 41,XX^{Y*} ($n=5$) and control mice ($n=6$) underwent ultrasound analyses with the Non-Targeted Contrast Agent Vevo MicroMarker. The agent containing gas filled micro-bubbles was administered intravenously (lower body perfusion). After initial perfusion, micro-bubbles were destroyed by high ultrasound pressure and the reperfusion period was analysed. In parallel, electrocardiograms (ECGs) were taken. Afterwards mice were sacrificed and testes removed for histological analysis of vascularization. Whilst ECGs did not reveal differences in heart function, the reperfusion time for testes was significantly increased in 41,XX^{Y*} mice (XX^{Y*} 28.8 ± 1.7 s; XY* 19.9 ± 2.8 s). Testes of 41,XX^{Y*} mice (XX^{Y*} 4.6 ± 0.10 mm^2; XY* 11.1 ± 0.34 mm^2) and the area covered by blood vessels (XX^{Y*} 0.025 ± 0.003 mm^2; XY* 0.040 ± 0.002 mm^2) were significantly smaller. Testicular blood vessel areas of adult males were assigned to four categories (I = <80 μm^2, II = 80–1000 μm^2, III = 1000–5062 μm^2, IV = >5062 μm^2). The blood vessel area of categories I and II was significantly decreased in 41,XX^{Y*} mice ($P<0.0001$). Taking the testis area into account, the area covered by vessels of category II and III is significantly elevated in KS mice. Blood vessels of category IV were missing in KS testes. These functional and morphological data strengthen the assumption that the observation made previously contributes to the endocrine phenotype seen in KS pointing to an affected vascular system in the disturbed testicular tissue of males with supernumerary X.

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EP712

The role of dopamine pathway on human sperm: *in vitro* effect of dopamine receptor agonists and antagonists on sperm motility, kinetics and viability

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Dopamine has been found in both semen and oviductal fluid and dopamine receptors (DRs) have been detected in male genital tract and spermatozoa, suggesting that dopamine system may control important reproductive functions in humans. Dopamine improves sperm motility and viability in animal models, although the underlying molecular mechanisms have not been fully elucidated. The aims of this study were to investigate DRs expression in human spermatozoa and to evaluate the *in vitro* effects of DRs agonists and antagonists on human sperm motility, kinetics and viability. DRs expression was assessed by immunofluorescence and western blot in spermatozoa from healthy volunteers and the effects of D2DR-like agonist cabergoline, D2DR-selective antagonist L-sulpiride, D4DR-selective agonist PD168,077 and D4DR-selective antagonist U-101958 on sperm motility, kinetics and viability were tested after 1 hour of treatment with serial doses of compounds. Sperm motility and kinetics were analyzed by Sperm Class Analyzer [SCA] 5.0, sperm viability was assessed by Vital Stain Dye. D2DR and D4DR are both expressed in human spermatozoa. Cabergoline significantly increased rapid progressive motile spermatozoa (RPMS) and decreased non motile spermatozoa (NMS). L-sulpiride showed opposite, although not significant, effects on sperm motility. PD168,077 and U-101958 did not significantly change sperm motility. Moreover, L-sulpiride significantly decreased curvilinear velocity (VCL) and increased wobble (WOB). All tested compounds did not affect sperm viability. Both cabergoline and PD168,077 induced Akt phosphorylation, compared to untreated spermatozoa. The results of the current study demonstrated that dopamine pathway may be involved in the modulation of human sperm motility and kinetic parameters, without affecting sperm viability, and that Akt could be regarded as a putative mediator; however, further experiments are being performed to identify the molecular mechanisms driving these effects.

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EP713

An audit on evaluation and management of men with hypogonadotrophic hypogonadism in a district general hospital in South-Wales

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Introduction
The current Endocrine Society guidelines (2010) recommend biochemical and radiological evaluation of men with HH to ascertain underlying hypothalamic and/or pituitary aetiology although the cost-effectiveness of this strategy is yet to be established. We did a retrospective audit to ascertain epidemiology, management and diagnostic outcomes for men with HH in our hospital practice against the current Endocrine society guidelines.
Methods
A total of 126 men with biochemistry consistent with HH were identified for the audit period from 2013–2015. Retrospective evaluation of these patients was done using a local electronic database (Myrddin) to retrieve relevant clinical information.
Results
The commonest symptoms in men with HH included erectile dysfunction (56%), reduced libido (23%), lethargy (15%) and excessive sweating (<10%). A significant proportion of men (36%) with HH were overweight (BMI>30) and/or had diabetes mellitus (25%). Biochemical abnormalities including a raised prolactin, secondary hypothyroidism and abnormal IGF1 levels were noticed in 15%, 15.8% and 4.8% patients respectively. Pituitary imaging was carried out in 67 out of the total 126 patients (53.1%). Radiological abnormalities including macroadenoma ($n=10$), microadenoma ($n=1$), empty sella ($n=5$), and non-specific cyst ($n=1$) were identified in 25.4% of the scans. Although, none of the men with a BMI>30 (along with no clinical/biochemical features of pituitary dysfunction) had any pituitary tumor detected on radiology.
Discussion/Conclusion
There has been an increase in number of referrals to endocrine centres for men with secondary hypogonadism related to global pandemic of obesity and diabetes mellitus. The majority of men with increased BMI (without clinical/biochemical features of anterior pituitary dysfunction) do not routinely warrant further radiological investigations. This is especially important in context of higher statistical probability of detecting an incidental pituitary lesion (adenoma or empty sella) leading to an increased health-economic burden. There is a need for larger multi-centric studies to reassess BMI related cut offs for further evaluation of men with HH.

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EP714

Positive effect of FSH therapy on quantitative and functional sperm parameters in idiopathic infertile men

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Follicle-stimulating hormone (FSH) therapy is a potential treatment option in idiopathic infertile men with normal FSH levels. In fact, a recent Cochrane meta-analysis showed that FSH treatment of men affected by idiopathic oligozoospermia significantly improves pregnancy rate. Hyaluronic acid (HA) binding capacity of spermatozoa is considered a marker of functional competency, consequently the evaluation of the percentage of HA bound spermatozoa in the ejaculate can serve as a proxy of sperm fertilizing potential.
Aim
1) to study the effect of HP-FSH treatment on routine sperm parameters and on HA binding capacity of spermatozoa; 2) to evaluate the effect of FSHβ promoter variant in FSH responsiveness
Materials and methods
Thirty five idiopathic oligo- or asthenozoospermic men were included in the study with FSH<8 mU/ml. After routine sperm analysis, HA Binding assay have been performed by using coated slides with HA before, 1 and 3 months intra-therapy and after 4 months of wash out from the therapy. *FSHβ* promoter -211G>T was analyzed by Restriction Fragment Length Polymorphism (RFLP).
Results
After 3 months of HP-FSH treatment we observed a significant increase of the Total Motile Sperm Number (TMSN) (16.8±19.4 vs 31.1±26.7; $P=0{,}000$). 53% of patients resulted "responders" (defined as an increase greater than the physiological oscillation) for TMSN. Similarly, the mean % of HA-bound spermatozoa showed a significant increase after one month (29.6%±13.6 vs 41.2%±19.7; $P=0{,}000$); 46% and 61% of patients resulted "responder" with an average of two fold increase after 1 and 3 months, respectively. Although the distribution of the allelic frequencies of *FSHB-211* between "responders" and "non-responders" did not result statistically different neither for HBA nor for TMSN, we observed a 100% responsiveness for TMSN in T/T genotype carriers.
Conclusion
Our study confirms that FSH therapy may improves spermatogenesis, both quantitatively and qualitatively in 53–61% of cases. For the first time, we report data showing a significant positive effect of FSH on a functional parameter, such as sperm HA binding already at 1 month i.e. during the phase called "spermiogenesis".

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EP715

Association between low testosterone and graft dysfunction early after heart transplantation: results from cross-sectional study

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Introduction
An inverse relation was found between testosterone and vasculopathy of the allograft in heart-transplanted men. We evaluated the correlation between serum testosterone levels and graft function early after heart transplantation.
Methods
In a cross-sectional study serum total testosterone levels prior to hospital discharge (19±3 postoperative day) was determined in 49 consecutive male patients who underwent heart transplantation between 2009 and 2013. Assessment of left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE) and left ventricular hypertrophy (LVH) by echocardiography was performed in all subjects. Low serum testosterone was defined as <11 nmol/L. LVH was defined as left ventricular wall thickness >1.1 cm. All patients received standard immunoinduction and maintenance immunosupression therapy.
Results
Low testosterone was present in 21 (43%) (Group A), and normal in 27 (57%) patients (Group B). The prevalence of osteoporosis was signifitancly higher in Group A compared to Group B (90% vs 60%, $P=0.02$). The two groups did not differ in age (58.7±7.2 years in Group A vs. 54.3±11.9 years in Group B), the presence of renal dysfunction, arterial hypertension, diabetes or hyperlipidemia, time of hospital discharge, donor age and allograft ischemic time. Both groups had comparable mean tacrolimus through levels, dose of mycophenolate and metylprednisolone. However, before discharge, patients in Group A had significantly lower LVEF (60±4.8% vs. 63.3±5.8% vs. Group B, $P=0.04$) and TAPSE (1.3±0.3 cm vs. 1.6±0.3 cm in Group B, $P=0.03$). The prevalence of LVH did not differ between the two groups. Before discharge, more patients in Group A were found to have low grade rejection (15% vs. 0% in Group B; $P=0.03$).
Conclusion
Low testosterone appear to be associated with inferior graft function and increased incidence of rejection early after heart transplantation. Immunomodulatory role of testosterone remains to be further elucidated.

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EP716

The investigation of oxidative stress-related parameters in congenital hypogonadism

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Introduction
Patients with hypogonadism are at increased risk of cardiac and metabolic diseases. The pathogenesis of increased cardio-metabolic risk in hypogonadal patients is not clear. Oxidative stress plays an important role in the pathogenesis

of cardio-metabolic diseases. The aim of this study was to search for any difference of the oxidative stress parameters between in patients with hypogonadism and healthy controls.
Materials and Methods
Thirty eight male patients with congenital hypogonadotrophic hypogonadism (CHH) (mean age 21.7 ± 1.6 years) and 44 body mass index (BMI) matched healthy male subjects (mean age 22.3 ± 1.4 years) were enrolled. The demographic parameters, homeostatic model assessment of insulin resistance (HOMA-IR) and oxidative stress parameters such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and malondialdehyde (MDA) were measured in patients and healthy controls.
Results
When compared to the healthy controls, triglycerides ($p = 0.02$), insulin, HOMA-IR, catalase and MDA levels ($P = < 0.001$ for all) were significantly higher, and the HDL cholesterol ($P = 0.04$), total testosterone, FSH, LH and GPx levels ($P = < 0.001$ for all) were significantly lower in patients with CHH. There were significant correlations between the total testosterone levels and catalase ($r = -0.33$ $P = 0.01$), GPx ($r = 0.36$ $P = 0.007$) and MDA ($r = -0.47$ $P < 0.001$) levels.
Conclusions
The results of this study show that young and treatment naïve patients with hypogonadism have increased oxidative stress related parameters such as serum catalase and MDA levels. There is significant correlation between oxidative stress parameters and testosterone levels. Prospective, randomized, controlled studies with larger number of cases are needed to prove the relationship between oxidative stress and increased cardio-metabolic risk in hypogonadism.

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EP717

Delay in the onset of male puberty: role of mutations in luteinizing hormone-beta gene

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The reawakening of hypothalamo-pituitary-gonadal axis at puberty is influenced by a number of hormonal and genetic factors along with certain environmental cues. In boys, puberty is initiated at around 9 years of age as plasma concentrations of luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone (T) begin to rise leading to development of secondary sex characteristics. The absence of signs of sexual maturation at the age of 14/15 years is regarded as delayed puberty. One of the main causes of delay in puberty is hypogonadotropic hypogonadism (HH), characterized by low LH, FSH and T secretion, resulting in absent or impaired sexual development. This study examined the endocrine and genetic basis of pubertal delay in boys. Blood samples were obtained from 30 boys of delayed pubertal development and 30 age matched controls. The plasma concentration of growth hormone (GH), LH, FSH and T were determined using ELISA. Based on low plasma concentrations of GH, LH, FSH and T, genetic analysis was performed for determining possible mutations in TACR3 and LH-β genes. TACR3 is expressed in the hypothalamus, whereas LH-β is synthesized by pituitary gonadotropes. One mutation, H148L, of TACR3 and two mutations, G56D and G122S, of LH-β were screened. DNA was extracted from blood samples of both groups by organic method, primers of exons of TACR3 and LH-β splice sites were designed and PCR-RFLP method was employed for analysis. The mutations H148L of TACR3 and G56D of LH-β were not found in any group, whereas the PCR product of LH-β digested by enzyme Eco01091 gave bands of 3 different genotypes in HH boys, GG (93.33%), GA (3.33%) and AA (3.33%). Thus, one heterozygous G122S mutation in one and one homozygous G122S mutation in another patient were identified. In conclusion, homozygous G122S mutation may cause pubertal delay in our local population.

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EP718

Is Testosterone (T) treatment safe and effective in men with HIV infection? A meta-analysis

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Background
Prevalence of hypogonadism is high (30%) in men with HIV. In these patients T treatment (TT) is currently used mainly to counteract wasting syndrome and/or HIV-related lipodystrophy, irrespective of patients' serum T. However, its effect and safety in HIV-infected men is still not completely known.
Aim
To investigate both beneficial and adverse effects related to TT in HIV-infected men using a meta-analytic approach.
Methods
An extensive MEDLINE search was performed using 'PubMed' with the following key-words: 'HIV' and: 'hypogonadism', 'TT', 'T', 'androgens' or 'sex steroids' from 1946 to April 2015. Meta-analysis included 19 placebo-controlled-clinical trials evaluating TT in HIV patients and was conducted according to PRISMA statement using RevMan.
Results
All 19 trials evaluated the effect of TT on body weight on a total of 952 subjects (TT group: 557; placebo group: 395). Patients' gonadal status was often not reported and most of patients were presumably eugonadal. All data are shown as standardized mean and Confidence Interval (CI). TT significantly improved total lean body mass (1.44 [0.82–2.07], $P < 0.001$), total body weight (0.99 [0.25–1.72], $P = 0.008$) and fat free mass (1.48 [0.85–2.12], $P < 0.001$). This improvement is characterized by higher heterogeneity ($I^2 = 84\%$, 88%, and 60%, respectively). Conversely, no beneficial effects were seen on total fat mass (−0.17 [−1.58–1.25], $P = 0.820$). TT was associated with an increased incidence of minor adverse events (OR = 1.50[1.11–2.01], $P = 0.008$) and increased mean serum PSA (0.10 ng/mL, [0.03–0.17], $P = 0.007$). No change in hemoglobin (0.39 g/dL, [−0.29–1.07], $P = 0.260$) was seen.
Conclusions
Our study suggests that TT in HIV-infected men is effective in improving body composition (increase in lean body mass), although the incidence of general adverse events is higher than in the placebo group. However, studies show a highest variability and the real benefits of TT in HIV-infected men remains still to be established.

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EP719

Aluminium oxide nanoparticles-induced spermatotoxicity, oxidative stress and changes in reproductive hormones and testes histopathology in male rats: Possible protective effect of glutathione

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There is a rising use of Aluminium oxide nanoparticles (Al_2O_3NPs) in many branches of industry and personal care products. Because of these uses, their impact on the environment must be considered and investigated. Almost nothing is known about the effects of Al_2O_3NPs on semen quality and reproductive hormones. Possible mechanisms for the cytotoxicity of Al_2O_3NPs are still being discussed, but oxidative stress may be responsible for their effect. Therefore, the objective of this study was thus to know the capability of glutathione as antioxidant agent against the effects of Al_2O_3NPs on sperm parameters, testosterone, FSH, LH, steroid enzymes, histological changes, lipid peroxidation and antioxidant enzymes in male rats. Animals were divided into four groups, group 1 was used as control, group 2 was treated orally with glutathione (100 mg/kg BW), group 3 was treated intraperitoneally (IP) with aluminum oxide nanoparticles (70 mg/kg BW; <50 nm), group 4 was treated with aluminum oxide nanoparticles plus glutathione. Rats were administered their respective doses every day for 77 day. Results showed that Al_2O_3NPs decreased final body weight, body weight gain, relative testes and epididymis weights, sperm count,

sperm motility, testosterone levels, 17- ketosteroid reductase, while increased abnormal sperm, follicle stimulating hormone, luteinizing hormone, 17β-hydroxysteroid dehydrogenase and weight of prostate gland. In addition, Al_2O_3NPs decreased the activities of antioxidant enzymes (GST, CAT, SOD, GPx) and reduced glutathione, while increased the levels of thiobarbituric acid reactive substances (TBARS) in both plasma and testes. Histological examination of testes showed that Al_2O_3NPs caused decrease in the number of spermatogenic cells in the seminiferous tubules, degeneration of germinal epithelium, disappearance in primary spermatogonia and round spermatid. The presence of glutathione with Al_2O_3NPs minimized its effect which improved the structural components of the testes and spermatogenic cells. The present data concluded that glutathione could be used as protective agents against the reproductive toxicity induced by Al_2O_3NPs.

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EP720

Adjustment of testosterone and dihydrotestosterone reference intervals to the male Portuguese population

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Introduction
In our practice we've been following some oncologic survivors patients with low-low/normal levels of testosterone who are asymptomatic. Aims: to determine the levels of total (TT) and free testosterones (FT) and dihydrotestosterone (DHT) in healthy men, in order to find the reference intervals (RI) adjusted to our population and compare them with those provided by the kit-producers (KP).
Methods
We collected blood samples from 125 healthy male blood-donors and determined, for each man, the levels of TT, FT and DHT. Age groups: A-21–30-years: 20 men; B-31–40-years 34 men; C-41–50-years: 34 men; D-51–60-years: 25 men; E-61–70-years: 12 men. In these assays we used Immulite2000, Free TESTO-RIA-CT and Dihydrotestosterone RIA for TT, FT and DHT, respectively. RIs were calculated through mean ± 2 S.D., being the RI described as −2 S.D.–+2 S.D.
Results

	TT (ng/dl)		FT (pg/ml)		DHT (pg/ml)	
	RI		RI		RI	
Age group	Calculated	KP	Calculated	KP	Calculated	KP
A	247–635	160–726	4.9–14.9	8.9–42.5	149–395	169–692
B	137–562		4.0–13.3		120–386	163–597
C	120–482		3.9–11.3	6.6–30	109–349	77–−440
D	104–478	129–767	2.8–9.3		64–306	93–413
E			2.8–8.6	4.9–21.6	61–281	

Conclusion
The RI that we determined are inferior and narrower than those provided by the KP. We highlight the need to verify if the RI provided are adjusted to our population's reality. It would also be important to include the paediatric population in next studies.

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EP721

Is testosterone deficiency a real problem of male IBD patients?

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There have been many discussions about testosterone role in inflammation and autoimmunity. Inflammatory bowel disease (IBD) is a chronic autoimmune disease in younger age groups. The aim ouf our study was to evaluate testosterone concentration and it's influence on disease acitivity and the quality of life.
In our cross-sectional study we measured total testosterone levels in males with IBD (Crohn's Disease, Ulcerative colitis). Age, BMI, main characteristics of IBD were also recorded as well as the disease activity (Harvey-Bradshaw Index for CD and Mayo score for UC) and the quality of life (SIBDQ).
We included 113 patient with IBD (CD 66, UC 47) with median age of 34 (CD) and 41 (UC) years. Disease was active in 10.6% of CD and 14.9% UC patients. Median duration of disease was 10.05 and 8.9 years respectively. The median testosterone concentration was 11 nmol/l for both groups. The level was less than 10 nmol/l in 34% and lower than 6 nmol/l in 4% of patients. We found a slight negative correlation of testosterone with disease activity in UC ($R=0.28$, $P=0.06$) and slight negative correlation to CRP in all IBD patients ($R=0.2$, $P=0.03$). There was also negative correlation between IBD duration and testosterone ($R=0.18$, $P=0.058$). The quality of life did not correlate with TST levels.
Testosterone deficiency in quite common among male IBD patients. It seems to be connected to the disease activity, inflammation and the duration of disease. Very low concentration of testosterone was rarely found. The quality of life seemed not to be affected while most cases were in the clinical remission.

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EP722

Hypogonadotropic hypogonadism – clinical spectrum: from sporadic to familiar forms

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Introduction
Congenital hypogonadotropic hypogonadism (CHH) is a rare disorder. It can be sporadic or familiar and is divided into anosmic hypogonadotropic hypogonadism (Kallmann syndrome - KS) and congenital normosmic isolated hypogonadotropic hypogonadism (idiopathic hypogonadotropic hypogonadism - IHH). A growing number of genes are involved in its etiology, suggesting the heterogeneity and complexity of this condition.
Cases Reports
Six cases of CHH are presented - 3 KS and 3 IHH cases. All KS patients were male and the diagnosis was suspected by pubertal delay (sparse hairbody and small testicles/penis for age) when they aged 13 years (one patient) and 18 years old (two patients). Smell was tested by ORL: two of them had anosmia and one had hyposmia. One patient also had bilateral deafness, congenital cardiomyopathy, cognitive impairment and thyroid papillary carcinoma. Its CT revealed vermis hypoplasia and an enlarged sixth ventricle. Olfactory bulbs were absent in the two other patient's MRI. Two of 3 IHH cases represented a familiar form (being sister and brother), while the other case occurred as a sporadic condition in a male patient (detected at 28 years old because of ginecomastia with no other symptoms). The female patient with familiar IHH was diagnosed at 18 years because of primary amenorrhea (karyotye 46,XX) and her brother was diagnosed at 22 years old because of pubertal delay. Both patients had positive genetic test and shared the same mutation. Genetic test (*KAL1, FGF1* and *GnRHR* genes) was negative in other 3 patients and still is in progress for one KS patient.
Conclusion
Although the cases presented share the main manifestations of CHH, each one has specific characteristics demonstrating the heterogeneity of this condition. They also highlight how diagnosis can be challenging and sometimes delayed to adult age, because distinction from constitutional delay of puberty may be difficult.

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EP723

Garcinia cambogia modulates ciprofloxacin-induced testicular histopathology through regulatory effects on the pituitary hormones

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Introduction
Garcinia cambogia is a plant with reported spermatogenic properties. ciprofloxcin is an antibiotic used in the treatment of of various bacterial infection but with reported toxic effects on the testes. The modulatory effects of *Garcinia cambogia* on ciprofloxacin-induced testicular toxicity was evaluated in this study.

Method
Twenty one (21) male Wistar rats were randomly divided into four (4) groups. Group A was given ciprofloxacin 150 mg/kg only, Group B was given 150 mg/kg ciprofloxacin and 400 mg/kg *Garcinia cambogia*, Group C was administered 400 mg/kg *Garcinia cambogia* only while Group D served as the normal control group and received 1.5 ml of distilled water (placebo). Administration lasted for 30 days and thereafter the animals were sacrificed; blood samples were collected for hormonal studies; and the testes harvested and processed for histological studies.
Results
Findings obtained showed significantly reduced concentration of luteinising and follicle stimulating hormones in ciprofloxacin-treated group compared to the Garcinia cambogia-treated and control groups at $P<0.05$. The concentration of testosterone in ciprofloxacin + *Garcinia cambogia*-treated group was significantly higher than in the ciprofloxacin-treated group. Histological analysis revealed improved seminiferous tubule architecture in *Garcinia cambogia* treated rats compared to the ciprofloxacin-treated group.
Conclusion
The results show that *Garcinia cambogia* extract has spermatogenic properties mediated through its influence on pituitary hormones, thereby ameliorating ciprofloxacin-induced testicular toxicity.

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EP724

Association of follicle stimulating hormone receptor single nucleotide polymorphisms with fertility in greek men

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Background and Objective
Although several epidemiological studies have been conducted, the impact of Follicle Stimulating Hormone Receptor (FSHR) polymorphisms on male infertility remains unclear. The aim of this study was to investigate the prevalence of specific FSHR Single Nucleotide Polymorphisms (SNPs) in the Greek population and associate the latter with the clinical phenotype.
Patients and Methods
We enrolled 96 subjects: men with idiopathic non-obstructive azoospermia ($n=78$) were compared with a control group with fertile men ($n=18$) for SNPs in FSHR positions −29, 307, 566 and 680. The SNP in position 566 was assessed by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) and the other three SNPs' (−29, 307, 680) with Single Strand Conformation Polymorphism (SSCP); all of them were validated with DNA sequence.
Results
No SNPs were detected in positions −29 and 307. The heterozygous SNP (AG) at position 680 was associated with different size of the right testis ($P=0.080$). There was no association between the 566 SNPs polymorphism and hormonal or semen parameters. The combination SNP 680 AA with 566 CT revealed significant association with FSH and LH concentrations.
Conclusions
In our study group, FSHR SNPs at positions −29, 307, 566 and 680 do not appear to play specific roles in male infertility. Larger studies may be needed to confirm these results.
FSH Receptor, FSHR, SNP, Polymorphism, male infertility, fertility.

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EP725

Clinical and metabolic profile of male-to-female transgenders in Zamboanga Peninsula

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Introduction
The effect of self-prescribed cross-sex hormone therapy on Male-to-Female (MtF) transgenders do not appear to have been well investigated and can be associated with potential serious longterm complications. The main purpose of this study is to look at the clinical and metabolic profile, and cardiovascular outcomes of MtF transgenders in Zamboanga Peninsula.
Methodology
This is a cross-sectional study, done to determine the clinical and metabolic profile of Zamboanga-based MtF transgenders on either self-prescribed or on supervised cross-sex hormone therapy. Demographic and biochemical characteristics were taken as well as feminizing effects and cardiovascular outcomes (e.g. hypertention) were also documented 30 study participants aged 18 years and above.
Results
All respondents reported self-prescribed practices on cross-sex hormone therapy. Oral contraceptives pills (OCP) containing Ethinyl Estradiol 30 μg + Levonorgestrel 125 μg + Fe 75 mg was the most common hormone drug used based on recommendations by respondents' friends (100%). Most respondents got their OCPs from pharmacies (60%) and public health centers (13%). Common side effects were decreased libido (100%), Breast pain (93%), acne (20%), mood swings (17%) and headaches (10%). Breast enlargement (100%), decreased morning erection (100%), decreased muscle mass (76%), smoother skin (70%), weight gain (66%) and change in voice (10%) were observed. Clinical profile of the study participant showed that 36% were overweight and 6.67% were obese, 60–70% were pre-hypertensive, and 10% have Hypertension. Metabolic profile revealed that respondents were in the pre-diabetics range (FBS 16%, 2 h 75 OGTT 40%, HbA1c 73%) and lipid profile showed 20% have borderline high LDL result and 3% have low HDL.
Conclusion
The result of this study showed that majority of MtF transgenders in Zamboanga peninsula not only self-prescribed cross-sex hormone, they tailor-make their own drug dose and administration on the basis of suggestions from friends who are not trained to do so. At least half of them experienced the desired feminization effects of the hormones. Impaired fasting glucose, elevated blood pressure and weight, and abnormalities in the lipid profile were common among the transgenders.

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EP726

Should we initially manage young males with Kallmann's syndroma by stimulation treatment until the freezing and storage of sperm?

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Introduction
Hypogonadotropic hypogonadism(HH) is mandatory treated with testosterone (T). However, gonadotropin(hCG/FSH) administration might be the challenging optimal therapy.
Case 1
Male, 23-y-old, hypophisectomy pp. adenoma hromophobum, one month later-FSH 1.5 U/L, LH 0.55 U/L. Primogonyl(hCG) test; testosteronemia: 0 day 0.069, 3 day 19.01 nmol/l. After 5 m in ejaculate no sperm. 5 m after introduction of hCG twice weekly 1,500 i.u. and FSH+LH 150 i.u. tree times weekly sperm reappeared, 22×10^6/mL (testicular volume normal). On testosteron parenterally, after 6 m, sperm 3×10^6/mL. Mood stable.
Case 2
Male, 19-y-old with anosmia- Sy Kallmann(KS), BH 182 cm, BW 85kg, sexual development (Tanner stages): genitals stage 2, testes 1.5 cm (on ultrasonography), penis 2 cm, breast size stage 3 (for female), pubic hair density- stage 2, with few darker hairs at base of penis. Reduced sex steroids with absent body hair distribution, cariotip 46 XY. LHRH test; FSH: 0' 0.81, 30 min. 3.27 U/L, LH 0' 0.15, 30 min. 2.81 U/L. hCG test; testosteron: 0 day 1.32, 3 day 2.81 nmol/L. After hCG 3×3000 i.u./week, testosterone 13.9 nmol/l, gynaecomasthia almost disappeared, male body shape, penis longer and widened, pubic hare- stage 5/6, new found sexuality but testes almost without change in size. Still changes in mood, but physically feeling well-being.
Case 3
Male, 26-year-old, KS, similar phenotype as Case 2. Libido and erection (penis 2.5 cm) present but without ejaculation. After hCG 3000j./2–3day he started with ejaculation, voice deeper, libido increased. In 33y. hCG and HMG administered. After 2m. in ejaculate sperm was detected 0.5×10^6/mL, after 4 month sperm 3×10^6/mL, and testicular growth was 4×2 cm. Patient with postive mood and after 5 m of tretment, with spem 4.2–9.2×10^6/mL, sperm frozen in storage tank containing liquid nitrogen.
Conclusion
Patients with HH should be treated until testes become enlarged and sperm conformed in ejaculate, initially. Beside eliminating psychosocial impact of small testes safety reasons (e.g. possible allergy on gonadotropins) should indicate the storage of a sperm before chronic testosteron therapy.

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EP727

The Etiology of Azoospermia

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Introduction
Azoospermia is identified in approximately 1% of all men and in 10 to 15% of infertile males. A precise diagnosis of azoospermia and systematic evaluation of the patient to establish the disease etiology are needed to guide appropriate management options. The development of intracytoplasmic sperm injection (ICSI) as an efficient therapy for severe male factor infertility has become an appropriate treatment for the majority of male reproductive tract deficiencies.
Objectives
The aim of this study was to evaluate the hormonal profile and the etiology of non obstructive azoospermic men.
Materials
We conducted a prospective study from 2014 to 2015. Twenty four azoospermic patients were screened for medical history, physical exam, measurements of serum total testosterone and FSH, PRL, sperm analysis, genetic testing, and sometimes MRI.
Results
The mean age of our patients was 36.13 years. The FSH was high in 13 cases: four cases of cryptorchidism, one case of microdeletion AZFc, one case of thalassemia one case was a cook, and 2 cases work in radar. For the five remaining no etiology was found. The FSH was low in 4 cases: two adenoma, one hypogonadotrophic hypogonadism and one probably mutation of the FSH gene. Finally the FSH was in normal range in 7 cases: one case of empty sellae, one hyperprolactinoma, one cryptorchidism and one 47 XYY male syndrome.
Conclusion
In the past, men with azoospermia were classified as infertile, and a sperm donor was initially considered one of the best options for conceiving. Currently, the knowledge that many causes of azoospermia can be reversed is admitted from the medical profession. Therapeutic perspective as testicular sperm extraction and ICSI have changed the prognosis of azoospermia.

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Neuroendocrinology

EP728

Women with idiopathic intracranial hypertension have a distinct andro-metabolic signature compared to polycystic ovary syndrome and simple obesity

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Context
Idiopathic intracranial hypertension (IIH) is characterised by elevated intracranial pressure and occurs predominantly in obese premenopausal women. Signs and symptoms of polycystic ovary syndrome (PCOS) often coexist in IIH. Here we compared the androgenic and metabolic phenotypes in IIH, PCOS and simple obesity.
Patients and Methods
We studied 25 patients with IIH (mean age 34.4 ± 9.2 years; mean BMI $37.8 \pm 5.2\,kg/m^2$), in comparison to 31 women with PCOS and 15 with simple obesity; all three groups were matched for age and BMI. Women with IIH were studied before and after a weight loss intervention (mean BMI change $-5.8 \pm 3.0\,kg/m^2$). In all participants we performed comprehensive metabolic phenotyping and steroid profiling. Serum androgens were measured by liquid chromatography-tandem mass spectrometry); 24-hour urinary steroid excretion was analysed by gas chromatography/mass spectrometry. Urinary steroid profiles were correlated with clinical parameters of IIH severity.
Results
Serum testosterone (T) in IIH was comparable to PCOS and significantly higher than controls ($P=0.01$). Serum androstenedione (A) was significantly increased in PCOS ($P=0.008$) but IIH did not differ from controls. Insulin resistance as assessed by HOMA-IR did not differ between IIH and controls; PCOS women had a trend towards significantly higher HOMA-IR values ($P=0.08$). Total glucocorticoid excretion was significantly higher in IIH compared to controls ($P=0.01$) and decreased after weight loss ($P=0.02$). Similarly, the urinary ratio of 5α-THF/THF, a marker of systemic 5α-reductase activity, was significantly increased in IIH compared to controls ($P=0.04$). An/Et ratio correlated significantly with baseline markers of ocular papilloedema in IIH ($R=0.47$, $P=0.02$).
Conclusion
These results indicate a distinct andro-metabolic signature in IIH, with increased T but normal A and HOMA-IR values. We propose the new term of "andrometabolic syndrome" that regularly features androgen excess and obesity and variably presents with additional features such as anovulation (PCOS) and raised intracranial pressure (IIH).

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EP729

The cyclin-dependent kinase 4/6 inhibitor LEE001 (ribuciclib) demonstrates antiproliferative effects in neuroendocrine tumor cells in vitro

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Cyclin-dependent kinases (CDKs) are crucial for the cell cycle regulation and alterations of the cell cycle and its regulators are often observed in human malignancies. CDK4/6 in particular orchestrates the G1 phase progression and the G1/S transition. Here we investigated the *in vitro* effects of the CDK4/6 inhibitor LEE001(Novartis, Basel) on the human neuroendocrine tumor (NET) cell lines BON1, QGP1 and NCI-H727. The cells were treated with different concentrations of LEE001 alone (1 nM to 10 μM) and in combination with 5-fluoruracil (5 μM) and everolimus RAD001 (10 nM). The cell viability decreased in a time- and dose-dependent manner. The combinational treatment with everolimus (RAD001) showed a significant enhancement in inhibition of cell viability when compared to single treatments in BON1, QGP1 and H727 cells. In contrast, the combinational treatment with 5-fluoruracil showed significant enhancement over single substance treatment only in H727. LEE001 showed a time- and dose-dependent G1 cell cycle arrest in all three cell lines. Western blot analysis showed that the expression level of cell cycle relevant proteins such as Checkpoint kinase 1 (Chk1), phospho-retinoblastoma (pRb) and CyclinB1/D1/D3 were altered by LEE001 treatment. Also, a compensatory upregulation of CDK4 in response to LEE001 treatment was observed. Furthermore, LEE001 treatment led to a suppression of the PI3K-Akt-mTOR pathway, as revealed by a decrease in phosphorylation of Akt and the mTOR target 4E binding protein 1. In summary, the CDK 4/6 inhibitor LEE001 exhibits promising anti-cancer properties in human NET cell lines *in vitro* and should be further investigated in neuroendocrine tumors.

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EP730

The oxytocin regulates kidney function through V_2 receptor

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During maturation of oxytocin (OT) prohormone, several bioactive intermediate molecules are formed. The plasma concentrations of these forms (OT-G; OT-GK and OT-GKR) increase markedly in rat circulation at the end of gestation. At low concentration in the circulation OT stimulates while OT-GKR inhibits diuresis. Since OT and OT-GKR show different effects on the urine flow, we hypothesized that OT-GKR modulates renal action by targeting the V_2 receptor.
Results
The 8-weeks-old Wistar rats were injected (i.e.) with vehicle, OT and OT-GKR or in combinations. OT (10 μmol/kg) increased urine outflow by 40% ($P<0.01$) and the sodium excretion by 47% ($P<0.01$). The treatment with 10 μmol/kg of OT-GKR decreased diuresis by 50% ($P<0.001$), decreased sodium by 50% ($P<0.05$) and lowered potassium by 42% ($P<0.05$). OT antagonist (OTA) reduced diuresis and natriuresis exerted by OT, whereas the anti-diuretic effect of OT-GKR was unaffected by OTA. The treatment with V_2 receptor antagonist

(V_2A) in the presence and absence of OT induced diuresis, sodium and potassium outflow. The V_2A in the presence of OT-GKR only partially increased diuresis and natriuresis.
Molecular docking showed potent binding energies of OT-GKR to V_2R as well as to OTR. Moreover, the binding affinity of OT-GKR to V_2R in renal sections is almost equivalent to that of AVP. Finally, the cAMP release from CHO cells overexpressing V_2 receptor has been induced by low concentration of AVP (EC50:4.2e-011), the higher concentration of OT (EC50:3.2e-010) and by very high concentration of OT-GKR (EC50:1.1e-006). The OT-GKR potentiated cAMP release when combined with AVP, but blocked cAMP release when combined with OT.
Conclusions
OT-GKR inhibits diuresis and natriuresis exerted by OT, suggesting an auto-regulation of the renal function by the OT/OT-GKR system. This led us to the conclusion that OT-GKR regulates the kidney effects by specific interactions with V_2 receptor.

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EP731

Abstract withdrawn.

EP732

Growth hormone increases ALAS2, the rate-limiting enzyme of Hbb in male rat hippocampus

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Objective
Growth hormone (GH) has long been known to have neuroprotective properties. Hypophysectomy (Hx) completely abolishes circulating endocrine GH. Also neuronal (non-erythrocyte) haemoglobin beta chain (Hbb) in the hippocampus decreases following Hx while GH infusions and injections robustly increase the levels approximately 2-4-fold in male rat hippocampus. Recently it has been revealed that Hbb protein is present in mitochondria in the mammalian brain. Current investigations have shown that neuroprotective potential is associated with mitochondrial function. To investigate the signalling pathway between GH and Hbb, we measured the transcript levels of delta-aminolevulinate synthase 2 (ALAS2), a mitochondria specific rate-limiting enzyme of the heme synthesis in the hippocampus of male rats. To further extend our study of the signalling pathway involved in neuroprotection, we also included ALAS1 and hypoxia-inducible factor 1-alpha (HIF1a) in male rat hippocampus.
Methods & Results
GH was administered as a continuous infusion (GH inf) or as two daily injections (GHx2) in hx male rats. The response of ALAS2, ALAS1 and HIF1a to GH in the hippocampus was assessed by Q-RT-PCR. ALAS2 increased 3-fold in the male hippocampus and there was a significant difference in ALAS1 between Hx and GHx2 and between HIF1a and untreated hippocampus.
Conclusion
The type of GH administration affects Hbb abundance probably by increasing the level of ALAS2.

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EP733

Impaired innate immunity in Cushing's syndrome: increase CD14+ CD16++ monocytes

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Introduction
Chronic hypercortisolism is marked by an increased cardiovascular risk pattern. Atherosclerosis is a chronic inflammation that involves both innate and adaptive immunity. Glucocorticoids (GC) are immune-suppressors and adrenocorticotrophic hormone (ACTH) possesses immune-modulatory activities. GC and ACTH may act in atherothrombotic inflammatory pathways.
Aim
To analyze the immune cells pattern in endogenous Cushing syndrome (CS) in order to investigate their atherovascular risk phenotype and to evaluate the immune modulator role of ACTH on this pattern.
Material and Methods
26 CS: 16 ACTH dependent (D), 10 ACTH independent (ID) and 12 healthy controls (C) were included and peripheral immune cells, respectively monocytes (MN), lymphocytes (L) and neutrophils (N) analyzed by flow cytometry for the presence of cell surface activation markers previously associated with atherosclerosis.
Results
Leukocytes, N, M, NKL were increased in CS ($P^* < 0.05$). Atypical CD14+ CD16++M were higher in ACTH-ID CS (8.9±3.5%) vs ACTH-D CS (4.2± 1.9%). Other tendencies: CD11b+ cells increased in ACTH-ID CS; CD15+, CD15+CD16+ and CD15+CD16+11b+N were higher in CS.
Conclusion
High chronic exposure to GC in CS increase in the absence of the protective immune-modulator presence of ACTH the non-classical atherovascular risk CD14+CD16++ monocytes.

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EP734

Serum concentrations of glucose, cholesterol and triglyceride in men with prolactinoma treated with cabergoline

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Introduction
Hyperprolactinemia has been associated with several metabolic abnormalities both in glucose homeostasis, insulin sensitivity, and in lipid profile. Moreover, it has also been reported that many of them seem to improve after normalizing serum prolactin (PRL) concentrations.
Objective
To study serum glucose, cholesterol and triglyceride in men with prolactinoma before and after chronic treatment with cabergoline.
Patients and Methods
A retrospective study in 27 patients (age 39.1±13.1 years; 20 macroprolactinomas (74.1%)) was performed. Serum levels of glucose, cholesterol, triglycerides, PRL, gonadotropins (FSH and LH) and testosterone were quantified in every patient before and after cabergoline therapy.
Results
Mean serum glucose (94.1±13.4 mg/dl), cholesterol (211.4±41.6 mg/dl) and triglyceride (132.6±83.9 mg/dl) at prolactinoma diagnosis (PRL 1200 (337–5507) ng/ml) were normal. Cabergoline therapy (time on therapy 56.9±46.0 months; cumulative dose 108 (49.5–239) mg) achieved a reduction in serum PRL (16 (2.9–44.2) ng/ml, $P < 0.001$) and an increase in serum testosterone (236.8± 161.4 ng/dl vs 365.8±155.2 ng/dl, $P = 0.032$) without significant changes in gonadotropin levels. Cabergoline did not modify serum concentrations of glucose (94.2±12.3 mg/dl) and triglyceride (128.9±61.2 mg/dl). However, it was accompanied by a reduction in serum cholesterol, although this decrease did not reach the level of the statistical significance (198.4±31.9 mg/dl; $P = 0.061$). No correlation between serum PRL and testosterone with glucose, cholesterol and triglyceride at prolactinoma diagnosis or at last clinical visit was found.

Conclusion
Both hyperprolactinemia and its chronic treatment with cabergoline do not modify glycemic and lipid profile in men with prolactinoma.

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EP735

Phenotype-genotype analysis in patients with GnRH deficiency in a single center

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Objective
Congenital hypogonadotropic hypogonadism (CHH) results from isolated GnRH deficiency and may present with normal sense of smell (nCHH), anosmia (Kallmann syndrome, KS) or in syndromic forms. Genetic defects are identified in approximately half of CHH cases and oligogenicity is noted in almost 10%. Further, spontaneous reversal of is seen in 15% of patients.
Methods
We analyzed the clinical characteristics of 37 Serbian CHH probands (34 sporadic, 3 familial). Genetic analyses were conducted in 15 probands. Rare variants (minor allele frequency $<1\%$) were considered mutations if they were nonsense, frameshift, splice-site-altering variants or missense variants predicted to be deleterious *in silico*.
Results
In total, 11/37 (30%) had KS, 22/37 (59%) were nCHH, and 4 were syndromic ($n=2$ 4H syndrome: HH/hypomyelination/hypodontia, $n=1$ CHARGE syndrome: coloboma/heart defects/atresia of choanae/retarded growth/genital anomalies/ear defects, $n=1$ HH+adrenal hypoplasia). Three male reversal cases were noted among the 33 KS/nCHH (10%). Genetic studies revealed mutations in 11 different loci in 12/15 (80%) unrelated probands. Two of three reversal cases were found to carry heterozygous mutations (*FGFR1* and *TACR3* respectively) and all three familial cases (2 nCHH, 1 KS) were found to harbor heterozygous mutations in *FGFR1*. Among the syndromic cases, both patients with 4H Syndrome harbor heterozygous mutations in *POLR3* while the patient with HH+adrenal hypoplasia has a hemizygous mutation in *NR0B1*. Exome sequencing revealed oligogenicity in one familial nCHH case (1/11, 10%) who harbors heterozygous mutations in *FGFR1*, *GNRH1*, and *LEP*.
Conclusions
This CHH cohort displays marked clinical heterogeneity including patients with 4H syndrome, CHARGE syndrome and congenital adrenal hypoplasia. We identified mutations in the majority (80%) of cases. Those patients without mutations did not exhibit any CHH-associated phenotypes. Exome sequencing is an efficient and effective tool for exploring the complex genetic architecture of CHH.

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EP736

The medical treatment with pasireotide in Cushing's disease: an Italian multicenter experience based on "Real Word Evidence"

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A recent phase III clinical trial has demonstrated that the treatment with the somatostatin analogue pasireotide normalizes cortisol secretion in 15–28% of patients with Cushing's disease (CD). The aim of the current study was to evaluate the effectiveness of 6-months pasireotide treatment on clinical and hormonal profiles in a group of CD patients with mild to moderate disease according with the real-word evidence. Thirty-two patients with CD unsuccessfully treated by surgery and with persistently increased urinary free cortisol (UFC) levels started pasireotide treatment at the dose of 600 mg bid. UFC, plasma ACTH and serum cortisol levels were measured every three months together with clinical and metabolic parameters. Five patients discontinued treatment during the first 6 months for adverse events, mainly gastrointestinal disturbances; among the remaining 27 patients, 14 with very mild, 6 with mild, 6 with moderate and 1 with very severe UFC increase reached 6-months follow-up; the study focused on the 26 patients with very mild to moderate disease. After 6-months pasireotide treatment, UFC levels were normalized (ULN <1) or nearly normalized (ULN between 1 and 1.1) in 22 out of 32 (68.7%) patients. A significant decrease of UFC ($P=0.004$), serum cortisol ($P=0.011$) and ACTH levels ($P=0.002$) were demonstrated in the entire cohort of CD patients. The decrease of UFC levels was accompanied by a significant decrease in weight ($P=0.000$), body mass index ($P=0.000$), waist circumference ($P=0.01$) as well as serum total cholesterol (0.023) and LDL cholesterol levels ($P=0.011$). Fasting plasma glucose ($P=0.003$) and glycosylated haemoglobin ($P=0.000$) levels increased significantly. Hyperglycaemia or deterioration of diabetes was documented in 67% whereas gastrointestinal disturbances, mainly diarrhoea, were documented in 31% of patients. Among the 18 patients with available pituitary MRI at baseline and at 6 months of follow-up, tumour remained stable in 13 patients and decreased in 4 patients; in particular, 1 macroadenoma became a microadenoma, 2 microadenoma became invisible. A slight enlargement was found in one macroadenoma. In conclusion, pasireotide treatment induces normalization of UFC in nearly 70% of patients with very mild to moderate CD during clinical practice, with consequent improvement in the clinical picture, but with occurrence or deterioration of diabetes or gastrointestinal disturbances in 31–67% of cases. These results confirmed the usefulness of pasireotide in controlling CD especially in patients with non severe disease.

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EP737

Sublingual desmopressin is efficient and safe in the therapy of lithiasic renal colic

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Background
Antidiuretic analogue desmopressin was tested in its intranasal form in renal colic, with variable effects.
Aims
We evaluated the effects of sublingual desmopressin in lithiasic renal colic, alone or combined with a non-steroidal antiinflammatory drug (NSAID).
Materials and methods
Our prospective single-blind study included an initial number of 371 patients with lithiasic renal colic randomized as follows: group NSAID (93 patients) received ketorolac 30 mg im, groups D60 and D120 (84 and 61 patients) received sublingual Minirin Melt, 60 and 120 μg respectively, whereas groups C60 and C120 (63 and 70 patients) received combinations of ketorolac and Minirin Melt. Pain intensity was assessed using the visual analogue scale before and thirty minutes after drug administration. Patients experiencing pain aggravation were rescued and excluded from the study.
Results
Dropout incidence was higher in the NSAID group than in the groups treated with desmopressin in monotherapy or combined with ketorolac ($P<0.05$). Pain intensity was diminished at least as potently by the therapy with desmopressin and ketorolac. The higher dose of desmopressin and combination therapies decreased pain intensity more than ketorolac alone ($P<0.05$). Mean pain decrease was higher in the pooled combination group (C) than in the NSAID group or pooled group treated with desmopressin in monotherapy (D) ($P<0.05$). Patients did not experience side effects and their blood pressure remained constant in all groups.
Conclusions
Sublingual desmopressin is at least as potent as NSAID in the treatment of lithiasic renal colic. Combinations of sublingual desmopressin and NSAID have additive analgesic effects.

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EP738

The effects of pituitary replacement therapies on body composition in adult patients with growth hormone deficiency

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Growth hormone deficiency (GHD) has become increasingly recognized as a cause of metabolic syndrome, characterized by altered body composition and adverse cardiovascular risk. The effects of other pituitary hormone deficiencies or their replacement therapies on the metabolic profile in this clinical setting are still largely unclear. In this study, we aimed to evaluating the effects of replacement therapies of central hypoadrenalism and hypothyroidism on body composition in a cohort of 33 patients (F 7, M 26, median age: 51 years) with treated (10 cases) and untreated (23) GHD. Twenty-two patients had glucocorticoid deficiency, whereas central hypothyroidism was found in 25 subjects. All patients were on replacement therapy with hydrocortisone (median daily dose: 25 mg, range: 10–40) and/or levothyroxine (L-T4 median daily dose: 1.27 mcg/Kg, range: 0.4–2.6). Patients were evaluated for their body composition by DXA and anthropometric measures. Subjects with untreated GHD showed higher total body fat percentage (30.9% range: 22–52 vs. 23.0%, range: 11–42; $P=0.03$) and waist circumference (105 cm vs. 88 cm; $P=0.009$) as compared to patients with treated GHD. However, no significant differences in body composition were observed between patients with treated hypoadrenalism and those with preserved adrenal function (total body fat percentage: 30.6%, range 11–52 vs. 26.8, range 13–45; $P=0.48$; waist circumference: 98.5 cm, range 75–130 vs. 103.0 cm, range: 75–140; $P=0.98$) and between patients treated with L-T4 and those with normal thyroid function (total body fat percentage: 29.6%, range 11–52 vs. 30.4, range 13–45; $P=0.82$; waist circumference: 99.0 cm, range 75–130 vs. 98.0 cm, range: 75–140; $P=0.91$). Moreover, daily dose of hydrocortisone did not correlate with total body fat percentage (ρ: 0.01; $P=0.9$) and waist circumference (ρ: 0.29; $P=0.27$). Likewise, no significant associations were found between L-T4 daily dose and total body fat percentage (ρ: 0.17; $P=0.4$) and waist circumference (ρ: 0.25; $P=0.30$) in patients with central hypothyroidism. This study suggests GHD is the main determinant of body composition in adult GHD patients and replacement therapies with hydrocortisone and L-T4 do not seem to exert relevant effects on this clinical outcome.

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EP739

Nuchal Skinfold Thickness: a novel parameter for assessment of body composition in childhood craniopharyngioma

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Context
Hypothalamic obesity, subsequent cardiovascular disease (CVD), and relapses/progression have major impact on prognosis in childhood-onset craniopharyngioma (CP). We analyzed nuchal skinfold thickness (NST) on magnetic resonance imaging (MRI) performed for follow-up monitoring as a novel parameter for body composition (BC) and CVD in CP.
Objective
Identify association of NST with body mass index (BMI), waist-to-height ratio (WHtR), caliper-assessed skinfold thickness, and blood pressure (BP) in CP and controls.
Patients and methods
In a cross-sectional study, 94 CP recruited in HIT-Endo, KRANIOPHARYNGEOM 2000/2007 and 75 controls were analyzed for associations of NST with BC and BP.
Results
NST correlated with BMI SDS ($r=0.78$; $P<0.001$; $n=169$) and WHtR ($r=0.85$; $P<0.001$; $n=86$) in total cohort and CP patients (NST–BMI SDS: $r=0.77$, $P<0.001$, $n=94$); NST–WHtR: $r=0.835$, $P<0.001$, $n=43$) and controls (NST–BMI SDS: $r=0.792$, $P<0.001$, $n=75$; NST–WHtR: $r=0.671$, $P<0.001$, $n=43$). Comparing NST with caliper-measured skinfolds, subscapular, and abdominal skinfold thickness revealed highest correlation ($P<0.001$) with NST in both CP ($r=0.802$; $r=0.710$) and controls ($r=0.724$, $r=0.730$). In CP patients, systolic BP correlated with NST ($r=0.575$, $P<0.001$), BMI SDS ($r=0.434$, $P=0.004$), and WHtR ($r=0.386$, $P=0.011$). Similar results were observed for diastolic BP in CP. In multivariate analyses, NST had predictive value for hypertension in post-pubertal CP and controls (OR = 6.98, 95%CI [1.65,29.5], $P=0.008$).
Conclusions
As monitoring of MRI and BC is an essential for follow-up in CP, NST could serve as a novel, clinically relevant, and easily determinable parameter for assessment of BC and CVD risk in CP patients.

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EP740

Nonalcoholic fatty liver disease and fatigue in long-term survivors of childhood-onset craniopharyngioma

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Objective
Hypothalamic obesity in childhood craniopharyngioma (CP) patients bares a high risk for development of metabolic syndrome. In metabolic syndrome, the development of nonalcoholic fatty liver disease (NAFLD) is known. The aim of this study is to detect the risk for NAFLD in childhood-onset CP.
Design
This cross-sectional study included liver computed tomography (CT); ultrasound analysis of abdomen; measurements of serum parameters, height, weight and body composition and daily medication of patients with childhood-onset CP.
Methods
Three hundred and eighty-four patients recruited in trials HIT Endo and KRANIOPHARYNGEOM 2000 were analyzed. 94 survivors were included by fulfilling the criteria of proven hypothalamic involvement (HI), a minimum time interval of five years between diagnosis and study, and a minimum age of 18 years at time of evaluation. A total of 19 patients agreed to participate. To quantify the degree of steatosis hepatis, analyses of liver density were performed once by non-contrasted CT of liver sections.
Results
NAFLD occurs in about 50% of CP patients with HI and is associated with elevated liver enzymes and homeostasis model assessment (HOMA) index. Body mass index (BMI) is not an effective predictive factor but body fat mass measured by near-infrared spectroscopy (NIRS) is. Over half of CP patients (60%) with NAFLD are treated with stimulating agents, with risk of hepatic side effects.
Conclusions
NAFLD is a major adverse late effect in childhood-onset CP. NIRS rather than BMI should be used to measure body composition and predict NAFLD. Stimulating agents for treatment of fatigue and daytime sleepiness in CP should be prescribed judiciously.

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EP741

Hypothalamic dysfunction revealed by magnetic resonance diffusion tensor imaging in childhood leukemia survivors treated with cranial radiotherapy but not in craniopharyngioma survivors

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Background
Metabolic complications with obesity are frequent in childhood acute lymphoblastic leukemia (ALL) survivors treated with cranial radiotherapy (CRT). Childhood onset Craniopharyngioma (CP) survivors without hypothalamic (HT) involvement are spared gross obesity. Magnetic resonance diffusion tensor imaging (DTI) provides information of microstructure function of the brain and quantified as fractional anisotrophy (FA), mean diffusivity

(MD), axial and radial diffusivity (AD, RD). Since MD in HT is reportedly impaired (increased) in obese compared to non-obese subjects, we investigated DTI in the HT.
Methods
Twenty nine ALL survivors on hormone supplementation were investigated 34 years after CRT (24 Gy). 17 CO-CP survivors with hormone supplementation but without HT damage were investigated. Comparisons were made with these two patient populations to 27 matched controls regarding DTI parameters in the HT and for BMI, fat mass, fat free mass and waist/hip measurements.
Results
We recorded reduced FA (0.27 vs 0.29, $P=0.04$), and increased MD (1.13 vs 1.00, $P<0.001$), AD (1.41 vs 1.25, $P<0.001$), and RD (0.99 vs 0.86, $P<0.001$) in the right HT and increased MD (1.42 vs 1.25, $P<0.001$), AD (1.75 vs 1.58, $P<0.001$), and RD (1.25 vs 1.04, $P<0.001$) in left HT in ALL survivors compared to matched controls. The CPs showed no difference in the HT for these parameters compared to controls. ALL survivors with a BMI $\geq$ 25 showed elevated MD ($P=0.03$) and AD ($P=0.02$) compared to ALL survivors with a BMI $<$ 25 and compared to controls with BMI $\geq$ 25 in the right HT. This was not the case in CP survivors or in controls.
Conclusions
Thirty four years after CRT for ALL, DTI measures are deranged in the HT. ALL survivors with a BMI $\geq$ 25 were presented with worse HT dysfunction. CP survivors were unaffected. The present data suggests changes in the microstructure of the HT in these ALL survivors.

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EP742

How frequently can we predict failure of fluid restriction in SIAD? Results of a multicenter prospective audit

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Context
Fluid restriction (FR) is recommended as first line therapy for SIAD by both the European[1] and the American guidelines[2] for management of SIAD. Not all patients respond to FR however, and the American guidelines have identified clinical predictors of failure to respond to FR. These include 1.Urine osmolality (UOsm) $>$500 mOsm/Kg 2. Furst formula (ratio UNa$+$UK/pNa) $>$ 1, and 3. 24 hour-urine volume $<$1500 ml
Objective
To ascertain the frequency with which patients with SIAD display at least one criterion for prediction of no response to FR.
Design
Prospective, non-interventional, multicenter study in Hospital Clínico San Carlos (Madrid) and Beaumont Hospital (Dublin).
Patients
Hundred and eighty three patients with SIAD were prospectively and consecutively recruited, 51 from Madrid and 132 from Dublin. The investigators did not interfere in the management of hyponatraemia unless specifically requested.
Methods
Collection of data for predictors of response to FR. Results are expressed as median with interquartile range (IQR).
Results
There was 100% ascertainment of the full diagnostic criteria for diagnosis of SIAD. Median plasma sodium was 128 mmol/l (IQR:125,130 mmol/l). 4 patients (2.2%) died during hospitalization. 75/183 (41%) patients had UOsm $>$500 mOsm/kg, 48/183 (26%) a Furst formula$>$1, 49/103 (47%) urinary volume $<$1500 ml/24 h. 109/183 (59%) had at least one criterion predicting no response to FR.
Conclusion
More than half of SIAD patients had at least one criterion which has been recommended to predict failure to respond to FR, the first line therapy for SIAD. If the predictors of non-response to FR are correct, our data challenges the conventional wisdom that FR is first-line treatment for SIAD. Further studies are needed to test the validity of the predictors of non-response in the US guidelines.

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EP743

Liraglutide restores the endocrine function of islet's β-cells and the altered lipid profile in early stages of life induced by food restriction in pregnancy

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Maternal food restriction during late pregnancy and lactation, increases the risk of glucose intolerance and metabolic diseases such as diabetes & obesity in rats. Liraglutide is a GLP-1 receptor agonists administered for treating DM2. The aim of this study was to elucidate if liraglutide given to pregnant rats may prevent the deleterious effects of malnourishment in male pups analyzed at 21 days of age.
Twenty eight Sprague-Dawley pregnant rats were included. Controls (CT) were fed ad libitum, whereas dams in restricted group were fed with 50% (50FR) daily intake of control dams. Pregnant rats were treated with liraglutide (100 μg/Kg/12 h; 50FR/LIR, CT/LIR) or vehicle (50FR/VEH, CT/VEH) from gestational day 14 to 21.Pups body weight were controlled after birth. During lactation the FR was reduced to 30%. At 21 days of age (D21) and before weaning, pups were sacrificed. Serum and tissue samples were obtained and stored at -80 °C until analysis.
50FR pregnant dams, gained 16% less body weight than controls, independently of the treatment with liraglutide. After birth, 50FR/VEH and 50FR/LIR male pups exhibited significantly decreased body weight at postnatal day 1, 7, 14 and 21 compared to CT/VEH. At D21, intraperitoneal fat pad is decreased in pups from FR-dams, without differences in mesenteric & gonadal fat pads nor adrenal glands' weight. 50FR/VEH males displayed significantly decreased plasma lipid profile (TG, LDL-HDL-total cholesterol). Glycaemia trends to be increased by FR, but not differences were observed. However, 50FR/VEH group had increased peptide-C levels compared to CT/VEH, and LIRA reverted the effect of FR. LIR treatment increased lactate plasma levels just in 50FR males.
In conclusion, LIR restores the endocrine function of islet's β-cells and the altered lipid profile induced by FR in pregnancy in early stages of life.

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EP744

Assessment of bilateral inferior petrosal sinus sampling in the differential diagnosis of the ACTH-Dependent cushing's syndrome

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Objective
The aim of this study was to assess the diagnostic accuracy of BIPSS with desmopressin stimulation in the differential diagnosis of ACTH-dependent Cushing's syndrome.
Patients and methods
Retrospective study of patients studied to our hospital for diagnosis of ACTH-dependent Cushing's syndrome (2000–2015). The histopathological results in patients who underwent a surgical procedure was considered the reference for statistical study of the accuracy of this technique. Statistical analysis: rates of assessment of diagnostic tests and Cohen's kappa coefficient as a measure of interrater agreement between two observations.
Results
BIPSS was performed in 31 patients, of these, 24 patients were operated: 79.2% Cushing's disease (CD), 8.3% ectopic Cushing's syndrome and 12.5% adrenal Cushing's syndrome. 84% of patients with CD had a central positive location in BIPSS (Sensitivity: 0.84, IC 95%: 0.67–1.00); 100% of patients without CD had a negative BIPSS for the central location (Specificity: 1.00, IC 95%: 1.00–1.00), 100% of patients with BIPSS positive for central location were diagnosed of CD (Positive Predictive Value: 1.00, IC 95%: 1.00–1.00), 63% patients with BIPSS negative for central location weren't diagnosed of CD (Negative Predictive Value: 0.63, IC 95%: 0,29–0,96). 88% of patients were correctly classified after BIPSS (Efficiency: 0.88, IC 95%: 0.74–1.00). Good agreement is observed between the location of pituitary magnetic resonance (MRI) or computed tomography (CT) and BIPSS ($K=0.625$; $P=0.002$).
Conclusions
BIPSS with desmopressin stimulation is useful in the differential diagnosis of ACTH-dependent Cushing's syndrome, and it shows good agreement with imaging tests used.

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EP745

Hormonal characteristics of recurrent ACTH-secreting pituitary adenomas

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Cushing's disease (CD) remission after primary surgical treatment is achieved in 70–90%, but recurrence ranges 18–25% after.
The aim of this work was to study clinical, hormonal and MRI indicators before and after surgical treatment in patients with recurrent CD to identify possible predictors of recurrence. We examined 49 patients with recurrent CD in the active stage (disease duration up to 3 years). Before neurosurgery blood ACTH (median 80.0 PG/ml) and cortisol (median 689.5 nmol/l), free cortisol level in daily urine (median 1336.5 nmol/24 h) and 23:00 free cortisol in saliva (median of 18.4 nmol/l) were increased. 99.4% of patients had decreased cortisol with 74.7% from baseline during HDDST, 10.6% were negative. Microadenoma in 69.9%, macroadenoma in 30.1%. ACTH levels were correlated with the tumour volume. According to the results surgical treatment patients were divided into 2 groups. The 1st group 19 patients (38.8%) in whom the remission developed and adrenal insufficiency (AI) signs appeared in 78.9% (15 patients), in 4 patients AI was absent. Remission lasted from 3 to 3.9 years, In 30 patients from 2nd group (61.2%) the remission was not achieved. In the group with remission there was a significant decrease blood ACTH and cortisol concentration in the early postoperative period (7–10 days) and the normalization of rhythm. The ACTH level was markedly decreased in the subgroup with AI. Remission was longer in all patients with AI. Cortisol levels reduction in patients with AI was 75% and in patients without AI - 65% in HDDST before the surgery.
Thus, the adenoma size (microadenoma), a more pronounced cortisol reduction during HDDST before the operation, the presence of AI and the average ACTH level below 10.0 PG/ml after surgery can be used as predictors of longer CD remission.

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EP746

Quality of sleep and salivary cortisol

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Introduction
Contradictory associations between sleep disturbances and changes in cortisol levels or unfavourable metabolic conditions like obesity and diabetes mellitus have been observed.
The aim of the present study was to examine salivary cortisol in persons with reduced sleep quality and to evaluate the relationship between sleep quality and metabolic parameters.
Methods
The Pittsburgh Sleep Quality Index (PQ8I) was used in 154 healthy persons (85 females; 27–76 years old; mean =56.3, SD =10.4 years) at the Medical University of Graz. Quality of sleep was related to morning levels of salivary cortisol, the Body Mass Index (BMI) and the Insulin resistance index (HOMA-IR).
Results
55 (35.7%) of the study participants showed a decreased quality of sleep. 37 (43.5%) of all women reported sleep disturbances in contrast to 18 (26.0%) of men ($P=0.025$). Salivary cortisol levels of male poor sleepers were significantly lower in comparison to the levels of male good sleepers ($P=0.007$). Correlation of the PQ8I with BMI or HOMA-IR did not show significant results.
Conclusions
Sleep disturbances are very common in our sample of healthy people. Particularly in men, reduced sleep quality (e.g., prolonged sleep latency) was associated with low morning levels of salivary cortisol. Missing correlations between sleep problems and metabolic symptoms are contradictory to the literature and need to be discussed. Our finding of low cortisol levels in poor sleepers represents malfunction of the circadian rhythm and substantiates the psychobiological significance of salivary cortisol.

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EP747

Limited value of the standard 8-hour water deprivation test in the diagnostic work-up of patients with suspected diabetes insipidus

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Background
Diabetes insipidus (DI) is characterized by polyuria and consequently thirst and polydipsia. Excessive water intake can also cause polyuria, *i.e.* primary polydipsia. It is of utmost importance to differentiate between the two disorders since the treatment is different.
Aims
To study the clinical value of the standard 8-hour as well as an extended water deprivation test in patients with polyuria and polydipsia.
Patients and methods
This was a retrospective, single centre study were results from 117 water deprivation tests performed between 2004 and 2014 were reviewed. The same protocol was used during the entire study period. Consumption of any liquids during the test was strictly prohibited. Weight, osmolality and specific gravity were measured on every occasion the patient urinated throughout the test. Following criteria were used for termination of the test: a) >3% weight reduction, b) Urine specific gravity >1.020 or, urine osmolality >800 mOsm/L, c) Intolerable adverse symptoms such as excessive thirst.
Results
Of 117 patients (70 women, 47 men), 21 (18%) were diagnosed with DI and 96 (82%) with primary polydipsia. The median (interquartile range; range) time to termination of the test was 14 hours (10-16; 3-36) in patients with DI and 18 hours (14–24; 7–48) in patients with primary polydipsia ($P=0.009$). In only 4 (20%) patients with DI and 5 (5%) patients with primary polydipsia the diagnostic criteria were met in less than 8 hours. Of those diagnosed with primary polydipsia, 26 (27%) did not reach either urine specific gravity >1.020 or urine osmolality >800 mOsm/L.
Conclusions
The standard 8-hour water deprivation test has a limited value in the diagnostic work-up of patients with polydipsia–polyuria syndrome. Despite an extended test for up to 48 hours, a partial DI may have been missed in as many as one fourth of the patients diagnosed with primary polydipsia.

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EP748

Severe carcinoid cardiac disease in a young patient with neuroendocrine tumor of unknown origin

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Carcinoid cardiac disease is a rare cause of intrinsic right heart valve disease with significant impact on mortality. We present the case of a young male patient (38 yrs old) complaining in the last 5 yrs of abdominal pain associated with flushing of the face that progressively worsened (up to 15 episodes/day) accompanied by diarrhoea and, in the last 2 months, by night sweats, distension of the abdomen, bilateral ankle swelling and progressive limitation in effort. Endocrine evaluation revealed high levels of serum markers for neuroendocrine tumor (NET) and multiple large liver metastases on the CT scan of the abdomen, confirmed on Octreoscan but with no identifiable primary. Biopsy of liver metastasis diagnosed a Grade 2 NET -Ki67 4%, and was suggestive for secondary determination from a small bowel NET. Due to the discovery of important ascites, echocardiography was performed and revealed important tricuspid and pulmonary regurgitations, severe right heart failure and very high level of pro-BNP (8Xupper limit). Somatostatin analogue treatment was started with significant improvement in symptoms and NET markers, thus allowing cardiac surgery with remission of symptoms related to heart failure, giving us time for search of the primary and deciding the adequate treatment for the NET.

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EP749

Molecular genetic analysis in familial isolated pituitary adenoma patients

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Introduction
FIPA- is a syndrome which includes pituitary adenomas with any kind of secretion in two or more members in a family in the absence of MEN or Carney complex; it also includes isolated family somatotropin syndrome (IFS).
Aim
Molecular genetic study of a gene panel in FIPA patient.
Materials and methods
Study included 1 family (2 men, 24 and 58 years) with pituitary adenomas with homogeneous secretion type — somatotropinomas. Median height — 170 cm. Level of GH — 80 ng/ml, IGF — 497.5, prolactin — 208.4. Brain MRI: macroadenomas (maximum size of 39 mm). One patient after combination therapy (somatostatin analogs in the maximum dose and primary surgery, without radiological therapy), another patient without any treatment at the time of the study. There were no normalization of GH and IGF.
Genomic DNA from a blood samples of patients underwent high-throughput sequencing on the Ion Torrent Personal Genome Machine (Life Technologies) using a custom-designed AmpliSeq panel for the sequencing of a panel of genes (MEN1, CDKN1B, PRKAR1A, GNAS, AIP, SDHA, SDHB, SDHC, SDHD, PRKCA, CDKN2C, CDKN2A, POU1F1, PTTG2).
Results
Direct sequencing revealed mutation in exon 6 of the gene AIP p.R271W, which was not previously described in studies.
Conclusion
We were able to identify a new AIP mutation in FIPA family.
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EP750

Nonfunctioning pituitary adenoma: a clinical and pathological study
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Objective
To assess clinical outcome after pituitary surgery in patients nonfunctioning pituitary adenomas (NFPA) surgically treated in the past 3 decades in three tertiary referral hospitals.
Methods
A multicenter retrospective study on clinical and pathological characteristics, treatment patterns, and outcome in patients with NFPA periodically followed up in specialized neuroendocrinology units who underwent surgery in the period 1982–2015 was performed.
Results
105 patients [54 women (51.4%)]; age 52.26 ± 14.07 yr were studied. The tumor was sporadic in 100 patients (95.2%) and in the context of a multiple endocrine neoplasia type 1 in 5 patients (4.8%; 4 women). The main reasons for consultation were neuro-ophthalmologic symptoms such as visual disturbances (71.4%) and headaches (44.8%). In the analysis of symptoms by sex, panhypopituitarism ($P=0.004$), central hypogonadism ($P=0.002$), and secondary hypothyroidism ($P=0.003$) were more commonly observed in men. 90.5% of the cases were macroadenomas ($n=95$), 15 of them (15.8%) giant adenomas (≥ 4 cm). Immunohistochemical staining was mainly positive for LH (17.1%) and FSH (15.2%). Ki67 index was studied in 41 patients, showing the majority (43.9%) a value $<1\%$. After a median of 57 months of follow-up, maximum tumor diameter decreased from 2.9 ± 1.0 to 1.2 ± 1.2 cm ($P<0.001$); the percentage of patients with no tumor on MRI was 25.7%. The percentage of patients with pathological visual fields decreased from 66.6% to 33.6%; whereas, panhypopituitarism increased from 6.7% to 14.3%. Surgery achieved complete cure (absence of tumor and normal pituitary function) in 12 patients (11.4%).
Conclusion
NFPAs surgically treated in our country show a similar distribution between men and women, although they are clinically more symptomatic in the first. Histologically, NFPAs are usually gonadotropinomas with low proliferation index. Although therapy is accompanied by improvement in visual fields, involvement of pituitary function does not improve over time. Complete cure is uncommon and long-term follow-up is needed.
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EP751

Pressure pain threshold and β-endorphins plasma level are higher in lean polycystic ovary syndrome women
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Aim
Evaluation of pressure pain threshold and β-endorphin plasma level in lean women with polycystic ovary syndrome (PCOS) and healthy controls. The associations between β- endorphins and pressure pain threshold were also investigated.
Materials and methods
In 48 lean women with polycystic ovary syndrome and 38 lean women without this disorder plasma β-endorphins and pressure pain thresholds were measured.
Results
The β- endorphins level was higher in the PCOS group compared to the controls (15.5 ± 4.37 pg/ml vs 6.9 ± 2.47 pg/ml, $P<0.0001$). In PCOS group pressure pain thresholds measured on deltoid and trapezius muscles were higher compared to the controls (9.33 ± 1.3 kg/cm^2 vs 5.19 ± 0.57 kg/cm^2, $P<0.001$; 8.23 ± 1.04 kg/cm^2 vs 4,79 ± 0.55 kg/cm^2, $P<0.001$). The β- endorphin levels positively correlated with pressure pain thresholds in polycystic ovary syndrome group. Increase in β- endorphin level of 1 pg/ml was associated with increase of pressure pain threshold value on deltoid muscle of 0.23 kg/cm^2 ($R=0.632$, $P=0.011$) and of 0.18 kg/cm^2 on trapezius muscle ($R=0.588$, $P=0.037$).
Conclusion
β- endorphin serum level as well as pressure pain threshold are higher in lean polycystic ovary syndrome group than in lean healthy controls. We found correlations between β- endorphin levels and pressure pain threshold in the polycystic ovary syndrome group. It may suggest the role of endogenous opioids in the pathogenesis of polycystic ovary syndrome and also that increases in circulating plasma β- endorphins concentration can increases pressure pain threshold and consequently may modulate pain perception in PCOS lean women.
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EP752

The hypotalamic-pituitary-adrenal axis changes in non-pituitary brain tumors survives and the best method of its diagnostic
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The number of the non-pituitary brain tumors survives increases and will be growing up in the future. Although the prevalence of secondary adrenal insufficiency (SAI) vary depending on the methods of diagnostic, we have a few data about their ACTH and DHAE-S status. The aim of our study was to describe the hypotalamic-pituitary-adrenal axis (HPAA) changes after craniospinal irradiation (CRT) and diagnostic utility basal cortisol (BC), DHAE-S, glucagon stimulation test (GST) in comparison with the insulin tolerance test (ITT) in this group of patients.
ACTH and cortisol (basal and during ITT), DHAE-S was examined in 31 medulloblastoma survives (15 females), aged Me = 19[17;22], 2–15 year after CRT and in 10 normal controls (Me = 21 [23;27] year), GST was performed in 19 patients and all healthy. The cut-off point for ITT was 550. After ITT patients was divided into subgroups: SAI and without SAI (W-SAI). Receiver-operating characteristic (ROC) analysis was performed to identify the thresholds for BC, DHAE-S and GST.
16/31 (51.6%) had SAI by ITT. All groups had the same ACTH level. BC was significantly higher in W-SAI patient (Me = 559 [374;688]) compare with healthy (Me = 363 [214;602] $P=0.037$) and SAI (Me = 353[271;388] $P=0.001$). SAI-patients had DHAE-S (Me = 3.1[2.2;3.9]) lower than W-SAI (Me = 4.8[2.6;6.4], $P=0.018$) and controls (Me = 6.4[3.3;8.4], $P=0.06$), W-SAI and healthy not distinguished ($P=0.4$) in DHAE-S level.
GST and ITT had the same maximal ACTH and cortisol level ($P=0.15$ and $P=0.6$, Wilcoxon test). ROC-analysis showed area under curve (AUC) for GST =

0.64 with optimal cut-off for cortisol = 580; for BC AUC = 0.72 with maximum specificity for cortisol more than 500; for DHAE-S AUC = 0.814 with optimal sensitivity/specificity ratio DHAE-S = 4.4.
Prevalence of SAI after CRT is high. W-SAI-patients have a tendency to increased BC while SAI-patients have a lower DHEA-S. GST may use as screening stimulation test when ITT is contraindicated while BC and DHAE-S levels in a grey zone.

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EP753

Prognostic factors of pituitary growth hormone-secreting tumors

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Background
Acromegaly is the consequence of excessive growth hormone (GH) secretion, usually produced by a pituitary adenoma. Transphenoidal surgery is the first-choice treatment; however, the development of new drug therapies in the last years, specially the somatostatin analogues (SSA), has open new and promising avenues for the treatment of pituitary tumors.
Objective
To determine whether a detailed knowledge of the clinico-pathological and radiological characteristics of the acromegalic patients and the adenoma molecular phenotype could help to predict the hormonal response to therapy in order to improve the management of patients with this pathology.
Material and methods
Observational study including patients with acromegaly, diagnosed at the Endocrinology and Nutrition Unit of the Hospital Reina Sofía from 2007 to 2012, in which surgery, radiology and molecular phenotyping of the adenoma was carried out.
Results
22 patients were included (38 ± 15 years old; 65% women). 3 patients meet cure criteria. These who meet cure criteria have lower triglycerides levels (86 ± 7 mg/dl), more LH (9 ± 10U/L) and FSH (15 ± 20) than those who do not (Tg 128 ± 54, $P = 0.021$; LH 2 ± 1, $P = 0.019$; FSH 3 ± 3, $P = 0.035$). Inferior-posterior diameter was lower in patients who meet healing criteria (15 ± 1 vs 19 ± 7; $P = 0.044$) and lower antero-posterior diameter (15 ± 1 vs 19 ± 7; $P = 0.044$). There were no differences about comorbidities or symptoms at diagnostic between two groups. Patients who meet cure criteria express more POMPC and GnRHR than those who do not (POMC 2 ± 3 vs 0 ± 0, $P = 0.036$; GnRHR 0.8 ± 0.1 vs 0 ± 0, $P = 0.034$).
Conclusion
Overall, our results indicate that there is a significant correlation between several pre-surgical parameters and the disease cure. Patients who meet cure criteria have lower infero-posterior and antero-posterior diameter; and express more POMPC and GnRHR.

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EP754

The use of a specific protocol for initiation of tolvaptan therapy in mild/moderate euvolemic hyponatremia secondary to SIADH: not a single case of overcorrection

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Introduction
ESE guidelines state a risk for overcorrection of serum sodium levels (SNa) with vaptans. We present the results of our protocol for initiation of tolvaptan(TV) therapy in SIADH.
Methods
Retrospective (2011–15). 86 patients with SIADH-induced mild/moderate hyponatremia received TV:7.5 mg day 1, ad-libitum liquids, no other Na-raising therapies. Conventional hospitalization (CH):66/86, day hospital (DH):20/86. Glycemia-corrected SNa determined at baseline (B), 6, 24, 48 hours post-initial dose. When the 6-hour SNa ascent (SNaAsc) was ≥ 5 mmol/L, we administered 3 mcg DDAVPsc, with iv 5% dextrose (2 ml/kg/h 2 hours or 3 ml/kg/h 3 hours), when SNaAsc was 6 or > 6 mmol/L respectively. Patients received TV15 mg day 2, after register of 24-hour-SNaAsc, or 7.5 mg when the 6-hour SNaAsc ≥ 5. TV dose was doubled on day 3 if SNaAsc < 3. Overcorrection: > 10 mmol/L 24-hour-SNaAsc (> 8 with Osmotic-Demyelination-Syndrome risk), > 18 in 48 h (> 16 with risk). SIADH etiology: ectopic (24/86), pharmacological (16/86), idiopathic of the elderly (9/86), neurological (12/86), others (24/86). Na mmol/L, Osmolality (Osm) mOsm/kg. T-test, X^2, Spearman's Rho. Results in Mean (SD).
Results
53/86 (61.6%) female, age 72.15 (13.03). Nadir SNa:120.53 (6.27). Baseline: SNa:128.24 (4.14), Plasma Osm: 266.43 (9.16), Urine(U) Osm:450.1 (153.32), UNa:85.18 (44.28). In mg/dl: Uricemia: 3.07(1.43), creatinine 0.67 (0.23). Furst:0.92 (0.36). 6-hour: SNaAsc: 2.2 (2.84), 6-hour-UOsm:229.63 (162.9). SNaAsc ≥ 5 in 13/86, 7/20 at DH, 6/68 with CH. NaAsc was higher in patients with lower BSNa ($R = -0.292$, $P = 0.006$), lower uricemia ($R = -0.382$, $P = 0.005$), and DH ($p = 0.01$). Patients with SNaAsc ≥ 5 had higher BUOsm: 559.46 (188.95) vs. others: BUOsm:438.56 (136.94) ($P = 0.032$). 24-hour: SNaASC: 3.73 (3.06). Those with 6-hour SNaAsc ≥ 5: 24-hour SNaAsc: 3.69 (3.43), vs. others: 24-hour SNaASC: 3.74 (3.0) ($P = 0.96$). Maximum 24-hour SNaAsc: 10mmol/L (2/86). 48-hour: SNaAsc from B:6.2 (3.94). Maximum 48-hour SNaAsc:15 (1/86). 42/86 (48.8%) patients had 48-hour SNa ≥ 135. SNa changes at 6.24 and 48 hours were all significant ($P < 0.001$). Two patients referred intense thirst.
Conclusions
With our tolvaptan protocol, there was not a single case of overcorrection. Tolvaptan is safe and effective in the treatment of SIADH patients with mild/moderate hyponatremia. Fluid intake at our Day Hospital must improve.

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EP755

Peripheral neuropathy and depressive symptoms in patients with diabetes.

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Objective
To examine the association between severity of diabetic peripheral neuropathy and depressive symptoms and investigated the potential mediators of this association.
Materials and methods
The Hospital Anxiety and Depression Scale (HADS) was used to assess depressive symptoms in 492 patients (mean age 62 years; 70% male; 72% type 2 diabetic) with diabetic neuropathy diagnosed by the Neuropathy Disability Score (NDS) and the Vibration Perception Threshold (VPT). Diabetic neuropathy symptoms, activities of daily living (ADLs), and social self-perception were measured by the neuropathy and foot ulcer-specific quality-of-life instrument, NeuroQoL; perceptions of diabetic neuropathy symptom unpredictability and the lack of effective treatment were assessed by the revised Illness Perception Questionnaire.
Results
Both the NDS and VPT were significantly associated with the HADS after controlling for demographic and disease variables. Although diabetic neuropathy symptoms mediated this association, with unsteadiness being most strongly associated with HADS, the relationship between foot ulceration and depression was non-significant. The association between diabetic neuropathy symptoms and HADS was partially mediated by two sets of psychosocial variables: 1) perceptions of diabetic neuropathy symptom unpredictability and the lack of treatment control and 2) restrictions in ADLs and changes in social self-perception.
Conclusions
These findings establish the association between diabetic neuropathy and depressive symptoms and identify potential targets for interventions to alleviate depressive symptoms in persons affected by diabetic peripheral neuropathy.

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EP756

Pharmacological effects of urocortin (Ucn) on nicotine-induced oxidative stress to cardiomyocytes

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Based on the known oxidative stress of nicotine, we examined the effects of Ucn I on nicotine-induced oxidative stress in HL-1 cardiomyocytes. HL-1 cardiomyocytes is plated on 96-well plate at a density of 2.0×10^4 cells/well with Claycomb medium containing 10% fetal bovine serum (FBS) and 0.1 mmol/L epinephrine. After starvation of FBS and epinephrine with Claycomb medium, cells were stimulated with or without (+/−)-nicotine, Ucn I and Ucn II. Cells were also stimulated with (+/−)-nicotine after knocking down of Ucn I mRNA. Oxidative stress is evaluated by conversion of 2′, 7′-dichlorodihydrofluorescin diacetate to 2′, 7′-dichlorodihydrofluorescein. (+/−)-nicotine exereted significant oxidative stress on HL-1 cardiomyocytes, while (−)-nicotine, a cis-trans isomer of (+/−)-nicotine, did not exert significant oxidative actions on HL-1 cardiomyocytes. Ucn I suppressed not only (+/−)-nicotine-induced oxidative stress, but also oxidative stress in standard culture condition in HL-1ardiomyocytes. In addition, knockdown of Ucn I by siRNA enhanced (+/−)-nicotine-induced oxidative stress. On the contrary, Ucn II alone, another agonist of corticotropin-releasing factor type 2 receptor, did not exert significant anti-oxidative stress action at the basal condition, but reduced (+/−)-nicotine-induced oxidative stress. The present results indicate that Ucn I may exert anti-oxidative actions on cardiomyocytes, of which mechanism of actions are still remained to be clarified.

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EP757

Persistence of obesity and overweight in patients with Cushing disease in remission

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Objective
Obesity and overweight persist in patients with Cushing's disease (CD) in remission, its persistence seems to be related to the duration of the disease. The aim of this study was to describe the persistence of overweight/obesity in patients with CD in remission and their relation to the duration of the disease.
Patients and methods
Descriptive study of patients with CD (1995-2015). Variables analyzed: age, sex, body mass index (BMI), time from diagnosis to remission, urinary-free cortisol (UFC), adrenocorticotropic hormone (ACTH), expression of proopiomelanocortin (POMC) in tumor. Statistical analysis: comparing mean with *t*-student, comparing proportions with McNemar and correlation study with Spearman's Rho.
Results
49 patients with CD. 44.43±15.29 years old. Women: 89.8%. Remission 63.6%, of this, the diagnosis: overweight 22.3% (16.7% grade I y 5.6% grade II) and obesity 50.1% (27.8% grade I, 11.1% grade II, 5.6% grade III y 5.7% grade IV). After remission: overweight 33.3% (19% grade I y 14.3% grade II; $P>0.05$) and obesity 38.1% (9.5% grade I, 23.8% grade II, 4.8% grade III; $P>0.05$). Patients with normal weight vs overweight/obesity in last revision: time from diagnosis of CD to remission 41.16±34.54 vs 30.71±31.99 months ($P=0.78$), UFC initial 509.86±700.44 vs 798.23±764.65 mcg/24h ($P=0.73$), ACTH initial 75.21±39.38 vs 91.68±65.47 pg/ml ($P=0.79$). BMI the diagnosis 30.26±7.70 Kg/m^2, after remission 29.60±6.39 Kg/m^2 ($P=0.38$). BMI has a strong positive correlation with POMC [$\rho=1$ ($P=0.01$)].
Conclusions
Overweight/obesity is not reduced significantly after remission of EC. In our series, the persistence of overweight/obesity is not associated with a longer duration of the disease before remisión or with initial levels UFG or ACTH, although a positive correlation between BMI and POMC expression in the tumor was observed.

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EP758

Treatment of mild-moderate hyponatraemic encephalopathy with intravenous bolus therapy of 3% hypertonic saline solution: a case series

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Introduction
Hyponatraemia is the most common electrolytic disorder in clinical practice. We designed a protocol, based on the latest consensus statements and adapted to our Hospital, for the use of 3% hypertonic saline solution (HSS) in patients with hyponatraemia.
Material and methods
Unicentric observational study of a case series. We collected data from 14 adult patients with severe hyponatraemia (serum sodium [SNa] <125 mmol/l) and mild-moderate hyponatraemic encephalopathy (no signs of brain herniation) treated with an intravenous bolus of 250 ml of HSS over 30 minutes and reevaluated 6 hours later. Our goal was to raise 4–6 mmol/l as soon as possible, and 6-8 mmol/l in 24 hours with a limit of 12 mmol/l. The bolus was repeated if SNa raised <3 mmol/l.
Results
Median age (IQR) was 69.9 (64.5–78.1) years, and 62% were female. Baseline median SNa was 120 (114.3–122.8) mmol/l. Median SNa 6 hours after the bolus was 124.4 (120.7–128.3) mmol/l, a median raise of 5 (4.4–6.2) mmol/l ($P<0.001$). One patient required an additional bolus. Median SNa raise 24 hours after the bolus was 6 (3.9–8.2) mmol/l ($P<0.01$) in 9 patients; there was no significant change between 6 and 24 hours. Median rise per 100 ml of HSS was 2 (1.7–2.5) mmol/l after 6 hours and 2.4 (1.6–3.3) mmol/l after 24 hours. No patients required treatment for overcorrection nor had adverse outcomes. No significant changes were observed in serum potassium and creatinine.
Conclusions
Our data suggests that this protocol is safe and effective to reach the goals in the treatment of severe hyponatraemia with mild-moderate encephalopathy in the first 6 hours, without noticeable side effects or overcorrection. Patients at low risk of osmotic demyelination may receive another bolus to reach a higher SNa in 24 hours. Larger studies are required to confirm these results.

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EP759

Review of neonatal hypoglycaemia and adverse neurological outcomes

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Introduction
Neonatal hypoglycaemia (NH) is a well-recognized cause of adverse neurological outcomes. While hypoglycaemic brain injury is well reported in the literature there is limited data on the effect of neonatal hypoglycaemia solely with other risk factors for brain injury excluded. The aim of study was to evaluate the long-term outcome in patients with a history of symptomatic NH and no other risk factors of brain injury.
Methodology
This retrospective cohort study examined the outcome among children with history of symptomatic NH. The study looks at babies born from January 2008 and January 2014 admitted to the neonatal intensive care unit. A total 6411 new born infants were identified. 850/6411 were recorded as having NH on neonatal electronic database. 518/850 were excluded for a gestational age < 36 weeks. After further inclusive and exclusion criteria were applied to identify patients with solely NH as a risk factor for poor neurological outcome, 94/855 patients met study eligibility. Data for these patients was reviewed from variety sources including neonatal discharge summary, community assessments, ophthalmology, paediatric medical notes and laboratory results. 2/94 patients were found to have adverse neurological outcomes. These two cases are presented and analysed.
Results and conclusion
We identified 94 eligible children with neonatal hypoglycaemia and no other risk factors for brain injury. 2/94 (2.1%) patients had NH related brain injury and adverse neurological outcome- both children had history of neonatal seizures. The remaining 92/92 (97.8%) had favourable neurological outcome and no neonatal seizures.
Our study concludes that neonatal hypoglycaemia causes global brain injury and second, neonatal seizure is a significant predictor of the potential long-term poor outcomes of isolated NH. Education of the parents/carers and health professional remains an important strategy. Further research on the effect of NH and NH related seizure on long-term neurological outcomes in needed.

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EP760

Morbimortality of hospitalized patients receiving parenteral nutrition and presenting hyponatremia

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Introduction
Hyponatremia is the most frequent electrolyte disorder found in clinical practice, and has been associated with increased morbimortalty. Hyponatremia is even more common among patients receiving parenteral nutricion(PN), a therapy increasingly in use. However, the morbimortality of hyponatremic patients on PN is unknown.
Methods
Retrospective study, selecting all patients receiving PN in a teaching hospital from 01/11/11 to 01/06/12. We evaluated hospital length-of-stay (LOS), in-hospital mortality, serum Sodium (SNa) at admittance, at start and end of PN, and at discharge. Hyponatremia defined as glycemia- corrected SNa $<$ 135 mmol/L, triglycerides $<$ 400 mg/dl. X^2, T-test, Mann.whitney U, Logistic regression. SPSS 15.
Results
Two hundred and twenty-two patients received PN (57.2% males). Median age 75[61–82]. 14.5% presented malnutrition (by BMI). Charlson index 3.3 (SD2.4). LOS: 30[20-40] days. Mortality: 17.7%. 50.4% (112/222) presented hyponatremia in at least one SNa determination, 27% in at least 25% of SNas, 15.7% in at least 50% of SNas, and 3% in at least 75% of SNas. 23.2% of hyponatremic NP patients died during hospitalization, as compared with 11.8% of normonatremics. However, only sustained hyponatremia (with 75% or more SNa determinations $<$135 mmol/L) was independently associated with increased mortality, following correction for age, gender, Charlson index, and BMI (OR 7.38 [IC 95%: 1.07–50.8]; $P=0.042$). LOS $<$30 days were found in 42.8% of PN patients with hyponatremia versus 72.7% with normonatremia. ($P=0.001$).Logistic regression analysis indicated that the absence of hyponatremia was associated with a shorter LOS ($<$ 30 days), even when adjusted for comorbilities (OR:3.89; CI: 95%: 2.11–7.18; $P=0.001$).
Conclusions
The presence of sustained hyponatremia is independently associated with increased mortality in patients receiving parenteral nutrition. The absence of hyponatremia is independently associated with a shorter hospital length-of-stay. Hyponatremia should not be overlooked in PN patients.

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EP761

The quality of life of patients with nonfunctional pituitary adenomas and growth hormone deficiency

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Aim
To assess the quality of life of patients with nonfunctional pituitary adenomas (NFPA) and growth hormone deficiency (GHD).
Materials and methods
Eighteen GHD patients with non-functional pituitary adenomas (NFPA), (12 F/6 M), aged 35.5$\pm$14.4 yr (mean$\pm$SD; range 23–58), body mass index (BMI) 28.6$\pm$0.6, with a history of adult-onset hypothalamic-pituitary disease, were recruited for the study. The examination included hormonal assessment (level of hormones, such as, prolactin, STH, LH, FSH, TTH, cortisol, T_3, T_4 and others), testing of GHD by insulin (ITT), perimetry, assessment of neurological status, clinical ultrasound of the thyroid and the genitals, investigation of psychological well-being and Quality of Life of adults with GHD (QoLAGHD). Complex roentgenologic examination of the sellar area by means of computer (CT) and magnetic resonance tomography (MRI) was performed in all patients.
Results
Using the ITT as our 'gold standard' with a GH response of 6.3 mU/L as our cut-off to define GHD. Endosellar macroadenomas up to 20 mm in diameter were found in 6 patients, 12 persons having large adenomas up to 40 mm in diameter with sellar growth.
Hormonal disorders in 16 persons (88.8%) with hypopituitarism being found in 14 (77.7%). General brain symptoms were present in 15 patients (83.3%). Hypopituitarism, that is, reduction in the levels of pituitary tropic hormones, such as, STH, LH and FSH was found in 77%, large pituitary tumors with supra-, para- and infrasellar growth being registered in the patients.
The investigation by questionnaire by QoLAGHD showed, that mean range data achieved 8.7$\pm$0.2.
Conclusions
parallel to decrease in other pituitary hormones STH level reduction is typical of patients with non-functional pituitary tumors; 2) patients with NFPA need in control of pituitary hormone levels, MRI/CT and evaluation of Quality of Life by investigation of psychological well-being.

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EP762

The histological structure of nonfunctional pituitary giant adenomas (NFPA)

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Aim of the research
To study the histological structure of nonfunctional pituitary giant adenomas (NFPA)
Materials and methods
We observed 11 patients with giant NFPA, among them 5 male and 6 female, mean age 37.8. All patients were undergone surgical treatment by transsphenoidal access in Center of Endocrinology of MoH RU in neurosurgery department during 2014–2015 year.
All patients were undergone the spectrum of analyses, including endocrine status assessment, clinical, biochemical, hormonal (GH, LH, FSH, prolactin, TSH, testosterone and others), radiological (CT/MRI of Turkish saddle), and histological study. All patients have pituitary adenoma more than 5 cm.
Depending on the type of cells found on the histological study, patients with NFPA (chromophobic adenomas) were divided into 3 groups: 1st group – small cell (undifferentiated) chromophobic adenoma – 5 patients, 2nd group – large cell chromophobic adenoma – 6 patients, and 3rd group – oncocytoma (none).
Results
Preliminary analysis of the research showed that among the observed patients the most disposed to invasive total growth had patients of the 1st group with small cell histological structure of NFPA. Besides, this patients had more frequent tumor relapse in post-operative period – 3 patients (27.3%), had acute manifestation of the disease with general cerebral symptoms and neuroendocrine disturbances (secondary amenorrhea in female, potency and libido decrease in male, metabolic syndrome, visual disturbances and others). Two female patients aged 27.5 from the 1st group were undergone repeated selective pituitary adenomaectomy 3 times.
Conclusions
1. Small cell NFPA have the most aggressive growth and tumor relapse. 2. Following research is necessary to study the markers of aggressiveness in all 3 groups.

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EP763

The comparison between neurological symptoms and histological structure in chiasm and sellar region giant tumors

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Aim of the research
To study special features of pituitary adenoma (PA) clinical manifestation depending on hormonal characteristic and histological structure, and reveal correlation between clinical manifestation and tumor pathology.
Materials and methods
Outcomes of surgery in 66 patients with PA were analyzed. Age of patients at surgery was from 18 to 71 years. Mean age of patients – 44 years.
According to K. Thapar classification (1977), 4 patients (6%) had a corticotropinoma, 11 patients (17%) had somatotropinoma, 11 patients (17%) had prolactinoma and remaining 40 patients (60%) had non-functioning pituitary adenomas (NFPA). PA was diagnosed in according with clinical signs, hormonal tests, neuroendocrine status and histological analysis. All patients were undergone surgical treatment by transsphenoidal access Center of Endocrinology of MoH RU in neurosurgery department during 2014–2015 years.

Results
According to histology, 47 adenomas (71%) were chromophobe, 15 adenomas (23%) were acidophilic and 2 adenomas (3%) were basophilic, and 2 adenomas (3%) were defined as compound.
Comparison between histological structure and clinical manifestation revealed that chromophobe prolactinomas showed progressive course, big size of the tumor with the tendency to extrasellar growth and barely respond to conservative treatment. Acidophilic prolactinomas performed gradual onset with the endocrine dysfunction, body mass changes, dysmenorrhea, galactorrhea, intracranial hypertension and erectile dysfunction in men.
Histology in 4 patients revealed basophilic structure of PA and clinical manifestation have seen in short period.
Clinical manifestation of NFPA presented in all patients with the focal symptoms, including dislocation and hypertension syndromes, visual and oculomotor disturbances. Besides, there apoplexy symptoms have seen which degree depended on the course of disorder.
Conclusions
In according with literature reviews and own study results early clinical symptoms of PA should be evaluated opportunely and indications for surgery should be defined taking into account clinical forms which decreases the complications development risk.

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EP764

Presence of adrenal lesions at diagnosis of cushing's disease

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Objective
Patients with Cushing's disease (CD) may have adrenal nodules or hyperplasia related chronic hyperstimulation by adrenocorticotropic hormone (ACTH). The aim of this study was **to describe** the prevalence of adrenal nodules or hyperplasia in patients with CD and their relation with ACTH levels at diagnosis.
Patients and methods
Descriptive study of patients with CD (1995–2015). Variables analyzed: age, sex, body mass index (BMI), ACTH, urinary-free cortisol (UFC), abdominal magnetic resonance (MRI) or computed tomography (CT). Statistical analysis: comparing proportions with the chi-squared and comparing means with Student's test.
Results
Forty-nine patients with CD. 44.43 ± 15.29 years old. Women: 89.8%. 33 patients with abdominal MRI or CT: 30.30% adrenal nodules and 18.18% bilateral adrenal hyperplasia. Patients with adrenal lesions vs no adrenal lesions: age 44.56 ± 10.43 vs 43.81 ± 18.9 years old ($P = 0.84$), ACTH 80.42 ± 60.80 vs 76.61 ± 60.32 pg/ml ($P = 0.87$), UFC 636.89 ± 675.26 vs 768.64 ± 786.56 mcg/24h ($P = 0.61$), IMC 31.90 ± 10.24 vs 33.22 ± 7.19 kg/m^2 ($P = 0.66$), woman 81.3 vs 93.8% ($P = 0.94$), remission of CD 66.7 vs 85.7% ($P = 0.94$).
Conclusions
Adrenal lesions are detected in half of the patients with CD which is performed abdominal MRI or TC, adrenal nodules are more frequent. The presence of adrenal lesions is not related with ACTH levels at diagnosis, neither with UFC, BMI, age, sex or remission of CD.

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EP765

History before diagnosis in childhood craniopharyngioma: associations with initial presentation and long-term prognosis

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Objective
Childhood craniopharyngiomas (CP) are often diagnosed after long duration of history (DOH). Tumor size, hypothalamic involvement (HI), and obesity are associated with reduced overall survival (OS) and functional capacity (FC). The effect of DOH and specific symptoms in history on presentation at initial diagnosis and long-term prognosis are unknown.
Design
Retrospective analysis of patients' records and prospective longitudinal follow-up.
Methods
Histories of 411 CP patients recruited in HIT Endo, KRANIOPHARYNGEOM 2000 were retrospectively evaluated for DOH, symptoms and characteristics. The effect of specific manifestations and DOH on clinical presentation and tumor characteristics at time of initial CP diagnosis and long-term outcome were analyzed. Main outcome measures were 10-yr OS and progression-free survival (PFS), FC, and body mass index (BMI) during longitudinal follow-up.
Results
Median DOH was 6 mo (range: 0.1–108 mo) and correlated with age at diagnosis. Tumor size, HI, degree of resection, and BMI at diagnosis were not related to DOH. In multivariate analysis adjusted for age at diagnosis, only hydrocephalus was found to have a relevant influence on DOH. Visual and neurological deficits were associated with larger initial tumor size and impaired 10-yr OS. Weight gain and growth failure were observed with longest DOH. PFS and FC were not related to any specific symptom. Endocrine deficits at diagnosis were associated with long DOH.
Conclusions
CP is frequently diagnosed after long DOH, especially in older children. However, DOH was not associated with tumor size, HI, survival or FC. Visual and neurological deficits necessitate rapid diagnostic work-up.

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EP766

Hydrocephalus and hypothalamic involvement in pediatric patients with craniopharyngioma or cysts of Rathke's pouch: impact on long-term prognosis

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Objective
Pediatric patients with sellar masses such as craniopharyngioma (CP) or cyst of Rathke's pouch (CRP) frequently suffer disease- and treatment-related sequelae. We analyzed the impact and prognostic relevance of initial hydrocephalus (HY) and hypothalamic involvement (HI) on long-term survival and functional capacity (FC) in children with CP or CRP.
Subjects and methods
Using retrospective analysis of patient records, presence of initial HY or HI was assessed in 177 pediatric patients (163 CP, 14 CRP). Twenty-year overall survival (OS) and progression-free survival (PFS), functional capacity, and body mass index (BMI) were analyzed with regard to initial HY, degree of resection, or HI.
Results
One hundred and five patients (103/163 CP, 2/14 CRP) presented with initial HY and 96 presented with HI. HY at diagnosis was associated ($P = 0.000$) with papilledema, neurological deficits, and higher BMI at diagnosis and during follow-up. OS, PFS, and FC were not affected by HY at initial diagnosis. HI at diagnosis (96/177) had major negative impact on long-term prognosis. Sellar masses with HI were associated with lower OS (0.84 ± 0.04; $P = 0.021$), lower FC ($P = 0.003$), and higher BMI at diagnosis and last follow-up ($P = 0.000$) when compared with sellar masses without HI (OS: 0.94 ± 0.05). PFS was not affected by HI or degree of resection.
Conclusions
Initial HY has no impact on outcome in patients with sellar masses. OS and FC are impaired in survivors presenting with initial HI. PFS is not affected by HY, HI, or degree of resection. Accordingly, gross-total resection is not recommended in sellar masses with initial HI to prevent further hypothalamic damage.

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EP767

Emotional behavior is modulated by liragutide in an age and gender manner in rats from food restriction mothers

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Food restriction (FR) of mothers during the perinatal period, can lead to disorders in emotional behaviors at offspring. GLP-1 may play a role in the regulation of anxiety-like behavior in rodents. The aim of this study was to asses if Liraglutide (a GLP-1 receptor agonist; LIR) given to pregnant rats may prevent the deleterious effects of FR in the anxiety-like behavior in pups at 21 days and two months of age males.
Twenty-five pregnant Sprague-Dawley rats were included. Food restriction (50%) respect to controls started at day 12 (D12) of pregnancy and CT group remain undisturbed. Rats were treated with liraglutide (100 μg/Kg/12h; 50FR/LIRA, CT/LIRA) or vehicle (50FR/VEH, CT/VEH) from gestational day 14 to 21. During lactation the FR was 30%. Anxiety-like behaviors were assessed using the open field test in pups at day 21 and two months of age. Animal performance was recorded in video for posterior analysis.
At D21, there were no differences in the time spent in 10, 20 or 30 cm or in the border between 50FR vs. control, either males or females. However, liraglutide significantly reduced the time spent in 10 cm and in the border, and increased the time in 20 or 30 cm just in 50FR males but not in females. Liraglutide increases 15.66 times the % of time spent at center of open field in 50FR males compared to CT/VEH, 26.6 times compared to CT/LIRA and 11.75 times respect to 50FR/LIRA females. However, at two months of age, no effect of liraglutide in the time spent in the center of 50FR males was observed.
In conclusion besides FR did not induce behavioral alterations at 21 days or two months of age, liraglutide reduced the % of time in the center only in 50FR male pups, indicating an age-dependent effect of liraglutide under non-stressed conditions.

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EP768

Characteristics and management of hospitalized patients with hyponatremia in an endocrinology department

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Hyponatremia is the electrolyte disorder most commonly encountered in hospitalized patients. The prevalence and characteristics of patients admitted with hyponatremia are analyzed in this study.
Description of methods/design: cross sectional study is carried out at the University General Hospital of Valencia, comprising a population of 350,000. 681 of the 30676 patients admitted during the period from January 2014 to December 2015 had hyponatremia included as a diagnosis at the discharge report. 72 patients admitted in Endocrinology due to hyponatremia are analyzed. We analyzed patient characteristics, mean length of stay, treatment used, serum sodium at admission and discharge, urine and plasma osmolality, urinary sodium and potassium, TSH and cortisol levels, as well as mortality and the presenter prior to hyponatremia.
Results
Diagnosis of hyponatremia in the discharge report appeared in 2.5%. Of these, 9.6% were admitted in Endocrinology because hyponatremia was the main diagnosis. Of the 72 patients there were 57 women, with a mean age of 77.8 ± 13.61 years. Mean length of stay was 5.7 ± 3.5 days and the months of May and June the highest incidence. The most common causes were diuretics (38%), SIADH (24%) and multifactorial etiology (23%). Sodium income was 119 ± 6 mEq/l and at discharge was 132 ± 3 mEq/l. 31% of patients had low sodium serum levels before admission. Mortality was 2.8%.
Conclusion
Among admissions by hyponatremia, most are women over 75 years and the diuretics were the main etiology. The previous high prevalence of hyponatremia in these patients suggests that a careful management and monitoring of them might prevent subsequent admissions for this cause.

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EP769

Factors influencing health-related quality of life in chronic endocrine diseases: results from a focus group discussion (qualitative research)

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Introduction
Improvement of health related quality of life (QoL) is one of the main goals defined by the WHO and besides reduction of mortality and morbidity an important objective for health outcomes. In chronic endocrine diseases, QoL often remains impaired despite cure or remission of the disease. In quantitative analyses, factors such as age, gender, BMI and depression, are associated with reduced QoL. However, aspects of social interaction and more complex individual concepts are difficult to obtain from classical quantitative research.
Therefore we performed a qualitative social research analysis based on a focus group discussion according to a predefined protocol which had been reviewed by an endocrinologist, a sociologist and an epidemiologist.
The aim of this project was to identify possible modifiable factors influencing patients' QoL in order to provide preventative strategies for improving patient management and long-term health outcome.
Results
Patients with chronic endocrine diseases were invited through a local support group. Patients ($n = 18$) were divided into two groups, each chaired by two persons (one medical doctor and certified sociologist). Mean age of participating women ($n = 11$) was 52.7 years whereas mean age of men ($n = 7$) was 55 years. Results from the discussion are categorized according to a) areas of health-related quality of life that are influenced, b) how patients were able to modify them and c) which interventions were tested.

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EP770

Study protocol: 'Health outcomes in pituitary adenoma's: focus on hormone deficiencies'

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Background
Acromegaly is characterized by hormonal excess of GH and IGF-1, however many patients suffer from hypopituitarism as a result from either disease or treatment. Quality of Life (QoL) is known to be reduced both in acromegaly, with mixed results on the role of biochemical control herein, and hypopituitarism. Studies report the level of surgery-induced hypopituitarism after acromegaly at 12.79% (CI 9.88–16.00%). Treatment of acromegaly aimed at normalization of hormone levels may therefore result in hypopituitarism with concomitant reduced QoL. Particularly Growth Hormone Deficiency (GHD) has been reported to be a risk factor for reduced QoL.
Aim
The primary aim is investigate whether correction of GHD, results in improvement of clinical outcomes. Second, we aim to investigate whether correction of corticotroph deficiency, thyroid deficiency, prolatin defiency as well as panhypopituitarism results in improvement of clinical outcomes, particularly when compared to correction of GHD. Third, we intend to investigate whether hormone deficiencies following other pituitary diseases such as Cushing's disease, prolactinoma and Non-Functioning Pituitary Adenoma (NFPA) have a similar effect on QoL when compared to acromegaly.
Outcomes
A composite score from the KIMS study group applying waist circumference, total cholesterol and disease specific QoL has been used to evaluate the clinical response to GH suppletion. We further augment this score to investigate the clinical response after other deficiencies, as well as evaluating the response after adequate suppletion. Individual QoL scores (both generic and disease-specific) and psychopathology scores (depressive symptoms and anxiety) will be used as secondary outcomes.

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Nuclear receptors and Signal transduction

EP771

The thyroid hormone antagonizes STAT3-dependent transcription in hepatocarcinoma cells

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The known functions of the thyroid hormones in the liver have expanded from their well-known roles in regulating metabolism to also participate in liver regeneration, senescence and hepatocarcinogenesis. The transcription factors STAT3 and NF-κB play a key role in liver homeostasis, in the response to infection and inflammation and in hepatocarcinoma development. Interleukin 6 (IL-6) and Tumour Necrosis α (TNFα) are the best-known cytokines responsible for hepatic stimulation of these signalling pathways. We have analysed the effect of thyroid hormones in the response of hepatocarcinoma cells to these factors. We found that triiodothyronine (T3) suppresses IL-6 signalling in cultured Hep3B cells, inhibiting the activation of the main cytokine downstream targets: STAT3 and ERK. In contrast, no inhibitory effects of T3 in the NF-κB response to TNFα were observed. In agreement with these results, T3 strongly antagonized IL-6 stimulated activity of a reporter plasmid bearing STAT-binding elements, while the hormone did not reduce activation by TNFα of a reporter plasmid containing NF-κB binding sites. Transcript levels of the IL-6 receptor or Gp130, essential for IL-6 signal transduction were not altered by T3, but the hormone significantly reduced stimulation by IL-6 of STAT target genes encoding acute-phase proteins, which are key components of the hepatic response to the cytokine. In chromatin immunoprecipitation assays, T3 significantly reduced STAT3 recruitment to its target promoters in response to IL-6. Moreover, IL-6 dependent increase of acetylated histone H4, a marker of transcriptional activation, was also suppressed by T3. Our results show that the thyroid hormones can counteract the cellular responses to IL-6 reducing its transcriptional actions. Through this mechanism, the thyroid hormones may modulate immune homeostasis and carcinogenesis in the liver, suggesting that they could be important targets for developing new therapeutic strategies for the treatment of liver diseases.

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EP772

Effects of vitamin D on endothelial-derived factors implicated in the atheromatic plaque vulnerability

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Introduction
Although the protective effects of $1,25(OH)_2D_3$ on the early stages of atheromatosis process have been investigated, data on its influence on factors implicated in plaque vulnerability are limited. During these stages metalloproteinases MMP-2, MMP-9, their inhibitors TIMP-1,TIMP-2, the RANKL-RANK-OPG system and MCP-1 play a critical role. We aimed to investigate the effect of vitamin D on the expression of the above factors on endothelial cells. **Methods**: Human aortic endothelial cells (HAECs) were incubated with VitD for 24, 48,72 hours at a concentration range 10^{-8} – 10^{-11} in the absence of TNF-α or with VitD for 24 hours in the presence of TNF-α at concentration 10ng/ml for the last 6 hours. The mRNA expression of the aforementioned genes was assessed by real time-PCR. Zymography for MMP-2 and MMP-9 activity was also performed. OPG protein levels were also evaluated by western blot.
Results
VitD did not significantly change the expression of MMP-9, MMP-2, TIMP-1 and TIMP-2 at mRNA level at various incubation times and concentrations. The expression of OPG at mRNA was significantly increased in the presence of TNF-a and this effect became more pronounced when cells were preincubated with Vit D at concentration 10^{-9} M. Preincubation with p38 MAP kinase inhibitor totally abolished this result.
When cells activated with TNF-a, preincubation with Vit D resulted in a significant decrease in *MMP-9* expression at 10^{-10} and 10^{-11}M and increase in *TIMP-2* expression while it didn't affect the expression of *MMP-2* and *TIMP-1*. Gelatin zymography revealed that Vit D decrease the active MMP-2 dose-dependently.
Conclusions
Vit D at physiologically achievable concentrations reduces the expression of *MMP-9* and induces the expression of *TIMP-2* at mRNA level implying a possible protective role in the later stages of atheromatosis, such as plaque vulnerability. Further studies are needed to elucidate the underlying mechanisms.

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EP773

One third of obese children are diagnosed with neurodevelopmental disorders

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Background
Child obesity has become a global health problem. The younger treatment starts the better outcome, but few treatment modalities are efficient. Whether obese children have an increased risk of neurodevelopmental disorders with worse treatment outcome is not studied. Objectives: To investigate the prevalence of ADHD, autism spectrum disorder (ASD) and other neurodevelopmental disorders in obese children. As a second objective gender differences were evaluated.
Methods
Seventy-six children (37 girls; 39 boys) were recruited at referral to a university outpatient clinic. The parents were interviewed regarding the child's psychiatric morbidity using The development and well-being assessment, and completed parental questionnaires such as The Autism Spectrum Screening Questionnaire/ ASQ14 and the Five to fifteen parent questionnaire all of these evaluating ADHD, ASD and other neurodevelopmental disorders. The parents were screened for adult ADHD using the Adult ADHD Self-Report Scale. Anthropometric and metabolic data was collected at the first visit and after one year of conventional life-style treatment.
Results
Twelve percent 1% and 18% of the children were diagnosed with ASD and ADHD respectively. Thirty percent of the children had at least one neurodevelopmental disorder and 20% had a parent who screened positive for adult ADHD. There was statistically significant more obese males with neurodevelopmental disorders ($P<0.05$). In the total group, mean (SD) body mass index (BMI) was 3.4 (0.6), insulin 31 (18.5) and age 12.4 (3.0), with a range of 2–6 kg/m^2, 6–110 and 5.1–16.5 years, respectively. There was no statistical difference in mean BMI, insulin, age and other metabolic variables between those obese children with neurodevelopmental disorders and without. No difference was found in treatment outcome after one year between those with neurodevelopmental disorders and without (delta BMI SDS 0.06 (0.36) versus 0.13 (0.33), P=ns). Conclusion: Neurodevelopmental disorders are over-represented in clinical populations of obese children, especially in males. Although we did not find any significant worse BMI outcome in those with neurodevelopmental disorders, it should be taken into account that many parents share their children's symptoms, when designing educational materials for parents.

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EP774

Optical isomers of statins enantiospecifically activate pregnane X receptor PXR and induce CYP2A6, CYP2B6 and CYP3A4 in human hepatocytes

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Statins are drugs used for the treatment of hypercholesterolemia. Statins have two chiral centers in their molecules, thus they form four enantiomers (3R5R-, 3R5S-, 3S5R- and 3S5S-). Regarding the most frequently prescribed statins, following enantiopure formulations are used in the clinics: 3R5R-atorvastatin, 3R5S-rosuvastatin and 3R5S-fluvastatin. Individual enantiomers of one drug can

qualitatively and quantitatively differ in their biological activities. In some cases, only one enantiomer is responsible for the therapeutic effect, while the opposite one may be inactive or can cause undesired or even toxic effects. Therefore, it is of value to study *in vitro* effects of individual enantiomers.
We investigated enantiospecific interactions of four enantiopure forms of atorvastin, rosuvastatin and fluvastatin with main transcriptional regulators of drug-metabolizing enzymes - aryl hydrocarbon receptor (AhR), glucocorticoid receptor (GR) and pregnane X receptor (PXR). Agonist and antagonist activities of tested compounds towards AhR, PXR and GR were determined using human reporter cell lines. Moreover, we have measured expression of drug-metabolizing enzymes CYPs on mRNA and protein level in primary human hepatocytes.
Basal and ligand-inducible transcriptional activity of PXR was dose-dependently influenced by all tested statins, and the potency and efficacy between individual optical isomers varied depending on statin and optical isomer. Statins did not influence the expression of CYP1A1/2 in human hepatocytes. All statins induced CYP2A6, CYP2B6 and CYP3A4, and the effects on CYP2C9 were rather modulatory. Overall, the potential for drug-drug interactions involving induction of P450s was higher for clinically used optical isomers of rosuvastatin, atorvastatin and fluvastatin, as compared to their respective enantiomers, which are not in therapeutic use.

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EP775

The impact of mycophenolate mofetil on androgen receptor activity in prostate cancer cells 22Rv1

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Mycophenolate mofetil (MYC) is widely used in transplant medicine as an immunosuppressant drug to prevent rejection in organ transplantation. In this work we investigated the effect of MYC on the activity of androgen receptor (AR) by employing gene reporter assay (GRA) and PCR in prostate cancer cell line 22Rv1.
Slight but significant activation of AR was observed for cells treated with MYC in stably transfected 22Rv1 cells (AIZ-AR). Moreover, significant stimulation of dihydrotestosterone (DHT)-inducible AR-dependent luciferase activity by MYC was observed. AR-target gene KLK3 (prostate specific antigen, PSA) mRNA was induced dose-dependently and consistently with GRA. DHT-inducible KLK3 mRNA was increased by MYC as well. Since we found that MYC induced the expression of KLK3 and activated AR, we investigated whether MYC affects the proliferation of prostatic cells. However, we observed opposite effect of MYC on proliferation. Only two lowest concentrations of MYC had positive effect on cell proliferation, but for 24h only, not for 48 hrs.
In conclusion, we found that MYC is an activator of AR and induced KLK3 mRNA in the prostate cancer cell line 22Rv1. However, we did not find correlation between AR activation by MYC and cell proliferation. In any case, herein we provide important findings which bring new information about mechanism of action of mycophenolate mofetil on AR.

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EP776

Effect of anthocyanidins on trascriptional activities of steroid and nuclear receptors

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Anthocyanidins are aglycons of anthocyanins, which are plant pigments responsible for floral and fruits color. Anthocyanidins possess beneficial pharmacological properties such as antioxidant, anti-inflammatory, anti-tumor and anti-diabetic. Anthocyanidins are contained in normal diet and might play role in food-drug interactions.
The aim of current study was to evaluate the effects of cyanidin, delphinidin, malvidin, pelargonidin and peonidin on the transcriptional activities of steroid and nuclear receptors.
The activities of glucocorticoid receptor (GR), androgen receptor (AR), estrogen receptor (ER), progesterone receptor (PR), thyroid receptor (TR), vitamin D receptor (VDR), pregnane X receptor (PXR), retinoic acid receptor (RAR) and retinoid X receptor (RXR) were assessed using either stably or transiently transfected luciferase gene reporter cell lines. The cytotoxicity assays and gene reporter assays were performed after the 24-h treatment of cells with increasing range of concentrations (10 nM – 50 μM) of tested anthocyanidins.
We found that some anthocyanidins in 50 μM concentration inhibited transcriptional activity of examined receptors. The inhibition down-to 49.4% for malvidin vs VDR, 49.3% for delphinidin vs RXR, 38.0% for malvidin vs RAR and 52.2% for pelargonidin vs PXR of maximal induction was observed.
Generally, certain tested anthocyanidins in the highest concentration inhibited transcriptional activity of studied receptors and none of the tested anthocyanidins in given concentration range caused significant induction of transcriptional activity of examined receptors.

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Obesity

EP777

A prostate cancer risk associated polymorphism regulates androgen mediated regulation of a novel long noncoding RNA, *IRX4lncRNA*

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Prostate cancer (PCa) is the second most common cause of cancer death in developed countries. Our *RNAseq* analysis identified a novel long non-coding RNA, *IRX4lncRNA* at chromosome 5p15. The expression of *IRX4lncRNA* was much higher in prostate tumor samples ($n=50$) compared to their matched controls. Moreover, knockdown of lncRNA reduced the cell proliferation of LNCaP cells and this lncRNA was down-regulated in the cells undergoing Epithelial to Mesenchymal Transition (EMT), which is a hallmark of PCa invasion.
Interestingly, differential regulation of *IRX4lncRNA* by androgens was observed in VCaP (up-regulated) and LNCaP (down-regulated) cells. *In-silico* analysis (Cistrome Finder Database) identified binding of two crucial transcription factors-AR and ERG, at this locus in VCaP cells and no AR binding in LNCaP cells (ERG negative). We also noted a correlation between *IRX4lncRNA* expression and ERG fusion in our RNA-sequencing data of a cohort of seven androgen-responsive patient-derived xenografts. Sequencing of this AR/ERG binding region identified a Multiple Nucleotide Length Polymorphism (MNLP, rs38668493) where a stretch of 47bp sequence is replaced by a novel 21bp sequence. VCaP cells have an intact AR/ERG binding site (47bp/47bp) whereas LNCaP cells have a disrupted AR/ERG binding site (21bp/21bp) which may explain the differential androgen responsiveness of *IRX4lncRNA*. This MNLP is in linkage disequlibrium (LD) with the previously identified PCa risk associated SNP, rs10866528, suggesting this MNLP may possibly be the functional genetic variant at this locus and guiding the AR/ERG binding to this locus and therefore, directing the androgen-mediated regulation of *IRX4lncRNA*. We are currently focusing on establishing the functional role of *this MNLP* in PCa.

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EP778

Is Pentraxin 3 a marker in pathogenesis of central obesity?

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Introduction
Pentraxin 3 (PTX3) is an acute-phase protein that shares structural homology with C-reactive protein (CRP). PTX3 is produced in macrophages, endothelial cells, and adipocytes in response to inflammatory stimuli, whereas hepatocytes are the main source of CRP. Because obesity and metabolic syndrome (MetS) are considered chronic inflammatory states, PTX3 might be involved in the pathogenesis of obesity and MetS as well as CRP. In this study, we aimed to investigate the relationships between PTX3, CRP, neutrophil-to-lymphocyte ratio (NLR) and BMI.
Methods
86 obese premenapousal women (aged 17–55 years) and 56 women with normal BMI took part in this study. Antropometric measurements including waist circumferences (WC) were done. Serum concentrations of plasma fasting glucose, insulin, Pentraxin 3, CRP, complete blood count were measured. NLR was calculated. HOMA-R is also calculated to determine insulin resistance.

	Obese	Control	P
PTX3 (Pentraxin 3) (pg/mL)	0.83	0.86	0.887
CRP (C-reaktive protein) (mg/dL)	0.68	0.38	**0.000**
Neutrophil (K/uL)	4.5	4.1	**0.039**
Lmphocyte (K/uL)	2.3	2	**0.001**
Neutrophil lymphocyte ratio	2	2.1	0.492

Results
PTX3 and NLR were similar in both groups. PTX3 and NLR were also similar in obese patients with or without insulin resistance. CRP is significantly higher in obese patients ($P < 0.01$). It was also significantly higher in insulin resistance obese patients ($P < 0.01$). There was'nt any correlation between BMI or any of the inflamatory markers. Multiple regression analysis showed that PTX3 is correlated with WC.
Conclusion
Although PTX3 levels were not determinative in obese patients and has no correlation with body fat, it may have a relation with central obesity. To clarify this further studies are needed.

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EP779

Skin autofluorescence is associated with the metabolic syndrome and its individual components

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Background
Skin autofluorescence (SAF) has been demonstrated to be associated with long-term cardiovascular complications in subjects with either diabetes or renal failure. Since the metabolic syndrome (MetS) is a risk factor for cardiovascular disease, the aim of the study was to assess the association between SAF and MetS as well as its individuals components.
Materials and methods
For this cross-sectional analysis, we included subjects 18–80 years of age who participated in the LifeLines Cohort Study. We excluded 2411 subjects who were known to have either type 1 or type 2 diabetes and/or had a serum creatinine >140 μmol/l, and included subjects who had SAF measurements available, leaving 78.799 individuals for analyses. Skin autofluorescence (SAF) was measured non-invasively with the AGE Reader in all participants (Diagnoptics BV, Groningen, The Netherlands). MetS was defined according to the revised NCEP ATP III criteria.
Results
From the total population, 11.619 (15%) subjects were diagnosed with MetS. Subjects with MetS were significantly older but had a higher creatinine clearance (both $P<0.001$) compared to individuals without MetS. Subjects with MetS (2.01 ± 0.24) had a higher SAF than those without MetS (1.90 ± 0.25) ($P<0.001$) even after adjusting for age. Furthermore, there was a gradual increase of SAF Z scores (adjusted for age) with increasing number of MetS components ($P<0.001$). Finally, the prevalence of particularly raised blood pressure and enlarged waist circumference increased with higher SAF.
Conclusion
We have demonstrated that higher SAF levels are strongly associated with an increased prevalence of MetS and its individuals components, in particular raised blood pressure and enlarged waist circumference. When taking these and previous observations on SAF with different clinically relevant phenotypes into account, the AGE Reader could be potentially used as an (additional) screening tool to identify individuals at high risk for developing metabolic and cardiovascular complications.

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EP780

Glucose and insulin up-regulate the cardiovascular biomarker GDF15 *in vivo* and *in vitro*: effect of meal content and obesity

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Introduction
Growth differentiation factor 15 (GDF15) has recently been characterized as a cardiovascular risk factor. GDF15 correlates with insulin resistance and obesity in cross-sectional studies and exerts anorexigenic effects in interventional rodent studies. GDF15 has been proposed as a possible therapeutic target in the treatment of obesity, however its meal- and nutrient-dependent regulation in humans has not been investigated previously.
Methods
Profiles of GDF15 plasma concentrations were studied in lean and obese individuals in response to carbohydrate-rich and fat-rich meals, a 75 g oral glucose load (OGTT) or fasting. Human hepatic HepG2 cells were stimulated with glucose- and insulin, and the effects on GDF15 mRNA levels and protein release in the supernatant were evaluated.
Results
In lean and obese individuals, fasting was associated with a steady decrease in plasma GDF15 concentrations. OGTT inhibited this decrease with GDF15 rising back to baseline levels 2–3 hours after glucose ingestion, while carbohydrate- and fat-rich meals did not have a significant effect. In HepG2 cells, glucose and insulin independently stimulate GDF15 transcription as well as secretion.
Conclusion
GDF-15 decreases during fasting and increases in response to high peaks in glucose and insulin concentrations following oral glucose ingestion in men. These changes are, at least in part, mediated via direct effects of glucose and insulin on GDF15 transcription and release. These data provide the first evidence on nutrient-related changes in GDF-15 concentrations in humans.

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EP781

Bariatric surgery: a health economic perspective of the prescription costs

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Introduction
The economic burden of obesity on healthcare systems is increasing. Bariatric surgery leads to considerable weight loss and health improvement. However, this surgery is costly and doubts about its affordability have been raised. Few studies have assessed outcomes such as drug use and costs after bariatric surgery. The aim of this study was to evaluate drug consumption and costs before and after bariatric surgery.
Methods
Retrospectively, databases of 72 patients who underwent bariatric surgery in 2014 were analyzed. Therapies and comorbidities related to obesity were reviewed preoperatively and at 6 months postoperatively. Drug prices were calculated accordingly to table prices of the National Health Service.

Results
Pre and postoperatively prevalence of comorbidities related to obesity were respectively: hypertension 38.9% vs 20.8% ($P<0.001$ McNemar test); type 2 diabetes 19.4% vs 9.7% ($P=0.016$ McNemar test); dyslipidemia 58.3% vs 33.3% ($P=0.001$ McNemar test); and sleep apnea 11.1% vs 4.17% ($P=0,125$ McNemar test). A sub-analysis of patients treated for these comorbidities ($n=33$) has shown that, preoperatively, costs related to drug and continuous positive airway pressure (CPAP) use were on average 1.26€/patient/day, whereas postoperatively these costs were on average 0.53€/patient/day ($P=0.015$ Paired sample t-test). Preoperatively, the median number of pills and insulin dose per patient per day was 2 and 60, while postoperatively these numbers decreased to 1 and 43, respectively ($P=0.002$; $P=0.043$ Wilcoxon test). These patients exhibited an improvement in their comorbidities which, remaining stable, could reimburse the costs of the bariatric surgery in 23 years.
Conclusion
Bariatric surgery can decrease medication requirements, resulting in significant cost savings to the National Health Service. This surgery is pricey, but the decrease of expenditures in prescription costs may allow a reimbursement of the investment, and this is more evident in patients with more associated comorbidities.

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EP782

Dietary and social factors associated to obesity among greek adolescent girls

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Objectives
To estimate the body mass index (BMI) distribution among Greek female adolescents in 2012 and to compare it with data from 2000, to find associations of obesity with dietary and social factors, as well as to determine the prevalence of acne, hirsutism and menstrual irregularities in the same population.
Methods
All female students ($n=380$) aged 12–18 years of two randomly selected high schools, after obtaining a written consent from their parents, underwent clinical evaluation and completed a questionnaire on their dietary habits, medical history and the educational and occupational level of their parents. Data collected in 2000 from a group of 2300 Greek female adolescents was used for comparison. Statistical analysis of the sample characteristics was performed.
Results
The percentages of normal, overweight and obese adolescent girls were 73.7%, 22.1%, and 4.2% respectively. The corresponding results in the control group of adolescent girls in 2000 were 81.87%, 14.48% and 3.65% respectively. Overall, differences in the BMI distribution were not statistically significant between 2000 and 2012 ($P=0.4341$). There was no difference in specific meal consumption among BMI categories. Higher BMI was associated with a mother of a lower social status (58.3% vs 41.6%, $P=0.037$). The prevalence of hirsutism and acne in the studied population was 11.6% and 36.3% respectively. Eighty three of the 349 girls who had attained menarche (24%) were experiencing menstrual irregularities. No relationship was found between BMI and the prevalence of acne, hirsutism, menstrual disturbances and polycystic ovary syndrome diagnosis.
Conclusions
Despite a slight increase, during the last decade, in the percentage of overweight and obese Greek adolescent girls, this trend was not statistically significant. Among the parameters studied, the only predictor of adolescent obesity was found to be the educational and occupational level of the mother.

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EP783

Relationship between lipopolysaccharide levels and the gene expression profile in adipose tissue from morbidly obese patients

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Introduction
Obesity is characterized by a low-grade inflammatory state which has been directly related to the development of insulin resistance and diabetes. Circulating lipopolysaccharides (LPS) have been proposed as a triggering factor for this inflammation. Likewise, adipose tissue (AT) capacity for lipid handling and storage is also a key factor for the development of obesity-related metabolic disorders. Animal studies have shown that LPS are able to modify the expression of key factors for AT function. Thus, the aim of this study was to analyze the gene expression of key factors for AT function and inflammation in AT from morbidly obese (MO) patients according to their LPS levels.
Methods
Visceral and subcutaneous AT (VAT and SAT) samples were obtained during bariatric surgery from 70 MO patients to measure mRNA levels. Plasma LPS levels as well as biochemical and anthropometric variables were measured. Patients were classified according to their LPS levels (high LPS levels, H-LPS group and low-LPS levels, L-LPS group). Gene expression was also analyzed after *in vitro* stimulation with LPS of AT explants from MO patients.
Results
H-LPS group showed higher mRNA levels of inflammatory genes (TLR2, CSF3 and IL6 in VAT; TLR2, MCP1, CSF3 and CD14 in SAT) than L-LPS group. By contrast, H-LPS group had lower mRNA levels of factors related to AT function (FABP4, SREBP1, FASN and Leptin in VAT and FABP4 in SAT). *In vitro* stimulation with LPS led to an increase in gene expression of inflammatory markers (TLR2, IL6, CSF3 and MCP1) and a decrease in the gene expression of factors related to AT function (PPARγ, SREBP1, FASN, FABP4, SCD and leptin) in VAT.
Conclusions
Circulating LPS can influence AT physiology in morbidly obese patients by decreasing the gene expression of key factors for AT function and by increasing the gene expression of inflammatory markers.

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EP784

The circulating fingerprint revealed by targeted metabolomic as biomarker of metabolic impairment in female overweight/obesity

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The comprehension of the network of metabolic processes may help the understanding of the molecular pathways driving obesity and related complications. However this is a hard task due to the large number of actors and their complex interplay. We aimed at exploring by targeted metabolomic the circulating metabolite profile in lean (NW, $n=42$; BMI: 18.5–24.9 kg/m^2) and age-matched overweight/obese (OB, $n=37$, BMI$\geq$25.0 kg/m^2), drug-free adult overnight-fasted women. Anthropometric, biochemical and hormonal data were collected. One-hundred-eighty molecules among aminoacids, biogenic amines, acylcarnitines, phosphatidyl-choline (PC), lysoposphatidyl-choline (LysoPC) and sphingomyeline (SM) were quantified by the Absolute p180 LC-MS/MS Kit (Biocrates Life Science AG). BMI effect on metabolite profile was investigated by the orthogonal partial least squares-discriminant analysis (OPLS-DA), resulting in the selection of 39 metabolites driving the NW vs OB separation ($R^2X=0.485$, $R^2Y=0.638$, $Q^2Y=0.505$, CV-ANOVA $P<0.001$). Then, the association between the metabolite model and the individual parameters of metabolic impairment was investigated. The BMI-adjusted stepwise multiple regression analysis revealed the following independent associations: waist circumference was positively associated to Glu ($P=0.040$) and Val ($P<0.001$) and negatively to PCaa-C42:2 and LysoPC-C18:2 ($P<0.001$). Glycaemia

positively correlated with Ala ($P=0.025$) and SM-C18:0 ($P=0.008$), and negatively with PCae-C34:3 ($P=0.004$). Insulin positively correlated with Val ($P=0.002$) and negatively with PCae-C34:2 ($P=0.001$). HOMA-index was positively associated to Tyr ($P<0.001$) and negatively to PCae-C34:2 ($P=0.001$). Triglycerides showed a positive correlation with PCaa-C24:0 ($P=0.036$) and PCaa-C38:3 ($P<0.001$) and negative correlation with PCae-C32:1 ($P=0.007$) and PCae-C36:3 ($P=0.012$). HDL were positively associated to PCae-C34:3 ($P<0.001$) and LysoPC-C20:4 ($P=0.038$) and negatively associated to Val ($P<0.001$). Finally, total cholesterol positively correlated with SM-C18:0 ($P=0.008$), SM(OH)-C22:1 ($P=0.024$) and PCaaC38:3 ($P<0.001$) and negatively correlated with Tyr ($P<0.001$). The targeted metabolomic approach allowed the identification of a specific metabolic fingerprint in female non-complicated obesity that should be further explored as early biomarker of dysmetabolism.

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EP785

Interventional changes of thyroid hormone levels do not affect circulating irisin levels in humans

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Introduction
Thyroid hormones and irisin increase energy expenditure and induce browning of adipose tissue. However, little is known about irisin physiology and regulation. Here we aim to elucidate whether thyroid hormones alter circulating irisin concentrations in humans.
Design and subjects
One cross-sectional (case-control) evaluation and two interventions were performed independently from each other, including previously thyroidectomized patients. C*ase-control study:* Ninety-six subjects under thyroxine treatment, were recruited to study any associations between anthropometric parameters, thyroid axis hormones and irisin and then divided into a "euthyroid" and a "subclinical hyperthyroid" group, based on their Thyroid Stimulating Hormone levels (TSH cut-off value of 0.3 mIU/L). *Interventional Study A:* Thirty-four patients that were followed-up for thyroid cancer, were studied during a 5-week withdrawal from L-T4 treatment, according to a standardized routine protocol for preparation for whole body scan and/or thyroglobulin measurement. Blood samples were drawn at baseline and at the end of the study period. *Interventional Study B:* Thirteen patients underwent a recombinant human TSH (rhTSH) stimulation protocol and without receiving radioactive iodine for whole body scan and blood samples were drawn at baseline, day 3 (i.e. at least 24 hours after the second intramuscular injection), day 5 and day 10.
Results
Serum irisin levels were not cross-sectionally associated with anthropometric parameters as well as TSH, free thyroxine and free triidothyronine, in either the whole cohort or in the euthyroid and/or subclinical hyperthyroid subgroups. There was no significant difference between euthyroid and subclinical hyperthyroid subjects ($P=0.60$). L-T4 withdrawal did not alter irisin levels ($P=0.33$). The effect of rhTSH stimulation on circulating irisin was also null ($P=0.60$).
Conclusions
Changes of thyroid hormone levels within the physiological or mildly supraphysiological range do not affect circulating irisin levels in humans. Therefore, irisin proposed metabolic effects are most likely independent from thyroid axis hormones.

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EP786

Chemerin correlates with obesity and metabolic syndrome and decreases after weight loss in children

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Introduction
Chemerin is a pro-inflammatory adipokine, which has been shown as a mediator between obesity and metabolic syndrome (MetS). The aim of this study was to evaluate the associations of chemerin with insulin resistance and the effects of lifestyle interventions on circulating chemerin levels in Chinese obese children.
Methods
A cross-sectional study was conducted among 225 obese children (101 with MetS and 124 without MetS) and 119 lean controls, and a lifestyle intervention was performed in a subgroup of 60 obese children for 6 months. Anthropometric parameters, clinical data and circulating adipokines (chemerin, leptin and adiponectin) levels were measured at baseline and after lifestyle intervention.
Results
Chemerin was significantly higher in obese children, especially in those with MetS [(96.8 ± 10.2) ng/ml vs. (104.7 ± 15.1) ng /ml vs. (113.6 ± 10.6) ng/ml, $P<0.01$], and negatively correlated with body mass index (BMI) ($r=0.45$, $P<0.01$), waist circumference ($r=0.38$, $P<0.01$) and homeostasis model assessment of insulin resistance ($r=0.41$, $P<0.01$). Independent of other well-known risk factors, chemerin was a significant predictor of MetS in children. In the longitudinal study, lifestyle intervention led to significant weight loss and lower chemerin levels [(114.9 ± 17.2) ng/ml vs. (102.8 ± 11.1) ng/ml, $P<0.01$]. Furthermore, changes in BMI significantly correlated with the decreasing magnitude of chemerin ($r=0.35$, $P=0.01$).
Conclusion
Serum chemerin is regulated by weight status and seems to be correlated with metabolic disorders in Chinese children.

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EP787

Reduced expression of chemerin in visceral adipose tissue associates with hepatic steatosis in obese patients

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Aims
Emerging data indicate that an impaired release of adipose tissue-derived adipokines could play a pivotal role in the development of non-alcoholic fatty liver disease (NAFLD). We aimed to evaluate whether circulating levels or visceral adipose tissue (VAT) expression of recently described adipokines associate with the histopathological disease severity and thus may contribute to the progression of pure fatty liver into an inflammatory and insulin resistant NASH status.
Methods
Serum levels of omentin, chemerin, monocyte chemoattractant protein-1 (MCP-1) and Secreted frizzled-related protein (Sfrp) 4 were measured using enzyme-linked immunosorbent assay (ELISA) in 81 obese patients with biopsy-proven NAFLD and 18 lean control subjects. Expression of the adipokines in VAT was measured using real-time PCR analysis and histopathological grading of NAFLD was scored using the NAFLD activity score (NAS) as verified by Brunt et al.
Results
While VAT expression of omentin and Sfrp 4 ($P=0.043$ and $P<0.001$; respectively) as well as serum levels of chemerin ($P=0.020$) were higher in NAFLD patients compared to controls, adipokine levels did not differ when NAFLD patients were subdivided into groups with simple steatosis, borderline NASH and NASH. Although BMI was similar among NAFLD subgroups, NAS was associated with HOMA-IR independent of age and BMI ($\beta=0.282$; $P=0.020$). Serum adipokine levels were associated neither with histopathological disease severity, nor with their VAT expression. Chemerin VAT expression however, was negatively associated with NAS ($r=-0.331$, $P=0.022$) and steatosis score ($r=-0.335$, $P=0.020$). Importantly, these associations remained significant when adjusting for age, BMI and HOMA-IR. Furthermore, chemerin VAT expression was significantly lower in patients with moderate or severe steatosis ($>33\%$) versus patients with mild steatosis ($<33\%$; $P=0.016$).
Conclusion
These findings suggest a protective role of locally distributed VAT-derived chemerin during the pathophysiology of hepatic steatosis and confirm the pivotal role of insulin resistance in NAFLD.

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EP788

Mean platelet volume in a patient with celiac disease: the relationship between metabolic syndrome, impaired fasting glucose and cardiovascular risk

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Celiac Disease (CD) is a chronic inflammatory disorder and requires life-long treatment and follow-up. Mean platelet volume (MPV), determinant of platelet function, is an independent risk factor for cardiovascular disease (CVD). Metabolic syndrome (MS) is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function. It is a risk factor for coronary heart disease, as well as for diabetes, fatty liver, and several cancers.

The aim of this study was to evaluate MPV and RDW values in CD patients and the relationships between MPV, RDW, MS, impaired fasting glucose (IFG) and cardiovascular risk.

Thirty-six CD patients (mean age 29.28 ± 13.35 years) and 30 healthy control individuals (mean age 31.56 ± 10.54 years) were included in the study. CD patients adhered to a strict gluten-free diet and at least one year are diagnosed. The controls were matched to cases according to age, gender and BMI. A diagnosis of CD was established by positive antibodies against gliadin and/or endomysium and confirmed with histological findings of duodenum biopsy based on modified Marsh classification.

MPV and RDW levels were significantly higher in CD patients than control group ($P < 0.001$ both). CD patients had significantly more often MS than control group ($P = 0.007$). Patients with MS had significantly higher MPV and RDW compared to those without MS ($P = 0.004$ vs. $P = 0.042$ respectively).

These results suggest that CD patients are susceptible to increased platelet activation and increased MPV and RDW values that contribute to an increased risk of cardiovascular complications. The results may have clinical importance, because the parameters indicating inflammation in MS may be the early markers of developing cardiovascular events.

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EP789

Intergenerational influence of paternal obesity on metabolic and reproductive health of the offspring: male-preferential impact and potential involvement of Kiss1-mediated pathways

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Obesity and its comorbidities are reaching epidemic proportions. Maternal obesity is known to predispose the offspring to metabolic disorders, independently of genetic inheritance. This intergenerational transmission has also been suggested for paternal obesity during the pre-conception stage, as it appears to have a negative impact on the metabolic and reproductive health of the offspring, likely via epigenetic changes in spermatozoa. However, whether paternal obesity sensitizes the offspring to the disturbances induced by high fat diet (HFD) remains poorly defined. We report herein the metabolic and reproductive impact of HFD in the offspring from obese fathers, with special attention to potential sex differences and alterations of hypothalamic Kiss1 system. Lean and extremely obese male rats were mated with lean, virgin female rats; male and female offspring from lean and obese fathers were fed HFD from weaning onwards. At postnatal day 120, the offspring were euthanized and several metabolic and reproductive parameters analyzed. The increase in body weight and leptin levels, but not glucose intolerance, induced by HFD were significantly higher in the male offspring from obese fathers. In contrast, no differences were detected in the female offspring from both paternal groups; actually, glucose intolerance was lower in HFD-fed females from obese fathers. Paternal obesity caused a decrease in LH levels and exacerbated the drop in testosterone caused by HFD, which was associated to reduced testicular expression of key enzymes of testosterone biosynthesis. In addition, LH responses to central kisspeptin-10 administration were suppressed in HFD-fed males from obese fathers. In contrast, paternal obesity did not significantly alter gonadotropin levels in HFD females; yet, LH responses to kisspeptin-10 were dramatically reduced in the female offspring from obese fathers. Our findings suggest that HFD-induced metabolic and reproductive disturbances are exacerbated by paternal obesity, mainly in males, while kisspeptin actions are affected in both sexes.

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EP790

Micronutrients status in bariatric patients-middle term follow-up for Sleeve Gastrectomy

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Introduction

Sleeve gastrectomy is a highly effective bariatric technique for morbidly obese patients thus nutritional deficiencies resulting need routine screening for proper evaluation.

Aim

Little is still known about the nutritional side-effects for this restrictive bariatric procedure and our study aims to evaluate the impact of sleeve gastrectomy on micronutrients status.

Methods

Our prospective study included 48 morbidly obese patients undergoing laparoscopic sleeve gastrectomy (LSG), with a mean age of 39.1 years and mean BMI: 43.5 kg/m^2. Serum level for nutritional parameters were evaluated: 25OHvitamin D, Vitamin B12 and folic acid.

Results

Baseline evaluation/6 months post-bariatric surgery (available for 16 patients): Correction for de nutritional deficiencies was realised, and supplementation continued after the bariatric procedure.

- Mean level of Vitamin B12 was stable: 326 pg/ml at baseline and 298.5 pg/ml at the 6 months follow-up; Vitamin B12 deficiency (<193 pg/ml) was found in 7/47(14.9%) patients and 6 months post-bariatric surgery evaluation showed persistent deficiency in 2/16 patients (12.5%);
- Mean level of Folic acid at baseline: 5.88 ng/ml was maintained in the normal range ($N > 3$ ng/ml) with minimal reduction at the 6 months evaluation: 4.43 ng/ml; Folic acid deficiency was objectified in 5/48 cases (10.4%) and was persistent in 1/16 patients (6.25%)
- The initial evaluation:average 25-hydroxy vitamin D (25OHD) level = 16.75 ng/ml with significant correction to 20.78 ng/ml at the 6 months follow-up; Vitamin D insufficiency (<30 ng/mL) and vitamin D deficiency (<20 ng/mL) were present in in 28/31 patients (90.32%) respectively in 22/31 patients (70.96%); The prevalence of vitamin D insufficiency and deficiency were significantly improved to only 8/15(53.33%) and 6/15(40%) patients.

Conclusions

The level of nutrients was maintained at normal mean levels after sleeve gastrectomy and our preliminary data show the correction of nutrient deficiencies in most of the cases were possible in a short follow-up term (6 months).

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EP791

Menopause and obesity

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Introduction

Many studies have shown that the transition to menopause or peri menopause that begins with onset of menstrual irregularities and ends with the last menstrual period, was often associated with changes in body composition and specifically central distribution of adipose tissue.

The objective is this study is to determine the prevalence of global and android obesity in postmenopausal women compared to premenopausal women in the general population.
Methodology
Descriptive and analytical cross-sectional study conducted among 1583 women aged between 18 and 64 years living in households Algiers drawn at random by the National Statistics Office. 39.9% of postmenopausal women are obese (BMI $\geq$ 30 kg/m^2) while only 26.1% of premenopausal women are obese. %) ($P <$ 0.0001). In multivariate analysis menopause does not appear to be a risk factor for global obesity OR 0.79 (95% CI 0.58 to 1.09) $P=0.159$, whereas it is a risk factor of abdominal obesity OR $=1.73$ (1.11 to 2.71) $P=0.016$.
Our results are supported by many studies that showed an acceleration in abdominal fat accumulation measured by DEXA and computed tomography.
Conclusion
All these studies suggest that the increased incidence of cardiovascular disease in postmenopausal women could be attributed to the increase in visceral fat.

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EP792

Waist-to-hip ratio is the most discriminative parameter detecting OGTT alterations in men

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Background
There is a clear relationship between obesity and carbohydrate metabolism alterations (CMA), such as impaired glucose tolerance (IGT) and T2D. OGTT is used for the diagnosis of those alterations, but is not performed in case of normal fasting glucose values (NFG). Moreover, BMI underestimates the diagnosis of obesity and body composition alteration can be crucial to the development of abnormal carbohydrate metabolism. This study aimed to examine the discriminating value of body composition study and anthropometric data compared with BMI in the diagnosis of CMA.
Objectives
Describe the prevalence of CMA in patients with NFG. Study the discriminating value of body composition [total body fat % (BF%) and visceral adipose tissue (VAT)] and anthropometric data to detect CMA in men with NFG.
Methods
We recruited 170 non-diabetic men >18-year-old with NFG ($\leq$99 mg/dl) who underwent a 75 g OGTT with a concomitant body composition and anthropometry study between 2000 and 2014. Body density was estimated by Air-Displacement Plethysmography (Bod-Pod®). BF% was estimated from body density using the Siri equation. Bioelectrical impedance analysis was used to determine visceral fat by the ViScan system (Tanita Corp®). Patients were classified by glucose tolerance on the basis of blood glucose levels according to WHO diagnostic criteria for diabetes (2006). The statistical software package SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Area Under the ROC Curve (AUC) was used for diagnostic test evaluation.
Results
Basal characteristics: BMI 36.05 ± 8.12, 30.54 ± 14.7 years, Physical activity level 1.56 ± 0.12, HOMA-IR 2.94 ± 1.87. The prevalence of IGT and T2D was 21.6% and 2.7% respectively. AUC of waist-to-hip ratio was 0.68, BF% 0.61, waist circumference 0.60, BMI 0.58 and VAT 0.54. All variables demonstrated a significant discriminating value (p-value$=0.023$).
Conclusions
In our population, CMA prevalence was 24.3% after OGTT, so normal fasting glycaemia does not rule out CMA. Among all the anthropometric and body composition parameters analysed, waist-to-hip ratio was the most discriminative detecting CMA in our population, and it could be helpful in order to select patients in which an OGTT should be performed. This can help to establish appropriate measures to reduce cardiometabolic risk in men.
Keywords: Obesity, Anthropometry, Body composition, Body fat, Visceral fat, Oral glucose tolerance testing

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Obstructive sleep apnoea syndrome – longitudinal outcomes and improvement predictors after bariatric surgery

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Background
Bariatric surgery has been associated with a decrease in multiple obesity-related comorbidities including obstructive sleep apnoea syndrome (OSA). This study aims to access the OSA evolution in obese patients who underwent bariatric surgery.
Methods
Retrospective longitudinal study of a population of obese patients who underwent bariatric surgery between January/2010 and July/2014 in our centre. Only patients who have undergone polysomnography both before and after surgery were included. We have evaluated anthropometric, metabolic and polysomnographic data.
Results
A total of 78 patients were included, 56 (71.8%) were female, with a median age of 51 years (interquartile range[IQR] 46.25–51.00), body mass index (BMI) of 44.04 kg/m^2 (IQR 40.56–49.17) and apnoea-hypopnoea index (AHI) of 36.90 events/hour (IQR 23.40–52.15). In the preoperative evaluation, 7.7% had mild, 33.3% moderate and 59% severe OSA. The majority of them (74.4%) were treated with continuous positive airway pressure and 20.5% were on bi-level non-invasive ventilation. After surgery (median revaluation time was 11 months) there were statistically significant reductions in AHI (36.9 vs. 11.4; $P<0.001$), Epworth Sleepiness Scale (8 vs. 5; $P<0.001$), sleep time with oxygen saturation below 90% (24.9 vs. 3.2; $P<0.001$) and desaturation index (31.40 vs. 8.55; $P<0.001$) and significant elevations in mean (91 vs. 93.55; $P<0.001$) and minimum (71.50 vs. 83; $P<0.001$) oxygen saturation. There was an improvement in OSA severity in 37 (47.4%) patients and OSA resolution in 13 (16.7%) patients. Only 43.6% continued to be treated with positive airway pressure. The AHI improvement was positively correlated with BMI reduction ($r=0.296$; $P=0.009$), total weight loss ($r=0.289$; $P=0.010$) and weight loss percentage ($r=0.249$; $P=0.028$) and negatively correlated with preoperative values of AHI ($r=-0.792$; $P<0.001$), BMI ($r=-0.259$; $P=0.022$) and weight ($r=-0.267$; $P=0.018$). After adjusting for age and sex, BMI reduction ($\beta=1.217$; $P=0.014$), weight loss ($\beta=0.418$; $P=0.035$), initial AHI ($\beta=-0.840$, $P<0.001$) and initial BMI ($\beta=-1.093$; $P=0.017$) were predictive of the AHI improvement.
Conclusion
Bariatric surgery has beneficial effect on OSA outcome. This effect seems to be dependent on weight loss and on the preoperative values of AHI and BMI.

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EP794

Whole body and regional fat and lean mass in Bulgarian women of different ages and body mass index

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Up-to-date dual-energy X-ray absorptiometry (DXA) offers an insight into body composition (fat and lean mass) in different body regions.
Objectives
To measure the regional fat and lean mass in women of different age and to describe age-related changes.
Material and Methods
One hundred and twenty women referred for DXA participated in the whole body (WB) study – age range was 20–75 yrs. They were subdivided in three age groups: 20–44 (20 premenopausal women), 45–59 (80 postmenopausal women), and 60–75 (20 women). WB DXA was performed on a Hologic QDR 4500 A bone

densitometer (Hologic Inc., Bedford MA) and software version 8.26:3. Total body and regional BMC, fat and lean mass were measured. Regional analysis included arms and legs (as the sum of both left and right), as well as trunk. Descriptive and regression analyses with age as independent variable were performed on an IBM SPSS Statistics 19.0 for Windows platform. The data were first analyzed as a whole and then separately for the different age groups.

Results

Comparing the 45–59 versus the 20–44 aged subgroups fat and lean mass showed a parallel decrease, while in the older subgroup (60–75 yrs) the decrease of fat was greater than that of lean mass. The percentage of fat mass was lowest in the oldest subgroup. Comparing the 45–59 versus the 20–44 aged subgroups fat and lean mass showed a parallel decrease in the legs, but fat showed a greater decrease than lean in the arms and trunk. Best fitting regression models with age as independent and WB lean and fat mass as dependent variables are shown.

Conclusion

Aging has a more pronounced effect on fat than lean mass. The reduction of both body compartments is different according to the region studied. This type of data could be useful in the study of sarcopenia.

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EP795

Effect of osteocalcin on fat distrubution in premenopausal obese women

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Introduction

Recent studies suggested that plasma levels of osteocalcin (OC) were negatively associated with both fat mass and plasma glucose. These findings may suggest that endocrine function of the osteoblast-derived osteocalcin on fat mass/glucose homeostasis in mice also might exist in humans. The aim of this study was to determine if osteocalcin has any effect on fat distrubution in different parts of body.

Methods

Eighty-six obese premenapousal women (aged 17–55 years) and 56 women with normal BMI took part in this study. Antropometric measurements including waist circumferences (WC) were done. Serum concentrations of fasting blood glucose, insulin, OC were measuresd. Body fat distrubution was evaluated by ultarsonography. Body fat thickness in four regions were measured. Total fat and fat ratio were also measured by Bioelectrical Impedance Analysis (BIA). Epicardial fat thickness (EFT) was measured by echocardiography.

	Obese	Control	P
Visseral fat thickness (mm)	54.17	30.04	**0.000**
Preperitoneal fat thickness (mm)	20.36	6.72	**0.000**
Subcutaneous fat thickness (mm)	34.38	18.59	**0.000**
Epicardial fat thickness (mm)	5.19	3.25	**0.000**
Osteocalcin (ml/min)	18.26	22.53	**0.000**

Results

Visceral (VFT), subcutaneous (SFT) and preperitoneal fat thickness (PFT) were significantly higher in obese subjects ($P < 0.01$). OC was significantly lower in obese subjects. There wasn't any correlation between OC and VFT, SFT,PFT or EFT. Leg fat mass measured by BIA was negatively correlated with OC ($P=0.005$, $r=-0.328$).

Conclusion

Premenopausal obese women have lower OC levels but this doesn' t seem to be correlated with body fat distrubution in any part of body.

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EP796

Decrease in arterial stiffness (AS) in morbidly obese (MO) patients after bariatric surgery (BS): Relationship with obstructive sleep apnoea (OSA), anthropometric parameters and low-grade inflammation (LGI)

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Materials and methods

We studied 30 MO patients with OSA without Continuous Positive Airway Pressure (CPAP) treatment, before and one year after surgery. All patients underwent overnight conventional polisomnography (CE-Series Compumedics, Victoria, Australia). Sleeve gastrectomy or Roux-en-Y gastric bypass were performed according to the local protocol. To asses AS, augmentation index adjusted for heart rate (IAx@75) was obtained by applanation tonometry (Sphygmocor® versión 7.0 AtCor Medical, Sidney, Australia). To assess LGI, TNFα, IL-6, IL1β, PCR and adiponectin levels were measured (*Milliplex Catalog, Merck Millipore*, *Madrid*). Average blood pressure (ABP), BMI and % body fat (%BF) by bioelectrical impedance (TANITA) were also measured. For statistical analysis SPSS version 19 was used.

Results

AS, ABP and LGI decreased after BS (IA@75 22.6±11.5 vs 19.0±12.8, ABP 102.3±9.02 vs 95.1±8.97 mmHg, TNFα 3.07±1.89 vs 2.47±1.3 pg/mL, IL6 0.64±0.87 vs 0.45±0.76 pg/mL) and adiponectin increased (15.3±8.83 vs 30.4±14.7 μg/mL), $P<0.05$ before vs after surgery. IA@75 decline correlated with BMI and %BF improvement ($r=0.532$, $P=0.002$; $r=0.491$, $P=0.006$, respectively) but not with LGI improvement. IA@75 decline was predicted by Apnoea Hypopnoea index (beta$=-0.489$, $P=0.009$) and %BF (beta$=0.426$, $P=0.021$), before surgery.

Conclusion

In patients with MO and OSA, the less OSA severity and the more %BF before surgery, the more AS improvement achieved after BS.

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Relationship between the severity of obstructive sleep apnoea (OSA), low-grade-inflammation (LGI) and Heme Oxygenase 1 (HO1) in morbidly obese (MO) patients, before and after bariatric surgery (BS)

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Introduction

HO1 is a new adipokine with a protective role against cellular stress and hypoxia[1]. MO presents with high low grade inflammation (LGI)[2] and high circulating levels or adipose tissue expression of HO1[3]. The effect of bariatric surgery on HO1 and its relationship with OSA and LGI has not yet been studied.

Methods

We studied 66 MO patients before and 1 year after BS. All of them presented OSA without Continuous Positive Airway Pressure (CPAP) treatment (20 mild, 16 moderate and 30 sever). OSA diagnosis was given after an overnight conventional polisomnography (CE-Series Compumedics, Victoria, Australia). Sleeve gastrectomy or Roux-en-Y gastric bypass were performed according to the local protocol. HO1 (Elisa Kit bioNova científica, s.l.Madrid) and LGI (TNFα, IL6, IL1β, PCR and adiponectin) were measured (*Milliplex Catalog, Merck*

Millipore, *Madrid*), before and after bariatric surgery. BMI, waist circumference, % body fat by bioelectrical impedance (TANITA) and HOMA insulin resistance index were also assessed. For statistical analysis SPSS-PC-plus version 19 was used.
Results
Plasma HO1 did not differ between OSA groups. After surgery, HO1 levels decreased significantly (7.11±2.99 vs 6.59±2.47 ng/mL, $P<0.01$, before vs after), however, this effect was only observed in those patients who had sever OSA (7.64±3.78 vs 6.88±2.88 ng/mL, $P=0.02$, before vs after). The decrease in HO1 levels correlated with HOMA improvement ($r=0.257$, $P=0.028$) but not with the improvement of the other adipokines.
Conclusion
Improvement of plasma HO1 in MO patients after bariatric surgery is related to the severity of OSA and the degree of insulin resistance but not to LGI.

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Serotoninergic influence of the developing of obesity in children

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Background
It is well known that many nuerohormonal and genetic factors influence on the developing of obesity in children. Serotoninergic system is determined to be one of the most important factors. Serotonin may induce lipogenesis or triacylglycerol synthesis in the liver and/or white adipose tissue.
Aim
To establish interactions between serotoninergic system and metabolic parameters in obese children.
Methods
We examined 280 children (boys/girls=157/123) with different forms of obesity (age – 14.2±2.1 yrs, BMI – 32.5±5.4 kg/m^2) and 80 normal weight control (boys/girls=35/45) (age – 14.3±2.1 yrs ($P=0.7$), BMI – 19.7±2,1 kg/m^2 ($P=0.0001$)). Blood samples were collected with the determining of serotonin, triglycerides (TG), fasting glucose, total cholesterole (TCh), low- (LDLP) and high density lipoproteid (HDLP) levels. Genetic assay with the determining of metilsallitilite levels of monoaminioxydase A gene (MAOA) and gene of serotonin transporter (SLC6A4) were made. The results were processed using SPSS 18.0.
Results
Obese children showed a significant increase of serotonin levels: obesity 259.2 [58.5, 378.3]; control - 131.7 [10, 276.1] ($P=0.002$, U=3426.5). There was a reliable correlation between serotonine and TG ($P=0.025$, rs=0.2), LDLP ($P=0.036$, rs=0.25) in obese children. We didn't find any reliable correlation between serotonine and glucose, TCh, HDLP.
During the genetical assay we found that obese girls have MAOA 3/3 genotype 3 times more often compared to control girls, MAOA 4/4 genotype was found in 37,5% control and 19,4% obese girls. We didn't find any significant differences between SLC6A4 gene between obese and control groups.
Conclusions
Serotonine levels are increased in obese children compared to control and have reliable correlations with TG, LDLP which can say about its influence on adipose tissue. MAOA 3/3 genotype seems to be interacted with obesity, additional investigations should be made.

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EP799

16p11.2 Microdeletion and Prader Willi syndrome: similarities and differences

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Introduction
Prader Willi syndrome (PWS) is the most common syndromic form of obesity, caused by the absence of expression of the paternally active gens on the long arm of chromosome 15.The 16p11.2 microdeletion has recently been recognized as a syndromic condition appearing to be a predisposing factor for overweight, being the second most common genetic cause of obesity. One possible causative gen-SH2B1- involving leptin and insulin signaling, has been identified, although other genes may play a role.
Case report
We describe a case series of seven patients diagnosed with 16p11.2 deletion in our hospital between 2013–2015 and compare their main features with PWS. Four of them were men with an average age at diagnosis of 9.9±6.1 years. Two of them were referred to our clinical genetics department with a suspected diagnosis of PWS. Five of them had a sex-specific BMI for age over 95th percent. The mean length of deletion was 530.7Kb [448–598].Two of them suffered seizures and one patient had sleep apnoea.In the same way as PWS individuals, patients with 16p11.2 deletion present with hypotonia at birth. They may exhibit developmental delay, intellectual disability, and/or autism spectrum disorder. Weight is variable in childhood, but hyperphagia and obesity usually starts from one year on in PWS and later in 16p11.2 deletion. On the other hand, individuals with 16p11.2 syndrome don't have short stature nor other hormonal deficiencies as PWS individuals do (thyroid or reproductive axis). They can suffer from minor cardiac malformations but not from scoliosis.
Conclusions
Since the implementation of array analysis, numerous microdeletion syndromes as 16p11.2 have been described. Further research is needed for a comprehensive characterization of a genotype-phenotype correlation. It should be considered as one of the genetic causes of obesity following PWS. It's important to identify clinical characteristics, leading to perform genetic testing and counseling.

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EP800

Phenylbutyrate inhibits diet induced obesity through inhibition of pyruvate dehydrogenase kinase

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Obesity caused by excess energy intake has been emerging as a major health concern in the world, with increased risk leading to diabetes, hypertension, nephropathy, and cardiovascular disease. A better understanding of the molecular mechanism on how obesity develops is of critically clinical importance. Accumulating data suggest that ER-stress is strongly related with development of obesity, implying that ER stress can be a therapeutically target of obesity. 4-Phenylbutyrate (PBA) which is known as a chemical chaperon has known to decrease ER-stress. However, the detailed molecular mechanism by which PBA decreases ER-stress remains elusive. To identify the effect of PBA on body weight gain, high fat diet (HFD) feeding mice were treated with PBA for 8weeks. As expected, HFD feeding dramatically induced body weight, but PBA treatment showed a resistance to HFD-induced weight gain. CT (computed tomography) scan image showed that abdominal and subcutaneous fat accumulation were dramatically decreased by PBA. Furthermore, fat composition analysis identified that whole body fat mass was decreased and lean body mass was increased by PBA as compared with control group. H&E staining showed that lipid accumulation in liver and fat tissues was decreased by PBA. To do further analysis the effect of PBA, we took advantage of genetic mouse model of obesity (ob/ob). Although we could not find significant difference in body weight by PBA, but blood glucose level was clearly decreased. Meanwhile, PBA improved glucose tolerance and insulin tolerance. Western analysis with Liver tissue samples from ob/ob mice showed that PBA decreased protein expression level of GRP78, ATF4 and CHOP as well as inhibited activities of protein pyruvate dehydrogenase kinase (PDK) which is an upstream kinase of pyruvate dehydrogenase complex (PDC) that is gatekeeper in pyruvate metabolism in mitochondria. These results suggest that PBA decrease diet induced obesity by alleviating ER-stress by modulating PDK activities.

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EP801

Comparison of the effects on comorbidities and the safety of gastric bypass and sleeve gastrectomy in morbid obesity patients

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Introduction
Obesity is a multifactorial disease associated with numerous comorbidities. Bariatric surgery is postulated as an effective tool in weight loss and improves associated pathologies. The aim of this study was to evaluate and compare the safety and the effects on major comorbidities associated with morbid obesity of gastric bypass (GBP) and sleeve gastrectomy (SG) 2 years after intervention.
Methods
Cohort study with intrasubject measures (before-after) in a sample of patients with morbid obesity who underwent bariatric surgery (GBP or SG). Demographic characteristics, anthropometric parameters and cardiovascular risk factors were analyzed, at baseline and 2 years after surgery. Surgical complications were classified into early (first month after intervention) and late (more than 1 month).
Results
211 patients were included. The mean age was 37.9 ± 9.8 years and 157 were female (74%). The mean baseline BMI was 51.13 ± 7.11 kg/m^2. Regarding the surgical techniques, 178 (84.35%) underwent BPG and 35 (16.4%) SG, without significant preoperative differences between groups. 2 years after surgery, the percentage of excess weight loss was 73.06 ± 14.06% in the BPG group vs 66.61 ± 18.46% in SG ($P = 0.02$). The resolution of hypertension, dyslipidemia and diabetes occurred in 75%, 93.96% and 86.95% respectively in the BPG group and 63.63%, 77.7% and 85.71% in the group who underwent sleeve gastrectomy. Regarding surgical complications, 15.5% had late complications in BPG group vs 3.1% in sleeve group, while the rate of early complications was 26.8% vs. 6.2% respectively ($P < 0.001$).
Conclusion
In our area, BPG is more effective in weight loss and resolution of dyslipidemia at 2 years, while both techniques are equally effective in resolution of diabetes and hypertension. The rate of surgical complications is lower in patients undergoing sleeve gastrectomy.

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EP802

A 4-year effects of body weight reduction on arterial function after bariatric surgery in morbidly obese patients

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Objective
To determine the long-term effect of weight loss on arterial function parameters in morbidly obese patients who underwent laparoscopic adjustable gastric banding (LAGB).
Subjects
Forty-eight Caucasian subjects mean age 47.38 ± 10.77 years and 32 (66.67%) were female with morbid obesity who underwent LAGB and completed 4 years follow-up.
Measurements
Patients were evaluated at baseline, 1 year and 4 years after LAGB for excess weightloss (EWL), arterial blood pressure (BP), metabolic factors including leptin, adiponectin, glucose, HbA1C, insulin, Homeostasis model assessment-insulin resistance (HOMA-IR). Endothelial function was evaluated as reactive hyperemic index (RHI) and assessed using the EndoPAT 2000 device and arterial stiffness was determined by cardio – ankle vascular index (CAVI) using a VaSera VS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan).
Results
Subjects achieved a 29.90 ± 14.76% EWL at one year and 36.57 ± 23.91% EWL at four years after.
Subjects demonstrated significant improvement in metabolic parameters: an increase in adiponectin level (from 10.42 ± 7.15 to 15.54 ± 9.30 $P < 0.001$) and a reduction in leptin (from 34.54 ± 16.45 to 30.71 ± 17.45 $P < 0.001$), glucose (from 6.23 ± 2.36 to 5.17 ± 0.54 $P = 0.002$), insulin levels (from 171.07 ± 206.32 to 64.68 ± 40.92 $P = 0.001$.), HbA1c (from 6.15 ± 1.01 to 5.70 ± 0.55 $P < 0.001$). Although, changes in average diastolic blood pressure did not reach significant differences after one and four years post-surgery, however systolic blood pressure was significantly lower four years after.
However, there were statistically significant increase in arterial stiffness after 1 years, but not significant differences were noted after 4 year (6.58 ± 1.77 to 7.03 ± 2.00 m/s; $P = 0.014$ vs to 7.12 ± 2.19 m/s; $P = 0.153$). While, endothelial function did not show any improvement (2.07 ± 0.51 to 2.01 ± 0.54% $P = 0.948$ vs to 2.05 ± 0.42% $P = 0.086$).
Conclusion
Weight reduction induced by LAGB was associated with significant improvement of metabolic parameters, as well as arterial stiffness but not with the endothelial function.

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EP803

Msr1 and Cxcl16 scavenger receptors in adipose tissue are positively associated with BMI and insulin resistance

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Introduction
Obesity is associated with an increasing risk of diabetes and atherosclerosis. Previous studies in animals show that oxidized low-density lipoprotein (Ox-LDL) can be captured by the adipocyte through different scavenger receptors (SR) and thus contribute to the worsening of insulin resistance (IR). We analyze the association between Ox-LDL levels and different SR present in adipose tissue and their relationship with the presence of obesity and insulin resistance (IR).
Design
We study serum levels of Ox-LDL-oxidized and different SR, as well as the levels of mRNA gene expression of different SR (lectin-like oxLDL-1 (LOX-1), macrophage scavenger receptor 1 (MSR1) and chemokine (C-X-C motif) ligand 16 (CXCL16)) in visceral (VAT) and subcutaneous adipose tissue (SAT) from 23 normal weight and 25 morbidly obese patients (MO) depending on their IR (low and high IR).
Results
Serum Ox-LDL and LOX-1 levels are higher in MO patients with high IR ($P < 0.05$). Serum MSR1 levels are higher in the MO patients ($P < 0.05$). MSR-1 mRNA expression level is higher in MO patients with high IR in VAT and SAT ($P < 0.05$). CXCL16 mRNA expression level is higher in MO patients in VAT and SAT ($P < 0.05$). LOX-1 in VAT is positively associated with body mass index (BMI), waist and hips circumferences and cholesterol, and negatively with the HDL-c and adiponectin. MSR1 and CXCL16 in VAT and SAT are positively associated with BMI, waist and hips circumferences, insulin, glucose, HOMA-IR and triglycerides, and negatively associated with adiponectin and HDL-c.
Conclusions
In this study we demonstrate the positive association between MSR1 and CXCL16 mRNA gene expression levels and BMI and IR.

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EP804

Medium-term evolution of ghrelin levels according to three types of bariatric surgeries and its relation with HDL and insulin resistance

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Introduction
Ghrelin is a gastrointestinal peptide involved in the regulation of body weight and energy balance. However, its behavior after bariatric surgery and its relationship with other biochemical variables is still under discussion. We aim to undertake a simultaneous evaluation of the changes in ghrelin levels after three types of bariatric surgery and its relationship with different variables.
Design
The study included 21 non-obese and 103 morbidly obese subjects before and 6 months after bariatric surgery (Roux-en-Y gastric bypass (RYGB) ($n=30$), biliopancreatic diversion of Scopinaro (BPD) ($n=47$) and sleeve gastrectomy (SG) ($n=26$).
Results
Ghrelin was decreased in morbidly obese subjects ($P<0.05$). A multiple linear regression model showed that ghrelin was positively associated with HDL-cholesterol before bariatric surgery ($P=0.037$). RYGB increased ghrelin ($P<0.05$), BPD did not modify significantly ghrelin and SG decreased ghrelin ($P<0.05$). The percentage of change in ghrelin levels (Δ-ghrelin) was associated with the type of surgery in a multiple linear regression model ($P=0.017$). When we performed the same analysis only with those morbidly obese subjects in which gastric fundus is not excluded (RYGB and BPD), Δ-ghrelin was negatively associated with Δ-HOMA-IR in a multiple linear regression model ($P=0.001$).
Conclusion
In conclusion, HDL-cholesterol could be involved in the regulation of baseline ghrelin levels in morbidly obese subjects. Changes in ghrelin levels after bariatric surgery would be associated to the presence/absence of gastric fundus. Insulin resistance would be associated to the evolution of ghrelin levels after bariatric surgery in those techniques in which fundus is not excluded (RYGP and BPD).

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EP805

Aripiprazole effects on triglyceride content of *in vitro* differentiating adipocytes

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Introduction
In vitro adipogenesis is a two-step developmental process in which an *undifferentiated mesenchymal cell* differentiates into a *preadipocyte*, which then undergoes a secondary differentiation step to become a lipid-filled *adipocyte*. The triglyceride accumulation is influenced by various endogenous and exogenous factors.
Methods
In an attempt to understand the antipsychotics effects on lipid accumulation during adipogenesis, aripiprazole and olanzapine effects on triglyceride content were studied.To induce adipocyte differentiation from mouse embryonic fibroblasts (MEF), these were grown to confluence and then cultured in adipogenic medium (DMEM +5 μM DEX +0.2 μM IBMX +10 μg/ml insulin) for 2 days and in a sustaining medium (DMEM +10 μg/ml insulin) for 12 days. Cells exposed to adipogenic medium ± pioglitazone were used as absolute and positive controls, respectively. Aripiprazole and olanzapine were used at different concentrations (0.5, 5 and 20 μM). On the 7th and 14th days after induction, the cells viability test and Oil red O staining were performed. The accumulated Oil red O was dissolved in 1 ml 100% isopropanol and spectrophotometric analysis was performed (results expressed in mAU). For statistical analysis Student's t test was used and the significance level was established at $P<0.05$.
Results
Aripiprazole and olanzapine had no cytotoxic effect at the concentrations tested. After 7 days no significant differences were observed in the triglyceride contents of the cells, but highest mAU was obtained in pioglitazone (238 ± 23.2) and 5 μM aripiprazole (272 ± 65.7) added cultures. Although a decrease of lipid accumulation in all of the cells was observed in the 14th day, in pioglitazone and 5 μM aripiprazole added cultures signficantly higher triglyceride contents were present than in the control cells.
Conclusion
Our results demonstrate that aripiprazole similarly to pioglitazone but not olanzapine increased the triglyceride content during *in vitro* adipogenesis in MEF cells.
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EP806

Copeptin, a marker of vasopressin, decreases significantly in early state after bariatric surgery

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Introduction
Copeptin, the C-terminal fragment of arginine vasopressin pro-hormone, has been associated with the metabolic syndrome (MetS), diabetes mellitus (DM) development. The aim of our study is to evaluate preoperative and postoperative alterations of copeptin in patients who underwent obesity surgery and evaluate any differences between sleeve gastrectomy (SG) and mini gastric bypass (MGB) in terms of copeptin levels.
Subjects and Methods
Twenty five consecutive patients, who were treated for morbid obesity by SG or MGB, between March and April 2015 were included in this study. Diagnosis of MetS was made according to NCEP ATP-III criteria. Blood samples were obtained from patients preoperatively and one month after operation. ELISA technique was used to measure copeptin level in plasma samples.
Resullts
SG and MGB were applied to 11 and 14 patients, respectively. Mean ages (35 ± 8.3 vs. 34.7 ± 7.7, $P=0.908$) and body mass indexes of the two groups were similar (44.3 ± 2.3 vs 44.2 ± 3.2, $P=0.948$). Mean preoperative copeptin levels of patients who had SG (0.715 ± 0.619 ng/ml) and MGB (0.577 ± 0.222 ng/ml) were similar ($P=0.003$). At postoperative 1st month mean weight loss of the patients was 12.4 kg. Postoperative copeptin levels were statistically significantly decreased in both groups compared with preoperative levels (SG; 0.628 ± 0.610 ng/ml, $P=0.03$, MGB; 0.474 ± 0.180 ng/ml, $P=0.01$).
Conclusions
Recent studies have demonstrated the association between copeptin level and DM and MetS. Our study is the first one to show that copeptin significantly decrease during early postoperative period after obesity surgery.

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EP807

Changes in SCD1 promoter DNA methylation after bariatric surgery in morbid obese patients are associated with free fatty acids levels

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Introduction
Epigenetic is acquiring great importance in complex diseases, providing mechanisms whereby environmental factors can influence complex diseases such as obesity and type 2 diabetes. Experimental animal and human studies have revealed the association between SCD1 and obesity and insulin resistance. The aim of this study was to evaluate whether metabolic changes after intervention are associated with DNA methylation pattern and if these changes are related to weigh loss.
Methods
The study included 65 subjects with morbid obesity underwent laparoscopic Roux-en Y gastric by-pass. These subjects were studied before and 6 months after bariatric surgery. Serum biochemical and hormone variables were measured. The methylation status of the CpG island region of the SCD1 gene promoter was determinated.
Results
DNA methylation levels of the SCD1 gene promoter increased after the intervention (1.54 vs 2.17, $P<0.001$). There were no significant differences in SCD1 DNA methylation levels between males and females, neither according to age (data not shown).
A negative association was observed between changes in SCD1 gene promoter methylation and changes in FFA and HOMA-IR ($r=-0.442$; $P=0.006$, and $r=-0.249$; $P=0.035$, respectively). On the opposite, a positive association was found between changes in SCD1 gene promoter methylation levels and changes in adiponectin levels ($r=0.389$, $P=0.019$).
Conclusions
The main finding of our study is the association found between changes of metabolic parameters and changes in SCD1 methylation levels after bariatric surgery.

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EP808

Increased Urocortin 3 blood levels in morbidly obese subjects are reduced after excess body weight reduction with laparoscopic sleeve gastrectomy

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Aim
To measure Urocortin3 (Ucn3) blood levels in morbidly obese (MO) non diabetic patients before and after laparoscopic sleeve gastrectomy (LSG) for excess body weight reduction and explore its relationship with b-cell function. Ucn3 is involved in insulin secretion in the presence of nutrient excess, a key feature of obesity, and may be an integral part of the compensation of β-cells function.
Methods
Nine MO patients who underwent LSG and 11 healthy non-obese subjects (HS) were studied. MO and HS had, preoperatively and 6 months postoperatively, a 2-hour, 75 g oral glucose tolerance test (OGTT). Blood samples were withdrawn at 0, 30, 60, 90 and 120 minutes for glucose, insulin, lipid levels measurements and for Ucn3 levels at 0 and 60 minutes. HOMAR, Matsuda index, insulinogenic index and desposition index were also calculated.
Results
In MO, six months after the operation, mean BMI and waist circumference decreased significantly (from 44.7 to 30.5 Kg/m^2 and 130.8 to 99.2 cm, respectively). Blood Ucn3 levels in MO decreased significantly 6 months after LSG (24.45 ± 9.42 vs 3.66 ± 2.71 pg/dl; $P=0.001$), down to levels similar to HS. Body weight reduction was followed by significant decline of fasting serum glucose and insulin levels ($94.9+10.3$ to $82.9+4.9$ $P=0.013$ and $25.6+16.4$ to $6.5+2.4$ $P=0.001$) and their areas under the curve ($17.288+3.625$ to $13.588+2.965$ $P=0.048$ and $12.947+5.176$ to $6.714+3.039$ $P=0.001$, respectively). Insulin sensitivity increased significantly ($P=0.001$), but first phase insulin release and b-cell function remained unchanged. Ucn3 concentrations were positively associated with insulin, BMI, HOMAR and triglycerides levels. However, in multiple regression analysis BMI was the only predictor.
Conclusion
Blood Ucn3 levels are significantly higher in obese non-diabetic subjects with hyperinsulinemia and insulin resistance. Reduction of excess body weight is followed by a parallel decrease of insulin and Ucn3 blood levels.

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EP809

Glucose transporter 1 suppresses melanocortin 4 receptor activity

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The melanocortin 4 receptor (MC4R) represents the major hypothalamic G-protein coupled receptor (GPCR) controlling feeding behavior and therefore body weight regulation. MC4R is highly expressed in the paraventricular nucleus (PVN) where hormonal and neuroendocrine signals from periphery and arcuate nucleus (ARC) are allocated. MC4R knockout in mice or natural occurring loss-of function variants result in hyperphagia and early-onset obesity. MC4R mutations represent the most frequent genetic cause for human obesity. Over the last years there is growing evidence that GPCRs tend to interact with other GPCRs or non-GPCR proteins. Analyzing a possible MC4R protein network by screening for new interaction partners, we found the glucose transporter 1 (GLUT1) to be a possible MC4R interacting partner. By immunohistochemistry we could demonstrate expression of GLUT1 on PVN neurons. Moreover, co-expression of GLUT1 and MC4R on different murine neuronal cell-lines could be shown, indicating a theoretical possibility that both proteins interact. Using two different assay systems, we furthermore could affirm a direct GLUT1/MC4R interaction. Functional studies revealed strong down-regulation of alpha-MSH mediated MC4R signaling by GLUT1 co-expression. As a possible mechanism, we identified a reduction in cell surface expression of MC4R due to GLUT1 co-expression. Uptake studies revealed that the MC4R itself has an impact on cellular glucose feed-in augmenting our hypothesis of a veritable connection between glucose sensing and MC4R signaling. Finally, gene expression analyses showed strong down-regulation of *Glut1* after three days of high-fat diet. Therefore, nutritional reduction of GLUT1 might increase MC4R action in controlling food intake.

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EP810

A body-wide transcriptome screen reveals high ghrelin gene (GHRL) expression in monocytes and supports a hypothesis of monocyte GHRL-derived hormones as critical mediators of the brain-gut axis and monocyte-adipocyte cross-talk in health and obesity

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Introduction
It is now appreciated that peptide hormones encoded by the ghrelin gene, *GHRL*, have roles in many biological systems and cell types. In particular, the hormone ghrelin is a therapeutic target and clinical marker for a range of pathologies, including diet-induced and genetic obesity. High-quality transcriptome (RNA-seq) data sets generated by consortia, such as the Human Protein Atlas (HPA) and

Encyclopedia of DNA Elements (ENCODE), now offer an opportunity to study the expression of any gene of interest in diverse cells and tissues.
Methods
We initially investigated *GHRL* expression in the human body by interrogating publically-available transcriptomes from 35 somatic cells and tissues, revealing relatively high expression in monocytes and associated tissues. In an effort to link monocyte *GHRL* more directly to functional outcomes, we next sought to compare its expression in 19 women before bariatric surgery and 12 weeks postoperatively.
Results
Monocyte *GHRL* expression was significantly reduced three months after bariatric surgery ($P=0.0001$ by Student's *t*-test; $n=19$). A previous study of the same cohort demonstrated diminished obesity-induced inflammation and an altered interferon-γ (IFN-γ) pathway in adipose tissue and monocytes post-operatively. Here, we show that IFN-γ modulates *GHRL* expression in the monocyte-derived cell line THP-1 ($P=0.0079$ by Mann–Whitney U test; $n=5$).
Conclusion
While it is well-established that ghrelin plays a role in appetite regulation and energy balance, the function of *GHRL* in immune cells has hitherto remained enigmatic. Here, we present data that further supports cross-talk between the endocrine and immune systems. We put forward the hypothesis that monocyte *GHRL*-derived hormones are critical mediators of the brain-gut axis and monocyte-adipocyte cross-talk. Future longitudinal studies are needed to firmly establish a role for monocyte *GHRL*-derived peptides in successful bariatric surgery and obesity-associated pathologies, such as Prader-Willi syndrome and metabolic syndrome, in general.

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EP811

Positive association between blood natural killer T cells and liver enzymes ALT, AST and GGT levels

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Introduction
Obesity is associated to a pro-inflammatory state with a different pattern of response from the classical response. Also, obesity is associated to non-alcoholic fatty liver disease (NAFLD). In this sense, natural killer T (NKT) cells are a subset of innate immune cells that abundantly reside within the liver and are readily activated by lipid antigens. However, the phenotype and functional characteristics of these cells are no clear in the immune homeostasis in obesity.
Methods
Peripheral blood *mononuclear cell* (PBMC) from 17 lean controls and 20 morbidly obese (MO) patients with normal levels of liver enzymes ALT, AST and GGT were isolated to address the association between iNKT cells and ALT, AST and GGT. PBMC were analyzed by FACS CANTO II flow cytometry.
Results
In PBMC, no differences were observed in the frequency of iNKT cells of MO and lean subjects. However, into MO group, we found a significant correlation between iNKT cells and ALT levels ($r=0.611$, $P=0.015$). No differences were observed in CD4+ and CD8+iNKT cells in PBMC from MO compared with lean subjects, but a positive correlation between CD4+iNKT cells with ALT ($r=0.476$, $P=0.043$) and GGT ($r=0.581$, $P=0.029$) was found. CD56+NKT and CD56+iNKT cells were increased in PBMC of MO subjects ($P<0.001$). The frequency of CD69+CD25+ iNKT cells (early and later activated iNKT) was significantly increased in PBMC from MO subjects ($P<0.001$). These activated iNKT cells presented a significantly and positive correlation with AST ($r=0.677$, $P=0.006$) and ALT ($r=0.693$, $P=0.004$).
Conclusions
MO subjects presented early and later activated lymphocytes and iNKT in PBMC. The direct association found between iNKT cells, both total and activated, in PBMC and serum levels of liver enzymes ALT and AST suggests that this type of cells might play an essential role in fatty liver disease associated to obesity.

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EP812

The effect of urbanization on adiposity and insulin resistance among Indonesian

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Background
The prevalence of obesity and type 2 diabetes (T2DM) in Indonesia is increasing. One of the major socio-environmental factors that might contribute to this is urbanization, which is associated with changes into more sedentary lifestyle and unhealthy diet. These changes can lead to obesity. The metabolic risks of obesity are mainly determined by the body fat content. The higher the body fat content the higher insulin resistance and hence susceptibility of T2DM. The contribution of adiposity to urban-rural differences of insulin resistance in Indonesia is currently unknown.
Aim
Our study aims to characterize the differences in adiposity and insulin resistance among urban and rural Indonesian, and to explore the time effects of urbanization.
Methods
We recruited 36 adult male participants with Flores ethnicity from a rural area of Ende (Flores) and 36-age-sex-ethnic matched participants from an urban area (Jakarta) who had already moved to Jakarta between 1 and 41 years. We measured body mass index [BMI (kg/m^2)], waist circumference [WC (cm)], waist-hip ratio (WHR), 4-sites skinfold [biceps SF, triceps SF, supra iliac SF, subscapular SF (cm)], body fat composition (BIA), fasting glucose (mmol/L), fasting insulin (IU/L), 2h-glucose post 75g glucose load [PPG (mmol/L)], HbA1c (%) and insulin resistance (HOMA-IR).
Results
Urban group has significantly higher BMI [24.5(4.7) vs 22.3(4.1); $P=0.042$], WC [84.9(13.4) vs 77.6(11.2); $P=0.014$], WHR [0.99(0.062) vs 0.93(0.058); $P=0.000$] and subscapular SF [16.9(9.0) vs 12.1(7.4); $P=0.016$]. These differences translate into significantly higher PPG [7.4(2.6) vs 5.7(1.6); $P=0.002$] and HbA1c [5.5(0.7) vs 5.1(0.6); $P=0.007$] among urban group, but no significant difference in HOMA-IR [1.38(1.05–1.76) vs 1.05(0.76–1.40); $P=0.173$]. After adjusting for age, there are positive correlations between the duration of stay in urban area and markers of adiposity, such as BMI ($r=0.553$, $P=0.014$), Fat Percentage ($r=0.465$, $P=0.045$), WC ($r=0.634$, $P=0.004$); but not with HOMA-IR ($r=0.301$, $P=0.210$).
Conclusion
The people who move to an urban areas have unfavourable adiposity profile which might put them at higher risk of having insulin resistance and hence T2DM in the future. These profile differences are correlated with the duration of stay in the urban area.

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EP813

Continuous glucose monitoring for evaluation of glycemic variability after bariatric surgery

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Introduction
Neuroglucopenic hypoglycaemia might be an underestimated threat of bariatric surgery, as Roux-en-Y gastric bypass (RYBG) or gastric sleeve. We aimed to evaluate glucose variability after bariatric surgery by continuous glucose monitoring (CGM) in a real-life setting.
Methods
CGM was used in twelve patients with clinical suspicion of hypoglycaemia after undergoing bariatric surgery (RYBG or sleeve), during seven days. CGM was through using iProTM2 CGM device (Medtronic, Northridge, CA) in all patients.

Results
Continuous glucose monitoring retrieved a total of 21 960 glucose data points that were evaluated herein. Ten of the 12 patients (83.3%) had previously undergone RYBG surgery and only 2 (16.7%) had undergone gastric sleeve, with a mean time after surgery of 3.25 ± 1.54 years. All patients had at least one episode of hypoglycaemia below 55 mg/dL (min 3; max 33). Total hypoglycaemia exposure was 11.79 hours per patient and CGM. During the monitoring period, 157(81.35%) out of 193 hypoglycaemic episodes, occurred in the post-prandial state. Glucose variability was evaluated by MAGE (3.205; RV 0.0–2.8), CONGA (3.955; RV 3.6–5.5), J-Index (10.94; RV 4.7–23.6) and SD (1.085; RV 0.0–3.0). Area under the curve for glucose <70 mg/dL was 1.025 and for glucose >180 mg/dL was 1.69.
Conclusions
Glucose variability is exaggerated after bariatric surgery: hypoglycaemia occurred mostly in the post-prandial period and glucose variability was increased by glucose fluctuations, as evidenced by MAGE. As a result, CGM may be a valuable diagnostic tool and may have a role evaluating treatment response to dietary modifications, drug therapy or surgical reintervention.

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EP814

Extra virgin olive oil and red wine polyphenols modulate fecal microbiota and reduce metabolic risk factors in high insulin resistant obese patients

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Objectives
This study evaluated the prebiotic effect of a moderate intake of extra virgin olive oil (Evoo) and red wine (Rw) polyphenols on modulating the gut microbiota composition and the improvement of metabolic risk factors in obese subjects with high insulin resistance (HIR).
Methodology
10 obese patients with HIR (HOMA-IR >5.5) and 10 lean subject with low insulin resistance (HOMA-IR $<$ 3.3) were included in a randomized and controlled intervention study. After a washout period both study groups consumed a normo-caloric Mediterranean diet with added Evoo (50 g/dayl) and the same diet plus red wine (270 ml /day) over a 30-day period for each one.
Results
The Chao and Shannon indices of each study group suggested similar bacterial richness and diversity in the fecal samples between both study groups. 16S rRNA pyrosequencing showed that the dominant bacterial composition differ significantly between the study groups after the two diet intake periods respect to their basal level. In HIR patients, polyphenols from Eoov and Rw significantly increased the number of fecal bifidobacteria and Butyricimonas (intestinal barrier protectors) and significantly decreased the abundance of Rikenellaceae, Desulfovibrionaceae and Prevotella (opportunist pathogen and mucin-degrading bacterial). Moreover, in the HIR patients, triglycerides, glucose and CRP levels decreased and HDL cholesterol levels increased after the two intake periods and this was associated with a rise in Bifidobacterium and Butyricimonas and a decrease in Clostridium, respectively.
Conclusion
A Mediterranean diet supplemented with Evoo and Rw polyphenols increased HDL levels and decreased triglyceride and CRP levels in HIR patients, improving associated cardiovascular risk. Changes in gut microbiota in these HIR patients could be responsible for the improvement of these metabolic markers. Modulation of the gut microbiota by Evoo and Rw polyphenols could be an effective strategy to manage metabolic diseases

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EP815

Prevalence of obesity in an Algerian adult population

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Introduction
The epidemiological transition has resulted in a major increase in the prevalence of obesity in our country. Obesity is closely associated with chronic diseases such as type 2 diabetes, hypertension and dyslipidemia.
The aim of our study is assessing the prevalence of general obesity, central obesity (OA), associated risk factors (type2 diabetes, hypertension and dyslipidemia) and try to provide information on determinants of obesity in Algerian adult.
Methods
This was a cross sectional study conducted among 2210 subjects (1583 women and 627 men) aged 18 to 64 years old, living in Algiers (Algeria).
Subjects were randomized, anthropometric parameters, socio demographic situation, information about the food habits and physical activity were collected using a questionnary.
Fasting blood glucose, cholestrol, triglycerids and blood pressure were measured.
Results
The prevalence of obesity (BMI $>$ 30 kg/m^2) was 24.9% (12.7% for males and 66.4% for females).
The prevalence of central obesity (WC $>$ 80 cm for women and 94 cm for men) was 66.4%, 41% for males and 76.4% for females.
Multi variable logistic regression showed that elderly, female gender, low educational level, a history of familial or personal obesity and menopause were at risk of obesity classified by BMI or WC.Wheras a young age, a higher level of education, male gender, celibacy and high physical activity were at lower risk of obesity.
Obese subjects defined by BMI or Waist circumference had an increased risk of type 2 diabetes, hypertension and dyslipidemia.
Conclusion
The characterization of these factors will contribute to defining more effective and specific strategies to screen and control obesity.

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EP816

Obesity may influence on measurements of choroid thickness in optical coherence tomography

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Introduction and aims
It is known that obesity is associated with retinal microvascular changes. Optical coherence tomography (OCT), a new imaging technique, is used to visualize the choroid. In addition, OCT can also give more beneficial information about systemic and eye diseases. We aim to investigate whether or not obesity may impact on choroid and macula thickness.
Material and methods
Forty-four subjects who were apply for obesity in our Endocrinology outpatient clinic [mean age 34.47 ± 8.10 years, body mass index (BMI) 40.11 ± 8.02 kg/m^2] and 44 age-matched healthy control subjects (mean age 31.18 ± 7.77 years; BMI 20.95 ± 1.86 kg/m^2) were included in our study. All of subjects in obesity group were selected according to BMI $\geq$ 30 kg/m^2 whereas control group was selected according to BMI $<$ 25 kg/m^2. Anthropometric measurements, routine systemic evaluations and eye examinations were performed. The central fovea thickness (FT), the central fovea choroidal thickness (FCT), the thicknesses of nasal 500 (N500) micron and nasal 1500 (N1500) micron, and the thicknesses of temporal 500 micron (T500) and temporal 1500 (T1500) micron were measured by using enhanced-depth imaging optical coherence tomography (EDI-OCT).
Results
It was found that measurements of FT, FCT, T500, T1500, N 500 in obese group were different from control group (250.94 μm vs. 266.04 μm in FT $P=0.004$, 345.84 μm vs.313.77 μm in FCT $P=0.007$, 343.36 μm vs. 313.95 μm in T500 $P=0.010$, 334.47 μm vs. 310.04 μm in T1500 $P=0.035$, 340.05 μm vs. 310.54 μm in N500 $P=0.014$). However measurement of N1500 point was not significantly different from control group. We also found that there was only a negative correlation between BMI and central foveal thickness ($r=-0.285$, $P=0.09$) by using Pearson's correlation analysis.
Conclusions
As a result, we showed that the choroid thickness in obese person is increase significantly. Therefore, obesity may influence on measurements of choroid thickness by OCT.

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EP817

Effects of bariatric surgery on blood pressure of non-hypertensive obese patients

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Introduction
Increased blood pressure (BP) above >115/75 mmHg presents an independent association with cardiovascular events. Although there is a clear benefit of bariatric surgery on BP of hypertensive patients, the impact in non-hypertensive patients remains largely unknown. Therefore, the aim of our work was to evaluate the impact of bariatric surgery on BP of non-hypertensive obese patients.
Methods
We evaluated a cohort of 224 non-hypertensive obese patients (90.8% women) that were submitted to bariatric surgery. We analyzed systolic BP (SBP) and diastolic BP (DBP) 12 months after surgery. The impact of preoperative parameters age, sex, BMI, waist-to-hip ratio, SBP, DBP, diabetes, dyslipidemia, smoking, glomerular filtration rate, C-reactive protein; type of surgery (adjustable gastric band, Roux-en-Y gastric bypass or sleeve gastrectomy) and the weight loss after surgery was also assessed. The statistical analysis was done with Student's *t*-Test, Pearson correlation and multiple regression.
Results
We observed a significant reduction of SBP (122.3 ± 10.9 vs 116.9 ± 14.5 mmHg, $P<0.001$) and PAD (77.5 ± 8.4 vs 73.1 ± 9.1 mmHg, $P<0.001$) in the 12 months after surgery. The subgroup of patients with initial-SBP 130–140 mmHg presented a greater reduction of SBP (−13.7 vs −0.2 mmHg, $P<0.001$) and DBP (−7.3 vs −2.5 mmHg, $P<0.001$). The reduction of SBP was positively associated with initial-SBP ($\beta=0.975$, $P<0.001$) and weight loss ($\beta=0.202$, $P=0.040$), and negatively with age ($\beta=-0.249$, $P=0.030$), BMI ($\beta=-0.549$, $P=0.030$) and initial-DBP ($\beta=-0.331$, $P=0.015$). The reduction of DBP was independently and positively associated with initial-DBP ($\beta=0.769$, $P<0.001$) and negatively with age ($\beta=-0.135$, $P=0.044$) and BMI ($\beta=-0.335$, $P=0.021$). The type of surgery and the other parameters analyzed did not have a significant impact on SBP or DBP variation.
Conclusion
Bariatric surgery contributes to a significant reduction of BP in non-hypertensive obese patients. The benefit appears to be more directly related to weight loss than to type of surgery. The impact of the procedure is greater in patients with higher initial-SBP, and smaller in older patients and those with higher BMI.

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EP818

Metabolically healthy obesity: exploring the paradox

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Introduction
Obesity is a chronic disease associated with multiple comorbidities, defined by BMI, without considering the metabolic state of the patient. There are few data on the proportion of obese patients without metabolic syndrome (MS).
Objective
To characterize patients considered to be metabolically healthy (MH) followed at the obesity outpatient clinic of one University Hospital, and to compare this group with a group of obese patients with MS.
Material and methods
We retrospectively studied 300 patients. We collected information about clinical and demographic parameters, body composition, biochemical profile and abdominal ultrasound. We used the criteria of NCEP ATPIII to define MS; patients without MS were considered to be MH.
Results
A total of 69.3% patients ($n=208$) were considered MH. MH patients had an age of 40.9 ± 12.6 y, 77.9% were female, had a weight of 107.2 ± 21.6 Kg, BMI of 40.5 ± 6.7 kg/m^2 (53.2% with obesity class III), waist circumference of 112.4 ± 10.9 cm and fat mass of 44.7 ± 7%. The most frequent comorbidities were hypertension (63.2%), hepatic steatosis (47.2%), psychiatric disorders (43.8%), dyslipidemia (43.3%), osteoarthritis (42.3%) and gallbladder lithiasis/cholecystectomy (17.5%). There was no statistically significant difference between patients with and without MS regarding gender, age, obesity class, body weight, BMI, waist circumference and % fat mass. Statistically significant difference were observed between the groups in glycemic parameters, blood pressure, HDL-C, LDL-C, TG and osteoarthritis.
Conclusion
There was a high prevalence of MH obese patients, who differed from their non-healthy counterparts regarding glycemic parameters, blood pressure, lipid metabolism and osteoarthritis (more prevalent in the patients with MS). However, more than half of MH patients had one or more conditions considered to be a comorbidity of obesity. A long-term prospective evaluation will be required to understand if there is a MH obesity or if this is inevitably associated with increased morbidity/mortality.

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EP819

Changes in testosterone levels and sex hormone-binding globulin levels in extremely obese men after bariatric surgery

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Objective
Obesity is a risk factor for hypogonadotrophic hypogonadism in men. Increase in body weight was found to be associated with decrease testosterone level and sex hormone-binding globulin (SHBG) level. The aim of this study was to evaluate the change in testosterone levels in extremely obese men after bariatric surgery.
Methods
This is a prospective study including 29 morbidly obese men undergoing bariatric surgery. Main outcomes were changes in serum levels of total testosterone (TT), free testosterone (cFT), SHBG, Estradiol, adiponectin and leptin at 1 and 6 months after bariatric surgery.
Results
The mean ages of patients were 31 ± 8 years and the mean BMI was 57.8 ± 11.2 kg/m^2. Sixteen patients underwent Roux-en-Y gastric bypass and 13 patients underwent sleeve gastrectomy. At baseline, 22 patients (75.9%) had low TT levels (<10.4 nmol/L) and 27 patients (93.1%) had low cFT levels (<0.31 nmol/L). Total testosterone and SHBG levels increased significantly at 1 month after surgery ($P=<0.001$) whereas cFT levels have not changed. At 6 months after surgery, TT, cFT and SHBG levels increased significantly (all p-values $=<0.001$) and 21 patients (72.4%) had normal TT levels. There were no changes in estradiol levels either at 1 month or 6 months after surgery. Leptin levels decreased and adiponectin levels increased significantly after surgery. Early increases in TT levels were associated with increases in SHBG levels ($R=0.472$, $P=0.042$) but not with changes in body weight, BMI, adiponectin or leptin.
Conclusions
Increases in TT and SHBG levels occurred early at 1 month after bariatric surgery while improvements in cFT levels were observed at 6 months after bariatric surgery. No change in estradiol levels was found. Changes in total testosterone levels tend to be correlated with SHBG levels but not with body weight or adipokines levels.

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EP820

Neutrophil-lymphocyte ratio and its relationship with insulin resistance in obesity

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Aim
In our study we aimed to investigate neutrophil/lymphocyte (N/L) ratio, variations in leukocytes and leukocyte subtypes and relationship between N/L ratio and insulin resistance (IR) in obesity.

Material and methods
In this study 250 obese patients data were scanned retrospectively and 96 patients that are convenient to inclusion criteria and has complete file information were included in the study. Forty healthy individual with similar age and sex distribution were selected among 120 personal medical records and included the study as control group. Patients 8 hours fasting blood glucose levels, insulin levels and hemogram parameters were determined. BMI and HOMA-IR values were calculated from patients weight and height.
Findings
White blood cells were significantly found to be increased in obese patients (8764 ± 2023 and 7712 ± 1932 respectively, $P = 0.006$). Neutrophil and lymphocyte counts were significantly higher in obese patients than control group (for neutrophils 5359 ± 1.788 and 4585 ± 1.473 respectively, $P = 0.017$, for lymphocytes 2615 ± 627 and 2287 ± 553 respectively, $P = 0.005$). However there was no statistical significant difference for N/L ratios between two groups (2.18 ± 1.00 and 2.10 ± 0.83 respectively, $P = 0.658$). Neutrophil numbers were found to be higher in IR obese than non IR obese (5780 ± 1628 and 4980 ± 1838, $P = 0.02$). N/L ratio was found to be higher in IR obese compared to non IR obese (2.39 ± 1.06 – 1.97 ± 0.91 $P = 0.04$). A positive correlation was found between insulin resistance and neutrophil, WBC counts. Another positive correlation was found between insülin level and N/L ratio, WBC and neutrophil counts.
Results
In our study leukocyte numbers and leukocyte subtypes were determined to be higher in obese compared to healthy individuals. However N/L ratio was significantly increased only in obesity with insulin resistance. Further studies are needed to clearly demonstrate the relationship between N/L ratio and insulin resistance or inflammation.

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EP821

Association of body fat distribution and carotid intima media thicknesss with Vitamin D in obese premenopausal women

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Introduction
It has been demonstrated that there are differences in the effect of body mass index (BMI) on the serum 25-hydroxyvitamin D levels (25-OH D); differences appeared stronger in subjects with higher BMI. In this study we aimed to assess the association between 25-OH D status and body fat distribution and caratid intima medai thickness.
Methods
86 obese premenapousal women (aged 17–55 years) and 56 women with normal BMI took part in this study. Antropometric measurements including waist circumferences (WC) were done. Serum concentrations of fasting blood glucose, insulin, calcium, PTH, 25-OH D were measured. Body fat distrubution was evaluated by ultarsonography. Body fat thickness in four regions and carotid intima media thickness (CIMT) were measured. Total fat and fat ratio were also measured by Bioelectrical Impedance Analysis (BIA).
Results
Visceral (VFT), subcutaneous (SFT), preperitoneal fat thickness (PFT) and the CIMT were significantly higher in obese subjects ($P < 0.01$). 25-OH D were similar and low in both groups. (13.38 ng/ml in obese and 13.99 ng/ml in controls). 25-OH D were correlated negatively with waist circumference ($P = 0.025$, $R = -0.263$) and VFT ($P = 0.002$, $R = -0.366$). Whereas PTH levels were positively correlated with WC ($P = 0.042$, $R = +0.241$). There wasn't any correlation with 25-OH D and SFT and PFT. Total fat mass measured by BIA was also negatively correlated wtih 25-OH D. CIMT was negatively correlated with 25-OH D ($P = 0.028$, $R = -0.269$) and positively correlated with PTH ($P = 0.018$, $R = +0.291$).
Conclusion
There are several studies investigated the relation between vitamin D and adiposity. They have different results concerning the relation between Vitamin D and BMI,waist circumference and fat distribution measured by different methods. Ethnicity, gender, and age may play a role in mediating this relation. This study showed that in premenopausal Turkish obese women, vitamin D may have a contributing factor on fat distribution so on cardiovascular risks in obesity.

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EP822

Visceral adiposity index as a marker of hepatic steatosis in overweight and obese premenopausal women

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Introduction
Visceral adiposity index (VAI), initially developed as an indicator of visceral adipose function for the assessment of cardiometabolic risk, has been also proposed for the detection of nonalcoholic fatty liver disease (NAFLD). However, the diagnostic performance of VAI as a marker of hepatic steatosis (HS) is still under investigation.
Objective
To evaluate the accuracy of VAI as a marker of HS in a cohort of overweight and obese premenopausal women and to compare diagnostic performance of VAI and of two other HS markers: fatty liver index (FLI) and lipid accumulation product (LAP) index.
Design
Prospective, cross-sectional study.
Patients – methods
Anthropometric measurements, biochemical testing and abdominal ultrasonography after excluding causes of secondary liver disease were performed in 110 overweight and obese premenopausal women, aged 18–45 years, including 40 women with polycystic ovary syndrome (PCOS). The three markers of HS - VAI, FLI and LAP - were calculated. The diagnostic performance of VAI, FLI and LAP was assessed with receiver operating characteristic (ROC) analysis.
Results
NAFLD was detected in 71/110 (64.5%) women (31 PCOS and 40 non PCOS) by ultrasonography. VAI, FLI and LAP values were higher in HS(+) compared to HS(−) women [2.3 ± 1.8 vs. 1.3 ± 0.7 ($P < 0.01$), 68.4 ± 28.1 vs. 33.3 ± 22.7 ($P < 0.001$) and 60.8 ± 41.7 vs. 28.6 ± 13.9 ($P < 0.001$) respectively]. The area under the curve (AUROC) for VAI, FLI and LAP was 0.71, 0.82 and 0.79, respectively.
Conclusions
These data indicate that calculation of VAI is useful for detecting NAFLD in overweight and obese premenopausal women. However, FLI and LAP seem to have a superior diagnostic performance.

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EP823

Hif-1α is positively associated with scavenger receptors Lox-1, Cxcl16 and Msr1 in adipose tissue

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Introduction
HIF-1α, a hypoxia marker, is an important factor for transcriptional regulation of cell metabolism and the adaptation to cellular stress. It modulates the function of phagocytic cells by stimulating surface receptors such as scavenger receptors. But little is known on their relationship in adipose tissue, whose increase has been associated with an increased risk of atherosclerosis. The aim of this study is to analyze in adipose tissue the association between mRNA expression levels of HIF-1α and different scavenger receptors, and their relationship with the presence of obesity.
Design
We study in 21 normal weight and 26 morbidly obese patients (MO) the mRNA gene expression levels of HIF-1α and different scavenger receptors (lectin-like oxLDL-1

(LOX-1), macrophage scavenger receptor 1 (MSR1) and chemokine (C-X-C motif) ligand 16 (CXCL16)) in visceral (VAT) and subcutaneous adipose tissue (SAT).
Results
HIF-1α and LOX-1 mRNA gene expressions are increased in VAT from MO patients ($P=0.025$ vs. $P=0.003$, respectively), but not in SAT. MSR-1 and CXCL16 mRNA gene expression levels are higher in MO patients in VAT and SAT (VAT: $P=0.001$ vs. $P<0.001$, respectively, and SAT: $P<0.001$ vs. $P<0.001$, respectively). HIF-1α mRNA gene expression in VAT has positively correlated with the weight, body mass index and waist circumference, and negatively with serum HDL and adiponectin levels. HIF-1α mRNA gene expression is positively associated with MSR1 and CXCL16 in VAT and SAT, and positively with LOX-1 mRNA expression only in VAT.
Conclusions
In this study we demonstrate the positive association in the adipose tissue between the mRNA gene expression level of HIF-1α, a hypoxia marker, and different scavenger receptors.

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EP824

Pro-inflammatory cytokines responses to acute exercise in athletes and sedentary controls: association with body composition and insulin sensitivity

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Balance between pro- and anti- inflammatory cytokines is necessary for the physiological functioning of the immune system. A chronic systemic inflammation is one of the causes of insulin resistance in obesity.
The aim of this study was to investigate the pro-inflammatory cytokines and visfatin response to an single bout acute exercise in athletes and non-athletes, as well as the possible relationship pro-inflammatory cytokines with body composition and insulin sensitivity.
Fifteen athletes with high percentage of body fat (the elite water polo players) and fifteen sedentary subjects participated in this study (age (years) 20 ± 2; 20 ± 1, respectively). All subjects were exposed to anthropometric measurements and one bout exercise test on treadmill in order to examine acute changes of cytokines. Blood samples were obtained at baseline levels, immediately after the exercise test and 30 minutes after recovery. Separated serum or plasma were used for cytokines (MIF, IL-17 and IFNγ) and hormone (visfatin, insulin) ELISA analysis and glucose measurement. Insulin resistance index (HOMA-IR) was calculated. Only, IL-17 level was significantly higher at rest and at the end of the test in athletes compared to non-athletes ($P<0.05$). In athletes, MIF and visfatin concentration increased significantly after exercise, but in recovery visfatin reduced and MIF increased ($P<0.05$). IFNγ level in both groups was significantly lower in recovery compared to the end of the test ($P<0.05$). There is no significant correlation between the parameters of body composition and concentrations of pro-inflammatory cytokines in the baseline values in both groups. In non-athletes, HOMA-IR was positively correlated with the level of IFNγ and IL-17 ($P<0.05$).
In conclusion, our findings show that acute exercise leads to an increase in pro-inflammatory cytokines in athletes. The positive correlation between pro-inflammatory cytokines and HOMA IR in sedentary subjects may indicate reduced insulin sensitivity and increased risk of earlier development of the metabolic syndrome.

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EP825

Physical function, quality of life and energy expenditure during activities of daily living in post-bariatric surgery patients and obese individuals

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Introduction
Bariatric surgery (BS) is an effective method to weight loss, however, some patients experience persistence of physical inactivity or even weight gain over the years. Furthermore, It is not clear if some surgical techniques, mainly those with disabsortive components, could be involved in the low physical performance through interfering with nutritional status This study aimed to evaluate physical function (PF), quality of life (QOL) and energy expenditure (EE) during activities of daily living in post-BS patients compared with obese individuals without BS.
Methods
Forty two subjects were included in the study: 21 post-BS patients (3 to 4 years post Roux-en-Y gastric bypass technique) with stable weight for at least 6 months (16 women, 41 ± 11 years old, BMI $=28\pm4$ kg.m^{-2}) (group PO); and 21 obese individuals without BS (16 women, 44 ± 9 years old, BMI $=44\pm6$ kg.m^{-2}) (group OB). PF was objectively assessed by the Glittre and Modified Glittre Activities of Daily Living (ADL) tests. QOL (SF-36), EE was assessed by the multisensor sensewear armband activity monitor during ADL, and the body composition was determined by bioelectrical impedance.
Results
OB group had worse PF (OB $=224\pm76$ seconds; PO $=143\pm39$ seconds; $P<0.0001$) as well as QOL ($P<0.05$ for all SF-36 domains) when compared to PO group. OB had also higher total EE in the Glittre ADL-test; however, 63% of the activity time was in low intensity EE. In the Glittre modified protocol, OB had also worse performance than PO when walking up/downstairs, rising/sitting in a chair and moving objects in shelves. In both groups, better PF was moderately-to-strongly correlated with lower percentage of fat mass.
Conclusions
Post-BS patients have better PF, QOL and perform activities under lower total EE than obese subjects, suggesting that BS is involved in recovering physical performance in these patients.

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EP826

The effect of gastric bypass surgery on lipid profile in obese patients with type 2 diabetes mellitus

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Introduction
Few studies have investigated the effect of gastric bypass surgery on lipid profile in obese patients with type 2 diabetes mellitus. We aimed to evaluate changes in lipid profile in obese diabetic patients undergoing Roux-en-Y gastric bypass (RYGB) surgery.
Method
We retrospectively analysed 71 obese type 2 diabetic patients (46 women, 25 men) who underwent RYGB surgery. Weight, body mass index (BMI), total cholesterol (TC), high-density-lipoprotein cholesterol (HDLc), low-density-lipoprotein cholesterol (LDLc) and triglyceride (TG) levels were evaluated before and 3 months after the surgery.
The study was conducted at the Inonu University, Turgut Ozal Medical Center. The same surgery team performed all operative procedures laparoscopically. Institutional ethics committee approved the study protocol.
Results
Mean age of the patients was 44.96 ± 9.66 years. Pre-operative mean BMI and weight were 45.72 ± 8.66 kg/m^2 and 138.78 ± 26.15 kg respectively. 3 months after the surgery both mean BMI and weight significantly decreased to 33.68 ± 6.15 kg/m^2 ($P<0.001$) and 101.55 ± 24.96 kg ($P=<0.001$) respectively.
3 months after the RYGB, there was a significant decrease in TC (213.62 ± 45.33 to 173.50 ± 35.29 mg/dl, $P<0.001$) and TG (272.53 ± 320.96 to 134.93 ± 58.52 mg/dl, $P<0.001$) and HDLc ($40.18\pm9,59$ to 37.19 ± 10.17 mg/dl, $P<0.005$) levels. However, decrease in LDLc (123.31 ± 42.32 to 109.52 ± 30.83 mg/dl, $P=0.126$) level was not statistically significant.
Changes (Δ) from preoperative TC (-40.27 ± 48.74 vs. -26.50 ± 54.70 mg/dl, $P<0.001$), LDLc (12.30 ± 48.02 vs. -11.02 ± 42.33 mg/dl, $P=0.058$) and HDLc (-1.67 ± 11.47 vs. -3.9 ± 9.31 mg/dl, $P<0.006$) levels were more prominent in patients with BMI ≥40 kg/m^2 compared to the BMI <40 kg/m^2 respectively.
Conclusions
Our results indicate that RYGB may have beneficial effects on TC, LDLc and TG but not on HDLc levels in obese patients with type 2 DM. Longer follow up period is required to validate our results.

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EP827

Evaluation of the use of parenteral nutrition premixed bags vs individualized nutrition in our hospital

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Introduction
Parenteral nutrition (PN) is indicated in patients in which gastrointestinal tract is inaccessible or is severely affected. In our hospital, specialists often use commercial three-compartment bags of PN that provide standard nutritional requirements regardless a total parenteral nutrition (TPN) with macro and micronutrients adjusted to each patient by Endocrinology and Nutrition Service.
Objectives
To assess the use of commercial premixed PN with respect to TPN with adequate daily requirements.Material and Methods: Cross-sectional study carried out during four months in patients who are treated with commercial premixed PN in our hospital. Pharmacy provided us the list of patients treated with that preparations. We collected the following variables: who indicates it, reason, duration, degree of malnutrition, monitoring performed and decision after our evaluation.
Results
Data from 104 patients were analyzed, 63% men. Average age: 63.5 ± 16.8 years. Reason for hospitalization: 58.8% elective surgery, emergency surgery 20.5% and 20.5% others. Reason to start commercial PN: 39.6% postoperative ileus, need of intestinal rest 36.6% and obstruction 6.9%.Our performance was accomplished by specialist interconsultation in 66.7% and the rest was for listing of Pharmacy (not advised by their attending physician).Mean time with commercial PN: 2.4 ± 2.1 days; 1.97 days in patients with interconsultation specialist vs 3.5 days when we were advised by Pharmacy ($P = 0.001$). 37.9% had moderate malnutrition and 35.6% had severe malnutrition.Commercial PN covered calories requirements in 21.1% and protein requirements in 5.6%. 22.8% had no indication of PN. 46.9% of the prescribed commercial PN advised by pharmacy were wrongly indicated vs 9% of commercial PN advised by interconsultation After our evaluation: 70.3% were changed to TPN and 19.8% were suspended.
Conclusion
Despite the availability of a Endocrinology and Nutrition Service, there are a high percentage of patients who are administered commercial premixed PN without adequate indication and a high percentage of patientsin which daily nutritional requirements are not warranted and need an individualized parenteral nutrition. ($P = 0.001$)
After our evaluation: 70.3% were changed to TPN and 19.8% were suspended.
Conclusion
Despite the availability of a Nutrition Service, there are a high percentage of patients who are administered commercial premixed PN without adequate indication and a high percentage of patientsin which daily nutritional requirements are not warranted and need an individualized parenteral nutrition.

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EP828

Hormonal response to physical exercise

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Aims
The effects of physical exercise on the endocrine system were monitored.
Material and method
The study included 60 young and healthy subjects.
The subjects were divided into two groups:
– group A (30) performed anaerobic exercise for 50 minutes: running on the treadmill at a speed of 8 km/hour, walking on the treadmill at a speed of 5 km/hour, and running on the treadmill at a speed of 8 km/hour;
– group B (30) performed aerobic exercise for 50 minutes: running on the treadmill at a speed of 15 km/hour, walking on the treadmill at a speed of 5 km/hour, and running on the treadmill at a speed of 15 km/hour.
All the studied subjects underwent the measurement of GH, PRL, cortisolemia, cathecolamines, insulinemia, estradiol before exercise, at the end of exercise, at one hour, 6 hours and 24 hours after exercise.
Results
During physical activity, a significant increase of GH in both groups occurred; the values remained high at one hour after exercise.
PRL increased during physical training proportionally to the difficulty of training in all the studied women, and returned to its initial value after the cessation of training.
Cortisol varied proportionally to the intensity of training. Physical exercise determined an increase of catecholamine secretion; the response was more marked for noradrenaline.We found a significant depression of insulin;estradiol secretion increased significantly in both groups of women;the values remained high at 24hours after cessation of physical training.
Conclusion
The imbalance between energy consumption and the much higher energy expenditure causes the onset of neuroendocrine mechanisms of adaptation of the body to increased physical exercise.

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EP829

Predicting the risk of colonic adenomatous polyps in obese patients by TANITA: a new and practical method

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Background/aim
Visceral obesity rather than generalized obesity has been recognized as a risk factor for development of colonic adenomatous polyps. We aimed to to find out whether there is association between the obesity parameters determined by TANITA such as fat percent, body mass index (BMI) and visceral fat rating and prevalence of colonic adenomatous polyps.
Material and methods
We conducted a cross-sectional study using a consecutive series of 231 cases who underwent colonoscopy during December 2012 to September 2013 at the Cumhuriyet University Hospital. The device TANITA BC 420 MA High Capacity Body Composition Analyser with integral printer(Tokyo, Japan) was used for determining obesity parameters mentioned above.
Results
We have found in our study that there was not any association of body mass index with colonic adenomatous polyp prevalance. However we have found that patients described as overweight and obese had significantly higher colonic polyp prevalance than patients described as healthy. We also found that patients with a visceral fat rating of >12 had a nearly three fold prevalance of adenomatous polyps.
Conclusion
In conclusion for the first time in the literature we used TANITA measurements to predict the patients at risk of colonic adenomatous polyps. We think that our finding of nearly three fold increased prevalance of adenomatous polyps above the cut off visceral fat value of 12 is important and can help us detect which patients need screening colonoscopy. However studies with larger number of patients are neeeded to confirm our results.
Keywords: Colonoscopy, colonic adenomatous polyps, TANITA, visceral fat rating

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EP830

Identification of adipogenesis specific microRNAs

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Introduction
Obesity associated with the risks of metabolic syndrome is a rising problem in Western societies but shows a wide depot- and sex-specific variation. A better understanding of the regulatory mechanisms underlying this different depot- and

sex-specific role is crucial to identify potential diagnostic and therapeutic targets. MicroRNAs are recently recognized important players in adipogenesis and fat metabolism. They post-transcriptionally regulate diverse biological processes, e.g. the proliferation and differentiation of cells. Here we studied the depot and sex hormone-specific regulation of microRNAs during differentiation. Methods: Inguinal (ING) and epididymal (EPI) white adipose tissue (WAT) of SV40 transfected, stable murine cell lines were used to evaluate fat depot specific expression profiles of selected microRNAs during the development from preadipocytes to mature fat cells both under control conditions and when chronically stimulated with dihydrotestosterone (DHT). Using a microarray approach microRNA candidates which were differentially regulated were identified. Adipocyte differentiation was monitored by Oil-Red-O staining and western blot analysis. Quantitative reverse transcription polymerase chain reaction (RT-qPCR) and western blot were used to validate and characterize candidate microRNAs and their possible targets. These results were confirmed as well in *ex vivo* separated preadipocytes and mature adipocytes from murine and human WAT depots. Results: In the present study we identified a panel of new microRNAs not related to adipogenesis so far. DHT stimulation decelerates the adipogenesis in both WAT depots, although effects are stronger on EPI WAT differentiation. In line with this, in both WAT depots the expression of most of the analyzed microRNAs decrease in DHT stimulated cells, compared to control treated cell. Conclusion: We identified new microRNAs whose expression is induced during adipogenesis and whose expression extent differs between inguinal and epididymal WAT. These microRNAs, as presumable regulators of adipogenesis, may serve as promising targets for a fat depot directed treatment of obesity.

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EP831

Level of fitness among overweight medical students in Uzbekistan

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Actuality
According to the World Health Organization, the escalating international epidemic of obesity is now the most significant contributor to ill health. More than 30% of US adults are obese, i.e. body mass index (BMI) 30 kg/m^{2,} and it is feared that one in three children born in the early 21st century will develop diabetes with a consequent reduction in lifetime expectancy. In Uzbekistan 20.2% of population is obese.
Aims of study
Examine prevalence of overweight and obesity rate and fitness levels among students of Tashkent Pediatric Medical Institute.
Materials and methods
We examined 104 medical students (24 males and 80 females) with mean age 23 ± 1.6 and 22 ± 1.9 years old respectively: checked their BMI, waist circumference, blood pressure, and also performed fitness test with checking heart rate before and after 20 squats. Heart rate increase percentage of less than 20 referred for excellent, 21–40 – good, 41–65 satisfactory, 66–75 poor, 76 and above – very poor fitness levels.
Results
Fourteen percent of students were underweight (BMI less than 18 kg/m^2), 66% of students had normal weight (BMI 18–25 kg/m^2), 17% overweight (25–29.9 kg/m^2), 3% obese (over 30 kg/m$^{2)}$. 61% of students showed good, 32% had satisfactory, 3.5% poor and 3.5% very poor levels of physical activity. 20% of overweight students were in very poor physical condition, while 25% of underweight students showed satisfactory fitness level.
Conclusion
Obesity rate among students is 3%, but overall rate together with overweight is 20%. Among overweight students 20% were in very poor physical condition.

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EP832

Comparison of Framingham and REGICOR scales for calculating cardiovascular risk in a cohort of patients with morbid obesity

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Introduction
The prevalence of obesity has increased, reaching epidemic proportions. Framingham and REGICOR scales predict the likelihood of developing a coronary event in the next 10 years. The aim of this study was to assess the concordance of these scales in the stratification of cardiovascular risk (CVR) in a cohort of patients with morbid obesity.
Methods
We designed a cross-sectional study in a sample of patients with morbid obesity evaluated from 2005 to 2012. The estimation of CVR at 10 years was determined according to the Framingham-Wilson Score and its adaptation to Mediterranean populations (REGICOR scale). These scales include the following variables: age, sex, total cholesterol levels, HDL cholesterol, systolic blood pressure, presence of diabetes (T2DM) and smoking. Depending on the results, they were classified into 3 categories: low risk ($<10\%$), intermediate (10–20%) and high ($>20\%$).
Results
A total of 211 patients were included. The mean age was 37.9 ± 9.8 years and 157 were female (74%). The mean BMI was 51.13 ± 7.11 kg/m^2. Regarding cardiovascular risk factors, 75 (35.7%) patients had hypertension, 75 (35.7%) dyslipidemia, 62 (29.5%) smoking and 53 (25.2%) T2DM. Total cholesterol mean levels were 197.27 ± 38.85 mg/dl and HDL 44.19 ± 11.53 mg/dl. The results for the estimation of CVR with the REGICOR scale were: 93.9% of patients with low risk, 5% intermediate and 1% high risk, while those with the Framingham score were: 77.2% low risk, 13.9% intermediate and 8.9% high. The mean CVR estimation was 3.08 ± 2.85 with REGICOR versus $6.16 \pm 7.02\%$ with Framingham ($P<0.001$). The Kappa index of agreement between the scales was 0.231.
Conclusion
In our series, the CVR estimated by Frammigham score was superior to that obtained by REGICOR scale. A positive correlation between both scales was obtained but with a fair agreement. These results support the importance of CVR scales adjusted for each population.

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EP833

Lipodystrophia ın a pregnant women wıth unregulated glycemıa

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Introduction
Many endocrinopathies such as acromegaly, Cushing's syndrome (CS), pheomochromocytom and lipodystrophia can be associated with insülin resistance and unregulated diabetes mellitus (DM).
Case report
A 37 –year- and 2 months pregnant women admitted to our out patient clinic for regulation of hyperglycemia. On physical examination; Blood Pressure: 140/95 mmHg, Body Mass Index: 31 kg/m^2, central obesity, acanthosis nigricans, muscles in lower bilateral extremities were thinner than other body areas. Ectopic fat accumulation (buffalo hump) and loss of subcutaneous adipose tissue were detected. She has T2DM which is unregularly, from the beginning of the disease and dyslipidemia and hypertension for 5 years. She have not taken any pharmaceutical agents which can deteriorate glucose metabolism. A lot of tests related to CS were performed at several times. Fasting plasma glucose: 210 mg/dl, HbA1C % 8.6, tryglycerid: 806 mg/dL, HDL-C: 41 mg/dl. Abdomen USG was performed for the fetal assessment and fetal heart's sound was not found. Then, medical abortus was performed. The causes of unregulated DM were searched. For the scan of CS, the venous sampling was obtained in the morning and 08.00 plasma cortisol: 17 mg/dl, ACTH 11 pg/ml, 24 hours urinary free cortisol level: 128 mcg (N:upper limit is: 74 mcg) and night salivary cortisol were normal. Overnight 1 mg dexametazon supresyon test: 1.58 mg/dl and then CS was excluded. Acromegaly, pheomochromocytoma, and thyroid disorders were excluded by scan tests of blood and urinary samples. She diagnosed with lypodystrophia because of specific physical feautures with metabolic abnormalities. Performance of genetically analyses (LMNA, AGPAT-2, BSCLZ, LLNA, ZMPSTE24, PPAR6) and further examination continued.
Conclusion
Like our patient, Lipodystrophia can manifests just a loss of subcutaneous adipose tissue related to severe insulin resistance and unregulated DM.

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EP834

The level of SCD1 in subcutaneous adipose tissue is associated with the presence of metabolic syndrome in morbidly obese patients

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Introduction
The stearoyl-CoA desaturase 1 (SCD1) is an enzyme involved in the metabolism of fatty acids, and seems to be involved in the regulation of atherosclerosis development. In this study we want to check the expression of SCD1 in visceral and subcutaneous adipose tissue and its relationship with the metabolic syndrome.
Methods
We measured SCD1 mRNA and protein expression in visceral and subcutaneous adipose tissue from 25 morbidly obese patients. Patients were classified into two groups based on whether or not to have metabolic syndrome (according to the IDF 2005 criteria).
Results
SCD1 mRNA expression in subcutaneous adipose tissue is significantly lower in those subjects with metabolic syndrome ($P=0.036$), while SCD1 protein is significantly higher ($P=0.005$). The subjects who meet the HDL or glucose criteria are those with lower SCD1 mRNA expression and higher SCD1 protein levels. In visceral adipose tissue, no association was found between SCD1 mRNA or protein levels and metabolic syndrome.
Conclusions
The presence of metabolic syndrome in morbidly obese patients seems to be associated with SCD1 levels in subcutaneous adipose tissue.

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EP835

Correlation between selected anthropometric, biochemical parameters and CRP- reactive protein concentration among patients with endocrine disorders

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Introduction
Anthropometric studies are one of the methods, by means of which it is possible to assess patient's nutritional status.
Aim
The aim of this study was to assess the relationship between the selected anthropometric as well as biochemical parameters and CRP- reactive protein concentration among patients with endocrine disorders.
Materials and methods
The studied group involved all patients hospitalized at the Endocrinology Department in the Piekary Medical Centre in Piekary Śląskie from 2nd January 2012 to 31st December 2012 who met the inclusion criteria - 299 subjects (264 women and 35 men). Anthropometric studies and body composition analysis were carried out and results of biological parameters were analysed. The following indices were measured: BMI, WHR, WHtR and biochemical tests as follows: $25(OH)D_3$, CRP and lipid profile. The study was retrospective and non-interventional. $\alpha=0.05$.
Results
Overweight or obesity was observed among 63% group ($N=188$) based of BMI score. Deficiency or serious deficiency of vitamin D was observed among 84% group. The mean concentration of $25(OH)D_3$ was 20.3 ± 8.3 ng/ml; CRP reactive protein 4.7 ± 7.4 mg/l; total cholesterol 212.1 ± 45.4 mg/dl; LDL cholesterol 124.9 ± 42.4 mg/dl; HDL cholesterol 61.5 ± 19.3 mg/dl; triglycerides 135.4 ± 76.3 mg/dl. 36% of patients were found to have high concentrations of CRP. There were observed positive correlation between BMI and CRP-reactive protein ($R=0.33$; $P<0.0001$); WHtR and CRP-reactive protein ($R=0.38$; $P<0.0001$); WHR and CRP-reactive protein ($R=0.26$; $P<0.0001$); percentage of body fat and CRP-reactive protein ($R=0.26$; $P<0.001$); waist circumference and CRP-reactive protein ($R=0.26$; $P<0.0001$).
Conclusions
Induction of inflammation was observed in all patients with abnormal body weight. Inflammation intensity (determined on the basis of CRP-concentration) was higher in overweight than obese patients.

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EP836

Retinol-binding protein 4 expression in subcutaneous neck adipose tissue and serum in patients with and without metabolic syndrome

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Retinol-binding protein 4 (RBP4) is considered as an important mediator of insulin resistance and metabolic syndrome (MS). In adipose tissue (AT)) it is mainly secreted from visceral depots. The residual metabolic risk which remains beyond that caused by visceral AT seems to be hold by upper body subcutaneous AT. This large pathogenic depot might be representative by subcutaneous neck AT.
The aim of this study was to examine and to compare RBP4 gene expressions in paired superficial and deep subcutaneous neck AT. We also investigated their associations with metabolic risk factors and serum RBP4.
Samples of both superficial and deep neck subcutaneous AT were taken in 38 patients during routine neck surgery. RBP4 gene expression was analysed by RQ-PCR method. Serum was taken preoperatively to determine insulin, glucose, triglycerides, HDL-cholesterol, C-reactive protein and RBP4. Anthropometric measurements and bioelectric impedance analysis were also performed. Study participants were divided in two groups - with and without MS according to revised NCEP ATP III criteria.
RBP4 gene expressions in AT and serum level were not different between our study groups. RBP4 gene expressions were significantly lower in superficial than in deep AT in the group without MS. In patients with MS different RBP4 gene expressions between layers of AT were not present. In the whole sample of participants superficial RBP4 gene expression positively correlated with fat mass, insulin and HOMA index. Serum RBP4 did not correlate with RBP4 gene expressions, but it correlated with waist circumference, insulin, HOMA index and triglycerides.
Our results indicate that superficial and deep neck subcutaneous AT might have a different secretory profile. Superficial layers with metabolically more favourable aspects are absent in subjects with MS suggesting that dysfunctional changes occur in all layers of upper body subcutaneous AT and might contribute to insulin resistance.

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EP837

Metabolic syndrome and insulin resistance: can they be predicted by clinical indicators in obese prepubertal children?

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Aim
To evaluate whether anthropometric indices and acanthosis nigricans can be useful markers for early detection of Insulin Resistance and Metabolic Syndrome (MetS) in overweight and obese children.
Methods
Data from 510 prepubertal children (40% boys), 12.9% overweight and 87.1% obese with mean age 9.7 ± 2.5 years were analyzed. Logistic regression analysis was used to investigate which factors were associated with HOMA-IR >3 and metabolic syndrome.
Results
MetS was found in 12.9% of the children. HOMA-IR >3, was found in 14.3% of overweight and 39.8% of obese children. Among children with MetS, 50% had

HOMA-IR >3 and they were all obese. The mean Body Mass Index (BMI) was greater in children with HOMA-IR >3 (29.3±3.1 vs. 26.1±3.1, $P<0.001$) (OR:1.31, 1.20-1.44). Also, children with HOMA-IR >3 had greater waist circumference (mean±SD: 94.7±9.6 vs. 85.6±10.4, $P<0.001$). Acanthosis Nigricans (OR=2.42, 95% CI: 1.23 – 4.79, $P=0.011$) and increased %fat (OR= 1.14, 95% CI: 1.05 – 1.25, $P=0.003$) were associated with greater likelihood for HOMA-IR >3. Waist-to-height (WHtR) was associated with greater odds for HOMA-IR >3 (OR=1.07, 95% CI: 1.02–1.18, $P=0.013$). Furthermore, increased WHtR tended to be associated with the presence of MetS (OR=1.07, 95% CI: 0.99 – 1.16, $P=0.100$), while for one unit increase in BMI the likelihood for MetS was found to increase about 16% ($P=0.001$).
Conclusion
The severity of obesity as evidenced by BMI, the presence of waist circumference to height ratio higher than 0.5**,** as well as the presence of Acanthosis Nigricans are clinical indicators for increased metabolic risk.
Keywords: Acanthosis Nigricans, insulin resistance, metabolic syndrome
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EP838

Association of sex hormones with metabolic syndrome among Egyptian males

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Metabolic Syndrome (Met S), is associated with increased risk of cardiovascular disease (CVD) and mortality, the presence of 1 or 2 components of the (MetS) increases overall mortality compared with the absence of any component of the (MetS). Epidemiological studies have shown that low testosterone is associated with MetS. While testosterone levels decline with age, Estradiol (E2) levels remain relatively stable resulting in a decreased testosterone: E2 ratio (T:E), Whether theses hormonal pattern changes play a role in the development of Met S should be further assessed.
Objective
To study the relation between endogenous sex hormones with different components of MetS.
Design
The study was conducted on 80 egyptian males divided into Gr 1: 40 males with Met S and Gr 2:40 healthy males of matched age.
Results
Gr 1 had significant higher body mass index(BMI)(Gr 1:32.3±3.8, Gr2:28.4±4), Waist circumference (WC) (Gr1:110.5±7, Gr2:100.7±6.4) systolic blood pressure (SBP) (Gr1:135.5±12.1, Gr2:117.3±3.6), diastolic blood pressure (DBP) (Gr1:94.3±10.6, Gr2:74.9±3.4) cholesterol (Gr1: 275.4±32.2, Gr2:155.7±29.9) LDL (Gr1:175.4±34.9, Gr2:77.8±31.1) TG(Gr1:301.6± 29.9, Gr2:138.3±24.5) Fasting blood sugar (Gr1:111.1±6.9,Gr2:90.8±9.5) Fasting insulin (Gr1:6.9±1.6, Gr2:4.1±1.7) HOMA-IR (Gr1:1.89±0.48, Gr2:0.93±0.39) E2 (Gr1:20.3±4.3, Gr2:14.6±5.6) and significantly lower HDL (Gr1:39.6±7, Gr2:50.2±4.8).Gr 1 had significant lower testosterone (2.1±0.64) than Gr2(3.27±0.58) lower T:E ratio (Gr1: 0.11±0.05, Gr2: 0.25± 0.09), and significant higher E2 (Gr1: 20.3±4.3, Gr2: 14.6±5.6) testosterone was significantly inversely correlated with weight, BMI, WC cholesterol, LDL, TG, FBS, Fasting insulin and HOMA-IR and positively correlated with HDL.E2 was significantly positively correlated with cholesterol, LDL, FBS, fasting insulin and HOMA-IR, Cutoff value for E2 (>16.78) with sensitivity 92.5% and specificity 82.5% and cutoff value for testosterone (<2.37) with sensitivity 67.5% and specificity 95%.
Conclusion
Patients with MetS had significant lower testosterone and T:E2 ratio and significant higher E2.Testosterone and E2 are significantly associated with various components of the MetS.
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EP839

Bad eating habits among type II diabetic patients at tertiary hospital: a case-control study

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Background
There is a strong association between type II diabetes mellitus (DM) and gaining weight. Lifestyle modification is an important factor for weight management to overcome the obesity as well as DM epidemics.
Aim of study
To find the differences of eating habits and Rosenberg Self-Esteem between DM patients and control and to find the strongest contributor of risk factors by study groups.
Methods
A hospital-based matched case-control study design was carried out on (250) patients with DM and control seen at Diabetic and Endocrine Centre and other outpatient clinics in Tertiary Teaching Hospital. A binary logistic regression model was used and a P-value of ≤ 0.05 was considered statistically significant.
Results
There were significant mean differences of Bad Eating Habits by study groups among all statements except (How many times did you sleep less than five hours at night). There were significant mean differences of Rosenberg Self-Esteem by study groups among for the statements (1, 3, 5, 8, 9 and 10). (35.2%) of DM patients had high Bad Eating Habits and Rosenberg Self-Esteem levels. There were direct weak significant correlations of Bad Eating Habits and Rosenberg Self-Esteem Scales by DM patients ($r=0.286$, $P=0.001$*) and control ($r=0.314$, $P<0.001$*). DM patients were 0.91 and 0.86 less likely to report bad eating habits and high Rosenberg Self-Esteem than control, respectively. DM patients were 19, 18 and 3 times more likely to have brothers and parent with DM than control as well as to have high HBA1c, respectively.
Conclusion
Assessing eating behaviors of diabetic patients as a routine nutritional assessment is an important implication in patient's health. Therefore, considering the complex association between diabetes and its health related consequences, there is a considerable need for educating diabetic patients.
Keywords: Bad Eating Habits, Type II Diabetes Mellitus, Rosenberg Self-Esteem Scale, HBA1c, waist circumference
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EP840

"The menstrual disorders in women with obesity in fertile age"

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The aim
To examine menstrual disorders in women with obesity in fertile age.
Material and methods
We observed the reproductive health of 25 women with obesity and infertility (1 st group). Second group of patients consisted from 25 healthy women without obesity. The age of patients of 1 st group was from 20 to 39 years old, in average 28.3±0.64. The age of patients of 1 st group was from 22 to 37 years old, in average 30.4±0.51/
To all patients have been conducted spectrum of investigations, which include clinical, biochemistry – whole blood and urine analysis, lipid spectrum, radioimmune hormonal analysis of the blood (prolactin, LH, FSH, insulin, estradiolum, testosterone, progesterone, free thyroxin, dehydroepyandrostendione, 17 oxyprogesterone), antimuller hormone). Besides of this, electrocardiography, ultrasound investigation of uteri and ovarium during 11–14 days of periods, and MRY of pituitary.
The results of the study
The investigation of hormonal profile of 1 st group showed that hormonal profile of 1 st group showed that average level of hormones in 14 day of periods was follow: LH- 21.1±2.1 mME/l (average norm - 28.7 mME/l), FSH -4.7±0.5 mME/l (average norma 22.1 mME/l), prolactin – 5.1±0.5 mmol/l (average norm is 5.7 mmol/l), free testosterone – 4.6 ng/ml (average norm < 1.0 ng/ml). Then, in 1 group of patients were found more low data of average levels of LH, FSH, free testosterone. The level of ACTH, TSH, free thyroxine and cortisol were normal.
Conclusions
We established, that in fertile age women with obesity in the basis if menstrual dysfunction take place hyperandrogenic anovulation on the condition of hyperinsulinemiya.
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EP841

"The ultrasound data of gonads in women with obesity in fertile age"

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The aim
To examine the ultrasound data of gonads in women with obesity in fertile age.
Material and methods
We observed the reproductive health of 25 women with obesity and infertility (1 st group). Second group of patients consisted from 25 healthy women without obesity. The age of patients of 1 st group was from 20 to 39 years old, in average 28.3 ± 0.64. The age of patients of 1 st group was from 22 to 37 years old, in average 30.4 ± 0.51/
In 1 st group women were distributed depend from body mass index (BMI) into 3 subgroups: with obesity of 1 st degree: (BMI = 28.0–30.9) — 7 (28%), with obesity of 2 degree (BMI = 31.0–35.9) — 8 cases (32%), with 3 degree of obesity (BMI = 36.0–40.9) — 10 women (40%).
In second group 23 (92%) women have normal BMI data (BMI = 20.0–25.9), and 2 patients (8%) — with deficits I of weight (BMI < 18.5).
The results of the study
The results of folliculomeriya showed high frequency of cases of follicul's persistencia y 18 (30%), anovulation 14 (23.3%) and atresia of folliculis 12 (20%), hypoovulatory syndrome - 8 (13.3%). The normal ovulatory period was found in 6 women (10%). Then, ultrasound investigation is noinvasive, access and sensitive method of evaluation of menstrual cycle and process of ovulation in women of fertile age with obesity.
Conclusions
We established, that in fertile age women with obesity in structure of disorders of periods more frequently be found secondary amenorrhea - 8 (32.0%), follicul's persistencia y 18 (30%), anovulation 14 (23.3%) and atresia of folliculis 12 (20%).

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EP842

Using on-line program of good nutrition and right diet helps to fight against obesity

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Introduction
It is too much easier and cheaper to obesity, than in the future to treat diabetes mellitus and its complications.
Materials and methods
We used an online system for patient education based on the video lessons, full of humor, pictures, and cartoons to convey the necessary information on good nutrition, necessary to do exercises and the need for exposure to the sun to our patients.
Study results
Watching the short movies, the patients formed the habits of good nutrition during the first month already, which includes a diet with restriction of fat, digestible carbohydrates and daily consumption of low-fat dairy products, slow carbohydrates, protein and fiber. Were also presented recommendations for compliance with the physical activity, as well as vitamin D consumption.
A patient was in touch with a doctor-endocrinologist, if he has any additional questions.
We examined data from a survey of 50 patients registered in the online system and 20 patients control group who were given the same recommendations on the appointment.
Surprisingly, persistent decrease in body weight by an average of 5.5 kg over 6 months was demonstrated in all patients of the main group, the consumption of milk and dairy products increased by 2.6 times, compared with patients in the control group. The exposure to the sun was observed 15 to 30 minutes daily, compared with the control group 5–10 minutes. Regular physical activity were the main group of 260 minutes per week, in control group 80 minutes per week.
Conclusions
So, we need to improve the quality of information material, including using online technologies to improve the quality and duration of life of our patients.

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EP843

Hypogonadotropic hypogonadism and obesity, what came first?

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Introduction
Morbidly obese patients raise many problems in therapeutic attitude, sometimes associating a cluster of obesity-related abnormalities: hypogonadotropic hypogonadism, metabolic syndrome, respiratory insufficiency, and high risk for cardiovascular disease. These afflictions can be reversed through weight loss, especially in young patients.
Case presentation
We present the case of a 41 year old male patient, smoker, with morbid obesity (BMI = 63 kg/m^2), who came to our clinic for investigations regarding 90 kg weight gain in the past 5 years, daytime sleepiness and sleep apnea observed by the family. Clinical evaluation revealed mild hypertension, tachycardia, skin hyperpigmentation, bilateral gynecomastia, and ochre dermatitis.
Paraclinical tests showed isolated hypogonadotropic hypogonadism with a testosterone level less than a quarter of the normal plasma value, testosterone = 53.3 ng/dl (*N*: 330–805 ng/dl), FSH = 1.11 mIU/ml (0.1–12.4 mIU/ml), LH = 3.69 mIU/ml (*N*: 0.1–8.6 mIU/ml), inflammatory syndrome, hypercholesterolemia, type 2 diabetes, normal renal and liver function. The patient had no prior investigation of the pituitary-gonadal axis. Pulmonary function tests showed moderate restrictive ventilatory disfunction, and after performing polysomnogram evaluation, he was diagnosed with severe sleep apnea syndrome and obesity-hypoventilation syndrome. CPAP therapy was started, improving the symptoms and diminishing daytime sleepiness. Pituitary imaging to further evaluate the etiology of hypogonadism is required.
Conclusions
Hypogonadotropic hypogonadism in male obese patients can be caused by visceral obesity, or can be a cause for obesity. Patients associating respiratory distress limit the therapeutical options. Testosterone substitution therapy can decrease oxygen saturation and worsen sleep apnea syndrome, leading to sleep cardiac arrhythmia, but more studies are required in this field. The only viable option is rapid weight loss, which can be achieved through bariatric surgery.

Keywords: Hypogonadotropic hypogonadism, obesity, obesity-hypoventilation syndrome, type 2 diabetes
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EP844

The role of smoking in endothelial dysfunction in patients with obesity

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Introduction and aims
Numerous studies in recent years have confirmed the existence of a link between endothelial dysfunction and vascular diseases, and lifestyle factors such as obesity, sedentary lifestyle and smoking.
Methods
We examined 108 patients with obesity (90 women and 18 men, mean age 54.62 ± 0.4 years). All patients underwent clinical and laboratory examination. Vasomotor endothelial function was evaluated by reactive hyperemia using ultrasonic device Aloka SSd-5500 located on the procedure Celermajer and collaborators. According to the formula counts% increase in vessel diameter: endothelium-dependent vasodilation (EDVD) = ((Diameter of the brachial artery after reactive hyperemia - the diameter of the brachial artery source) / diameter of the brachial artery source) × 100%.
Results
The level of smoking patients EDVD significantly higher normal values - the percentage of increase was 6.81 ± 1.08%, while non-smokers - 12.28 ± 1.08%. Patients prone to smoking, level of MAU exceeded the normal value amounted to 26.3 ± 8.22 g/l and in non-smokers - 17.64 ± 1.25 mg/l. Homocysteine levels in non-smokers was 11.47 ± 0.74 mol/l, in smokers - 13.72 ± 0.60 mkml/l.
Conclusions
Obese patients prone to smoking have a sign of endothelial dysfunction.

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EP844B

Effect of supplementation with chitosan on food intake, weight gain, and cardiometabolic risk indices in Wistar rats fed normal diet *ad libitum*

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Introduction
Prevalence of obesity is increasing globally and in Saudi Arabia in particular. Obesity is associated with increased risk of diabetes and cardiovascular diseases. Therefore, studies to control obesity and its effect on health are important. Chitosan has been recommended as a suitable functional supplement for controlling obesity; and consequently; its associated complications. However, results were inconclusive.
Aim
To investigate the effect of chitosan supplement on food intake, weight gain, glucose homeostasis,insulin resistance, lipid profile, and markers of obesity, inflammation, and oxidative stress in Wistar rats fed normal diet ad libitum.
Animals and Methods
Two groups of three months old male Wistar rats were studied. Group A (Control, $n=10$), fed normal chow, and Group B (Test, $n=10$), fed normal chow with 1% w/w chitosan added. Food was allowed ad-libitum. At the start, then at end of 12 weeks of supplementation with chitosan, rats were weighed, and fasting blood samples were drawn for measurement of glucose, lipid profile, insulin, leptin, gamma glutamyl transferase (GGT), and tumor necrosis factor α (TNF-α). Atherogenic index (AI), HDL:LDL cholesterol, and homeostatic model of insulin resistance (HOMA-IR) were calculated.
Results
Chitosan significantly reduced means of total and LDL cholesterol, serum leptin, triglycerides, and AI, and increased means of food intake, HDL: LDL cholesterol in groups B, compared to group A ($P<0.05$ in all cases). However, there was no significant difference in means of weight, GGT, or TNF-α between groups.
Conclusion
Chitosan increased appetite without additional weight gain, but had no effect on markers of inflammation, and oxidative stress. However, it had beneficial effects on lipids profile, hence may be a good option to reduce risk of diabetes and cardiovascular disease (CVD). More work with dietary control,,measurement of excreted fat, and fecal microbiota might elucidate its action and effect further.

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Paediatric endocrinology

EP845

Safety and tolerability of once-weekly administration of CTP-modified human growth hormone (MOD-4023): phase 2 study in children with growth hormone deficiency

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Objective
Growth hormone (GH) replacement therapy currently requires daily injections. This may cause poor compliance, inconvenience and distress for patients. CTP-modified human GH (MOD-4023) has been developed for once-weekly administration in growth hormone-deficient (GHD) adults and children. In the present Phase 2 study, the safety and tolerability of once-weekly subcutaneous (SC) administration of MOD-4023 were evaluated in GHD children.
Design and methods
Randomized, controlled Phase 2 study conducted in 53 pre-pubertal GHD children receiving SC injections of one of three MOD-4023 doses once-weekly (0.25, 0.48, and 0.66 mg/kg/week) or daily hGH (34 μg/kg/day) as control arm for 12 months. Safety assessments included monitoring of adverse events, injection site reactions, vital signs and physical condition, as well as laboratory assessments, such as glucose and lipid metabolism, blood biochemistry and immunogenicity.
Results
The analysis included safety data for all 53 patients that completed 12 months of treatment with either MOD-4023 ($n=42$ patients) or hGH ($n=11$). No severe adverse events (AEs) were reported during treatment with MOD-4023. Twenty-eight patients (66.7%) reported 101 AEs during treatment with MOD-4023. This rate was similar to that observed for the daily arm, in which 8 patients (72.7%) reported a total of 30 AEs. No evidence was found of injection site-related AEs such as local discomfort, swelling, erythema or lipoatrophy. Laboratory assessments supported the tolerability of MOD-4023 treatment, and no significant overall changes were observed in glucose levels, insulin, HbA1c, or vital signs. No anti-CTP Abs were detected and no neutralizing activity was observed.
Conclusions
MOD-4023 demonstrated an excellent safety and tolerability profile during treatment for up to 12 months using a dose ranging from 0.25 to 0.66 mg/kg/week, with no unexpected AEs considered to be related to MOD-4023. These results support the continued clinical development of once-weekly MOD-4023 for the treatment of children suffering from GHD.

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EP846

Pharmacokinetic and pharmacodynamic modeling of long acting human growth hormone (MOD-4023) in growth hormone deficient children

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Introduction
OPKO Biologics has produced a long-acting human growth hormone (hGH), MOD-4023, containing three copies of a naturally-occurring peptide (C-terminal peptide, CTP) that markedly increases growth hormone's in vivo residence. We describe the development and validation of a pharmacokinetic (PK) and pharmacodynamic (PD) model to characterize the relationship between MOD-4023 dose, serum concentrations (Cserum), and IGF-1 responses in healthy adults, GHD adults, and GHD children.
Design/Methods
MOD-4023 PK and PD were studied following its administration to healthy adults ($N=18$), GHD adults ($N=46$), and GHD children (age 3–11, $N=42$). In children, doses were 0.25, 0.48, or 0.66 mg/kg weekly; Genotropin® hGH ($N=11$, 34 μg/kg daily) was the comparator. Data from healthy adults were used to develop PK/PD models; models were then applied to GHD adults and children. Serum concentrations were fit to a linear compartmental model with first-order absorption and an absorption lag. An indirect response PD model (1) (in which MOD 4023 increases input to IGF-1's central compartment) was applied to serum IGF-1 data. Covariates (age, body size, gender, organ function) were entered into the PK/PD models if justified statistically. Analyses were performed using mixed-effects (population) methods.
Results
In adults and children, a two-compartment PK model fit Cserum well. The indirect response model generally fit IGF-1 well. In children, systemic parameters scaled allometrically; baseline IGF-1 increased with age. The MOD-4023 PK/PD models predict the relationship between administered dose, Cserum, and IGF-1 response with various dosing regimens.
Conclusion
A linear PK model with first-order absorption fit concentration data well. Systemic PK parameters varied with body size. The indirect response model generally fit IGF-1 data in GHD children. Based on the analysis, the model can assist in safety monitoring, and guide dose modifications. This model may be used to support dose selection and dose modification in future clinical studies.
Reference: 1. Sun et al. JPET 289:1523–1532, 1999

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EP847

The structure of genetically determined types of short stature in Uzbekistan according to retrospective analysis

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Goal
To carry out a retrospective analysis of case histories of children and adolescents with genetically determined types of short stature who admitted a paediatric department of a clinic of Research Institute of Endocrinologyduring 2003–2013.
Materials and methods
An analysis of case histories of children and adolescents with short stature 3 to 17 years who undertook inpatient treatment in paediatric department of RIE clinic during 2003–2013 is carried out.
Results
During 2003–2013, 642 children and adolescents with stunting and disorders of sexual development (236 boys or 36.8% and 406 girls or 63.2%) were hospitalised and examined; of them there were 197 children at the age of 3–11 years (30%) and 455 adolescents aged 12–17 years (70%). Mean age of patients at diagnostics makes 12.7±3.9 years. The following structure of genetically determined types of short stature is found: TS -57.1% (average age 13.8±3.5 years); with multiple deficiency of adenohypophysis hormones (MDAH) – 23%; the ratio between boys and girls made 1.5:1; primordial dwarfism in 5.2%; hypochondroplasia in 4.6%; Noonan syndrome in 3.2%; Sekkel syndrome in 2.4%, Rassel-Silver syndrome in 2.1%; PraderWilli syndrome in 1.5%; Laron syndrome in 0.9%.
Conclusions
Results of the retrospective analysis show:
In Uzbekistan the greatest percent of children and adolescents with genetically determined types of short stature is made by patients about TS and MDAH, in comparison with other genetic variants of short stature;
- Late diagnostics and a low level of detectability of children with genetically determined types of short stature in the Republic.

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EP848

Pediatric case of atypical course of DIDMOAD (Wolfram) syndrome in Armenia

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Introduction
Wolfram Syndrome is a rare autosomal recessive progressive neurodegenerative disorder with estimated prevalence of 1 in 500,000 r, also known as DIDMOAD syndrome for its four most common features (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness). Patients present with nonautoimmune and non-HLA linked diabetes mellitus associated with optic atrophy in the first decade, diabetes insipidus and sensorineural deafness in the second decade, renal tract abnormalities early in the third decade and multiple neurological abnormalities, like cerebellar ataxia, myoclonus, and psychiatric illness early in the fourth decade.
Case report
An 8 years old boy was diagnosed with type 1 diabetes with ketosis on presentation and treated with insulin. However, upon diabetes compensation polydipsia and polyuria continued and the following week diabetes insipidus was diagnosed. MRI of the brain was only significant for posteriorarachnoid cyst 1.5×2.5×1.7 cm between the cerebellar hemispheres. Genetic analysis for Wolfram syndrome was not available at that time, therefore patient underwent annual optic nerve funduscopy, audiometry and ultrasound of the urinary tract. After 5 years, he developed hearing loss and early signs of macular atrophy, as well as ureteral dilation. Finally, genetic analysis was abroad and WFS1 gene mutation was identified.
Conclusion
Taking into account that in some countries genetic analysis for Wolfran Syndrome may not be readily available, annual survey for all the components of the syndrome is recommended. This is especially important in atypical and fast progressing cases of Wolfram syndrome.

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EP849

Evaluation of creatine kinase levels during growth hormone treatment

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Objective
To investigate the changes in serum creatine kinase (CK) levels during the treatment of patients with growth hormone (GH).
Methods
We evaluated 715 cases who were treated with GH retrospectively. The clinical data of 20 children with severe CK elevation (>500 IU/L) were analyzed.
Results
CK elevation was recorded in 96 of the cases (13.5%) during GH theraphy. 20 of these patients had severe CK elevation. The mean age of the cases with severe CK elevation was 11.5±3.4 years and mean serum CK level was 828.9±400.1 (504–2246) U/L. The time elapsed between the beginning of treatment and CK increase was 20.5±12.8 (3–48) months. 8 of the cases used GH formulations containing m-cresol. We found no significant differences in CK levels according to age, gender, height, growth velocity, diagnosis, lenght of the needle used and GH preparations.
Conclusion
Severe CK elevation was found in 2% of the patients on GH treatment. The effects of GH on muscle should be evaluated during follow up.

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EP850

Methylphenidate and central precocious puberty

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Aims
Attention Deficit Disorder & Hyperactivity Syndrome (ADHD) is identify attention deficit,impulsivity hyperactivity before the age of seven years old. ADHD is a serious disease which could cause corruption of daily lifetime and needed to be taken *psychostimulant drugs. This case brings on that these kind of drugs can have unexplored side effects*. In this study; it was reported 7 precocious puberty (PP) cases which *used methylphenidate due to ADHD* and investigated interrelation between methylphenidate and precocious puberty.
Methods
This study consisted 7 cases which used methylphenidate due to ADHD. All the cases with various pubertal complaints were admitted for family history, a detail physical examination, pubertal staging and anthropometric evaluations. Puberty precocious (PP) was diagnosed on the appearance of breast development before the age of 8 years in girls and testes enlargement before 9 years in boys. The initial evaluation of cases with PP included determinations of height, weight, pubertal stage, bone age, pelvic ultrasound, neuroradiological imaging and evaluation of the hypothalamic-pituitary-ovarian axis by measuring basal and GnRH stimulated LH and FSH peaks, and the plasma concentration of estradiol. Patients were followed for at least 6 months after diagnosis was made.
Results
The study group consisted 7 precocious puberty (PP) cases (4 girls, 3 boys; the mean age 10.7±2.9 years old) with ADHD. Breast development in 4 girls and testis enlargement in 3 boy cases were determined.. Basal hormonal levels (thyroid-surrenal-prolactin) were normal range. Results of LHRH stimulation tests in all the cases were demonstrated central pubertal responses. Radiologic evaluations of hypotalomohypophisial region were normal in all the cases. One of the cases which developed pubertal progression in follow-up was started on GnRH analoque theraphy.
Conclusion
Glutamine, dopamine and noradrenaline are most important excitatory neurotransmitters that have a role in the starting of puberty. Depending on the effect of *methylphenidate cumulating of dopamine and noradrenaline in the synaps gap could cause inducing puberty by effecting its own receptor*. As a result; using psychostimulant drugs at childhood may accelerate puberty.
Keywords Attention Deficit Disorder and Hyperactivity Syndrome Methylphenidate Central

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EP851

Prepubertal IGF-1 and physical features among egyptians with recently diagnosed type 1 diabetes

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Introduction
T1DM is caused by immune mediated destruction of pancreatic β-cells, leading to partial, or absolute insulin deficiency.The most frequent age of onset is 12 years. IGF-1 is a polypeptide with 70 amino acids and its chemical structure is similar to insulin. IGF-1 is associated with early development and has anabolic effect in adults. IGF-1 regulates many physiological functions, including glucose metabolism, cell survival and proliferation.
Objectives
To compare IGF-1 levels in type-1 diabetic children with that of healthy controls and to find relationship between IGF-1 and physical features in T1DM
Patients and Methods
This study involved 85 children less than 12 years old.Seventy Patients with T1DM selected according to ADA 2014 criteria for diagnosis of diabetes from pediatric diabetes clinic at Ain Shams University hospital divided into 2 groups based on duration of diabetes to T1DM > 1 year duration and T1DM < 1 year duration. fifteen normal children attending the pediatric general clinics as a control group. height, weight, arm span, upper body segment, lower body segment, body mass index, parents height beside Fasting blood glucose, HbA1C, IGF-1, FSH, LH were assessed.
Results
Height percentile significantly higher in T1DM > 1year group median 50 (10 to 75) than T1DM < 1 year (median 10 (3 to 44) *P*-value 0.007). IGF-1 level in group T1DM > 1 year median 90 (70 to 110) (ng/ml) was significantly lower than other groups (*P*-value 0.0008). IGF1 has a significant positive relation with Aram span in group T1DM < 1year (*P*-value 0.024), positive significant relationship between mother height and IGF-1 level in group T1DM > 1 year (*P*-value 0.013).
Conclusion
IGF-1 level is reduced in recent onset T1DM but still can have some effect on somatic features even in the pressence of longstanding diabetes.

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EP852

Puberty spectrum in neurofibromatosis – case reports

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Neurofibromatosis 1 (NF1) is a rare disease determined by mutations in the RAS-MAPK pathway. It can cause precocious or delayed puberty.
Case 1
A 11 years 9 months old girl known with Neurofibromatosis – Noonan Syndrome (NF-NS) was admitted for severe growth deficit (-5.14 SDS). She had over 20 café au lait spots, hypertelorism, pterigium colli, B1 P1. At 18 months she had had surgery for pulmonary stenosis and after that a left ventricular tumor proved to be neurofibroma at biopsy. She had low IGF1, normal thyroid function and empty sella on MRI. Her bone age was 8. hGH therapy was started with satisfactory results. After 2 years, at a bone age of 13 she showed no signs of puberty. A triptorelinum test was negative. She was diagnosed with delayed puberty and estrogen was started with good results.
Case 2
A 5 years old boy was admitted for pubertal evaluation. The clinical exam showed a tall child (+2.79 SDs) with café au lait spots and subcutaneous neurofibromas. He was G4 P2 with a 25 ml testicular volume. A triptorelinum test confirmed central precocious puberty. Bone age was 10. The cerebral MRI showed multiple neurofibromas and a hamartoma in the third ventricle. He was diagnosed with NF1 and central precocious puberty. Treatment with triptorelinum was started. At 7 years he presented a seizure and a MRI showed an infiltrative tumor in the right thalamus. The biopsy showed a pilocytic astrocytoma. Radiotherapy and chemotherapy were started and continued for 18 months with monthly iv treatment. The evolution was favorable and a MRI after the completion of treatment showed no residual tumor. At the age of 9.6 years treatment with triptorelinum was stopped and puberty resumed. He was 1.65 DSD with a bone age of 13.
Conclusions
NF1 can cause all types of pubertal abnormalities and patients should be monitored closely.

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Pituitary – Basic

EP853

Human non-functioning pituitary tumors invasiveness: inhibitory effects of dopamine receptor type 2 (DRD2) agonist and cofilin involvement

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Non-functioning pituitary tumors (NFPTs), although benign in nature, frequently present local invasiveness that strongly reduces neurosurgery success. Medical therapy is still under debate, although dopamine (DA) receptor 2 (DRD2) agonists may induce tumor shrinkage in some patients. Aims of this study were: 1) to evaluate the effect of DR2D agonist BIM53097 on migration and invasion of NFPT cells, 2) to investigate the molecular mechanisms regulating the motility of these cells, focusing on the role of cofilin, an actin severing protein involved in actin remodelling required for migration, 3) to test cofilin expression and its phosphorylation levels in NFPT tissues characterized or not by invasion of the cavernous sinus.
Our data demonstrated that BIM53097 significantly reduced migration (-42±6% $P<0.05$) and invasion (-32±2%, $P<0.01$) and increased about 4-fold cofilin phosphorylation at Ser3 in cultured cells derived from human surgically removed NFPTs, these data being replicated in HP75 cell line. Both these effects were completely abolished by an inhibitor of ROCK, a Rho-associated kinase involved in cofilin phosphorylation. The overexpression of wild type or phospho-deficient (S3A) cofilin in HP75 cells increased cell migration (+49±6% and +57±9% *vs* empty vector, respectively, $P<0.05$), suggesting a causal role for active (dephosphorylated) cofilin in cell motility.
Interestingly, we observed that most invasive tumors showed nearly absent P-cofilin, in contrast to high levels of P-cofilin showed by most non-invasive tumors by both immunohistochemistry and western blot analysis (0.008 and 0.524 median P-cofilin/tot-cofilin ratio, respectively, $P<0.05$).
In conclusion, our data demonstrated that DRD2 agonist reduces NFPT cells migration and invasion through a molecular mechanism that involves ROCK-dependent phosphorylation of cofilin. Moreover, NFPT invasion of the cavernous sinus associates with increased active (dephosphorylated) cofilin, suggesting that cofilin phosphorylation status might be a novel molecular marker of the invasive behaviour of NFPTs.

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EP854

AIP inactivation leads to pituitary enlargement in the Zebrafish embryo model

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Introduction
Patients with aryl hydrocarbon receptor-interacting protein (AIP) gene mutations are predisposed to large, invasive, GH- or PRL-secreting pituitary tumours, occurring at a younger age and poorly responsive to treatment. The zebrafish (ZF) model provides anatomical and functional similarities to human neuroendocrine system.

Methods
AIP knock down (KD) ZF embryos were generated using antisense morpholino oligonucleotides injected at one-cell stage. Control embryos were injected with 5-base mispaired oligonucleotide as control morpholinos (CM). Wild type (WT) embryos from the same batch served as uninjected controls. All embryos were incubated in the same conditions for 5 days, and observed during development. At 120 hours post fertilization (hpf) whole mount immunostaining of all embryos was performed with anti-PRL antibodies (rabbit anti-salmon polyclonal 1:2000). A total of 15 embryos (5 from each group) were randomly selected for digital microscopy. Pituitary staining was assessed by image analysis software (NIH ImageJ 1.48v).
Results
Overall developmental delay and retardation was observed in the AIP KD compared to WT and CM control groups. KD embryos exhibited reduced total body length, transitory midbrain enlargement, pericardium enlargement and swim bladder under-development. Assessed by the PRL staining, pituitary in the AIP morphants appeared to be larger, ventrally shifted and round shaped compared to oval or kidney shaped pituitary in the WT. Pituitary size in AIP morphants ($1621.9 \pm 87.2\ \mu m^2$) was significantly larger then in WT ($574.1 \pm 357.8\ \mu m^2$ $P=0.04$) and CM ($626.0 \pm 223.6\ \mu m^2$ $P=0.02$) with no statistical difference between the two control groups ($P=0.90$).
Conclusion
AIP Morpholino Knock Down zebrafish embryos demonstrate brain, pericardium, and swim bladder anomalies and general developmental delay, pointing to wide developmental role of AIP gene. AIP morphant embryos exhibit larger surface of PRL immunostaining in the pituitary compared to controls suggesting possible increase in proliferative activity (hyperplasia or tumour) at pituitary level in the absence of AIP gene function.

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EP855

Biguanides: A new potential therapeutic option for pituitary tumors?

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Pituitary adenomas (PA) comprise a commonly underestimated pathology in terms of incidence and associated morbimortality. Somatostatin and dopamine analogs constitute the main medical treatment for PA. However, an appreciable subset of patients are resistant or poorly responsive to these drugs, and hence, the search for new therapies to control tumor growth and/or hormone secretion is crucial. Biguanides such as metformin (MF; commonly used to treat type-2 diabetes), phenformin (PF) and buformin (BF) have been shown to exert antitumor actions in different tumor types, but their actions in PA cells have not been reported. The aim of this study was to determine the effect of these biguanides on key functional parameters (i.e. cell viability, hormone secretion, calcium signaling) in human PA cell cultures: 7 corticotropinomas (ACTHomas), 5 somatotropinomas (GHomas), and 3 non-functioning PA (NFPAs). Expression profile of somatostatin (ssts) and dopamine receptors (DRs) showed typical receptor profiles for each pathologies (ACTHomas: sst5 > sst2 > sst1; GHomas: sst5 ≥ sst2; NFPAs: sst3 ≥ sst2; and DR2 was the most abundant DR in all these PAs). Interestingly, MF moderately, albeit consistently reduced cell viability in PA cells, while treatment with PF and BF reduced cell viability more noticeably, with the effect of PF very particularly intense in ACTHomas. These effects might involve a calcium-dependent mechanism, since treatment with these biguanides clearly altered the kinetics of cytosolic free calcium. Finally, MF and BF showed a non-significant trend to reduce ACTH secretion in corticotropinomas, whereas, in primary pituitary cell culture of two primate species, MF significantly decreased ACTH and GH release. Taken together, our results reveal a clear inhibitory effect of biguanides on PA cell viability *in vitro*, and given their demonstrated clinical safety suggest a potential therapeutic role of these compounds for the treatment of patients PAs.

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EP856

Selection and validation of reliable reference genes for RT-qPCR analysis in a large cohort of pituitary adenomas

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Background
Real-time reverse transcription quantitative PCR (RT-qPCR) has become the method of choice for quantification of gene expression changes. Inappropriate data normalization and inconsistent data analyses are some limitations of RT-qPCR. Pituitary adenomas are frequent tumours and the interpretation of increasingly published data within this field is hindered by the lack of a proper selection and validation of stably expressed reference genes.
Aim
To find and validate the optimal reference gene or combination for reliable RT-qPCR gene expression in both non-functioning (NFPA) and hormone secreting (ACTH and GH) pituitary adenomas.
Material and methods
Thirty commonly used reference genes (PCR array reference gene panel, BioRad, Hercules, CA) were quantified by RT-qPCR in 24 pituitary adenomas (12 NFPA, 8 GH and 4 ACTH). Data were analyzed using three programs: GeNorm (Qbase+), Normfinder and BestKeeper having different algorithms to identify the most stable reference gene/combination of reference genes. The top candidate genes were validated in a larger cohort of adenomas (144 NFPA, 63 GH and 19 ACTH).
Results
In all adenomas, ALAS1 and PSMC4 were the most stable reference genes as estimated by GeNorm and Normfinder, whereas Bestkeeper ranked RPL30 and RPS17 as the two most stable genes out of 10 carefully selected genes. The best gene combination was ALAS1 and PSMC4 (GeNorm) or PSMC4 and GAPDH (Normfinder). The validation experiment (GeNorm) showed that ALAS1 and PSMC4 in NFPA and PSMC4 and GAPDH in hormone secreting adenomas were the most stable gene combination. The best ranked reference genes were not identical in different subgroups of adenomas.
Conclusions
Differences in stability between top-ranked genes in the reference gene selection programs were minor. PSMC4, ALAS1 and GAPDH were stably expressed in pituitary adenomas and a combination of two of them will serve as the most robust choice of reference genes.

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EP857

Combined clinical and gene expression profiling in human ACTH-secreting pituitary tumors

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Introduction
We have previously reported on the considerable variability in ACTH-secreting pituitary adenomas in terms of responses to major modulators *in vitro* (Pecori Giraldi et al J. Neuroendocrinol. 2011). Further studies revealed also differences in gene expression profiles in specimens analyzed by microarray analysis. Aim of this study is to correlate transcriptome expression pattern in archival human ACTH-secreting adenomas with clinical features of patients prior to and after surgery.
Methods
Forty human ACTH-secreting pituitary adenoma formalin-fixed paraffin-embedded specimens were cut into 20 μm thick sections and RNA extracted using Recover All Total Nucleic Acid Isolation Kit (Invitrogen, Carlsbad CA, USA). RNA (300 ng) was hybridized to Human HT-12V4 expression bead Chip (approx 29000 transcripts) and analyzed with WG-DASL-HT assay (Illumina, San Diego CA, USA). Patients' clinical charts were reviewed and data analyzed by Principal Component Analysis (JMP, Statistical Discovery, SAS Institute,

Cary NC, USA). Combined clinical and expression analysis was perfomed on R-studio and functionality of identified genes assessed by DAVID and Cytoscape.
Results
Clinical and expression data clustered in three major groups, with 18, 4 and 18 patients, respectively. 1259 genes were significantly expressed ($P<0.001$) and clinical variables which proved predictive of clustering were adenoma size and plasma ACTH concentrations. Differential expression analysis among clusters revealed up- and downregulation of several hundred genes which could be annotated to functions including granule lumen (enrichment score 2.6), phosphorylation (enrichment score 2.07), aminoacid ligase (enrichment score 2.08) and ubiquitin pathway (enrichment score 1.8).
Conclusion
Combined clinical and gene expression analysis of human ACTH-secreting adenomas allowed the identification of three major clusters. Functional annotations revealed the involvement of distinct pathways in individual clusters, paving the way to a greater understanding of the variability of human corticotrope tumors.

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EP858

Temozolomide has no direct effect on the normal and pathological hormone production in the anterior pituitary and in pituitary tumors

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The chemotherapeutic agent temozolomide (TMZ) has been applied for the treatment of pituitary carcinomas, atypical pituitary adenomas and prolactinomas resistant to dopamine agonist treatment with considerable success. Both shrinkage of the tumors and a drop of excessive hormone production were observed in TMZ-responsive patients. In order to clarify whether the TMZ-induced suppression of hormone secretion was a consequence of tumor shrinkage or caused by direct effects on hormone production we comparatively studied the effect of TMZ on growth and hormone production in the ACTH-releasing AtT20 and in the GH/PRL-secreting GH3 cell lines, in a series of primary cell cultures of human endocrine-active pituitary adenomas and in cell cultures of normal rat pituitaries. In the rapidly growing AtT20 and GH3 cell lines TMZ treatment reduced both cell numbers and hormone secretion but had no effect on hormone production per cell demonstrating that the reduction of hormone secretion was a consequence of the inhibition of growth of these cells. In 11 hormone-secreting pituitary adenomas (5 somatotroph, 1 lactosomatotroph, 2 lactotroph, 2 corticotroph and 1 thyrotroph tumor), in which no or very little effects of TMZ on growth were observed, TMZ did not alter GH, PRL, ACTH and TSH secretion, respectively. Neither basal nor releasing-hormone stimulated secretion of ACTH and GH as well as basal or bromocriptine-suppressed PRL secretion was affected in rat pituitary cell cultures by TMZ. In conclusion, TMZ had no direct effect on hormone secretion in normal pituitary and pituitary tumors indicating that TMZ-induced suppression of hormone levels in patients with pituitary carcinomas may have been a consequence of tumor shrinkage.

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EP859

A C-terminal inhibitor of HSP90 decreases GH-promoter activity and growth hormone secretion in a cellular model of somatotrophinomas

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Heat shock protein 90 (HSP90) plays a pivotal role in maturation and stabilization of proteins in conditions of stress. Many HSP90 client proteins are involved in oncogenic signaling and cancer progression, therefore HSP90 inhibitors have a potential as pharmaceutical agents. We reported a strong HSP90 overexpression in corticotroph adenomas and the treatment with C-terminal HSP90 inhibitors has potent anti-tumorigenic and anti-secretory effects in these tumors *in vitro* and *in vivo*. In the present study, we extended this investigation to the potential role of HSP90 in the pathogenesis of GH-secreting pituitary adenomas. We observed intense HSP90 immunoreactivity in 8 out of 25 GH-secreting pituitary tumors. To study the therapeutic potential of HSP90 inhibition in these tumors, we treated the GH-secreting tumor cell line GH3 with C- and N-terminal HSP90 inhibitors and measured luciferase activity under the control of the rat GH promoter. The C-terminal HSP90 inhibitors KU174 and novobiocin dose dependently decreased GH promoter activity and KU174 was more effective than novobiocin with maximal luciferase inhibition at 4 μM for KU174 (52%, $P<0.05$) and at 100 nM for novobiocin (33%, $P<0.05$) compared to control. In contrast, the treatment with the N-terminal inhibitor 17-AAG did not suppress GH promoter activity. KU174 significantly decreased GH levels, with maximal effect at 4 μM (85% secretion inhibition compared to controls). These results show a putative role for HSP90 in the tumorigenesis of some GH-secreting pituitary tumors and a potential for HSP90 C-terminal inhibitors for the management of excess GH secretion. Further experiments are needed to clarify the role of HSP90 in GH-secreting tumors and the mechanisms driving the inhibitory action of C-terminal HSP90 inhibitors on GH production and secretion.

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EP860

Evidence for better response to somatostatin analogues in acromegalic patients treated with metformin

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Somatostatin analogues (SSA) are the mainstay of pituitary-targeted pharmacological treatment in acromegaly, but are characterized by high incidence of resistance in half of cases. The successful management of acromegaly involves in addition to targeting biochemical control the treatment of the metabolic comorbidities and hypopituitarism. In this study we analysed the impact of the concomitant antidiabetic treatment and hormone replacement on the response to SSA. Data were collected from 49 acromegalic patients: 45 had transsphenoidal surgery (35 as primary therapy), 36 SSA (11 as primary treatment). All patients with diabetes mellitus (25%) received metformin. Hypopituitarism affected 18 patients. Binary logistic regression analysis (SPSS software) showed no correlation between SSA ($P=0.71$) and transsphenoidal surgery ($P=0.541$) on pituitary insufficiency incidence. Regression analysis showed no correlation between IGF-I lowering response to SSA and substitution treatment with hydrocorticosterone, testosterone or L-thyroxin (variance inflation factor <3). Linear regression analysis showed no correlation between age, gender, disease duration, hormone substitution modalities and change of IGF-1 levels after SSA treatment. However, the same analysis showed correlation between metformin therapy and IGF-I levels after SSA treatment ($P=0.031$; R-square change: 0.135; R-square: 0.321). *In vitro* investigation on 7 human acromegalic tumours showed that metformin (500 μM) enhances the GH-suppressive effect of octreotide (1nM) (% of control 63 ± 13 versus 81 ± 12). Metformin alone significantly suppressed GH secretion at the 1mM concentration (64 ± 13) and similar observations were obtained on the rat GH promoter activity and GH secretion from rat immortalized GH-secreting GH3 cells. These preliminary observations indicate that hormone replacement does not affect SSA response, but metformin treatment improves it in terms of IGF-I reduction.

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EP861

The vasoinhibin solution structure appears unfolded, dynamic, and features aggregation

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Background
Full-length human prolactin (protein data bank identification P01236), the precursor of vasoinhibins, is structurally classified as a class-I helical cytokine

with a four-helix bundle core and only a minimal degree of dark regions. Experimental data on the solution structure of vasoinhibins are not available.
Methods
A recombinant, human vasoinhibin with a molecular mass of 16.7 kDa, comprising amino acids 29-176 of prolactin, was expressed in E. coli and purified. Nuclear magnetic resonance (NMR) spectra were obtained (1D 1H, 2D TOCSY, 500/700 Mhz, and 2D NOESY, 950 Mhz). A homology modelling of the expected three-dimensional vasoinhibin structure, employing the I-TASSER web server, was performed. The purified vasoinhibin sample was subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis and Western Blotting was performed using polyclonal and monoclonal, epitope-mapped anti-prolactin and anti-vasoinhibin antibodies.
Results
1D NMR spectra at several conditions of pH, buffer and temperature demonstrated broad vasinhibin signals in a very narrow region with small differences between all spectra. Titration with trifluoroethanol and lithium chloride had minimal effect. TOCSY and NOESY experiments corroborated the results of all 1D experiments. Sodium dodecyl sulfate polyacrylamide gel electrophoresis and Western Blotting analyses demonstrated an anti-vasoinhibin antibody immunoreactive band with an apparent molecular mass of 16 kDa, consistent with the presence of the recombinant vasoinhibin-protein. Further immunoreactive bands of unknown identity with molecular masses of 28 and 35 kDa were detected.
Conclusion
Broad and little dispersion of few NH signals are interpreted as an unfolded vasoinhibin-protein in fast motion. Further NMR-studies are also complicated by possible aggregates of higher molecular masses. The homology model of the vasoinhibin structure did not correspond to NMR-data, and is thus considered unsuitable. The vasoinhibin structure hence retains a high degree of darkness.

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EP862

The silent somatotroph tumours

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Introduction
Silent somatotroph tumours are GH immunoreactive (IR) pituitary tumours without clinical and biological signs of acromegaly. In our series, they represent 16% of all the somatotroph pituitary tumours. The aim of our study was to compare the somatotroph tumours with and without acromegaly to a better characterization of these silent tumours.
Materials and methods
Fifty-nine tumours with acromegaly and 21 silent somatotroph tumours were studied. They were classified into monohormonal (pure GH) and plurihormonal (GH/PRL/±TSH) and into densely (DG) and sparsely granulated (SG) types. The proliferation (Ki-67 index, mitosis count), the differentiation (expression of somatostatin receptors SSTR2A-SSTR5 and Pit-1) and the secretory activity (% of GH IR cells) were compared in the 2 groups of patients.
Results
The silent somatotroph tumours were more frequent in women than in men ($P<0.01$), most of them (76% versus 35%) were plurihormonal ($P<0.01$), more frequently SG (67% versus 46%) and showed a lower percentage of GH IR cells ($P<0.0001$) than the tumours with acromegaly. In somatotroph tumours with and without acromegaly, the expression of both SSTR2A-5 was significantly lower in SG tumours than in DG ones ($P<0.0004$ and $P<0.02$ respectively). The silent plurihormonal tumours were larger ($P<0.01$), had a lower percentage of GH IR cells ($P<0.0001$), a higher Ki-67 index ($P<0.006$) and a lower expression of Pit-1 ($P<0.002$) than the plurihormonal tumours with acromegaly.
Conclusions
The silent somatotroph tumours are different from the tumours with acromegaly. However, the monohormonal GH tumours with and without acromegaly are very similar. In contrast, the frequent silent plurihormonal tumours are less differentiated and more proliferative than the plurihormonal tumours with acromegaly. A low secretory activity of these tumours might explain the normal plasma values of GH and IGF1 and the absence of clinical signs of acromegaly.

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EP863

Polychlorinated biphenyls affect apoptosis of pituitary cells through extrinsic and intrinsic pathways

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Introduction
Polychlorinated biphenyls (PCBs) are environmental pollutants that modulate endocrine functions, induce tumorigenesis, and regulate apoptosis in several tissues; however, their effects on the apoptosis of pituitary cells is unknown.
The aim of this study was to evaluate the PCBs influence on the apoptosis of normal pituitary cells and elucidate the molecular mechanisms involved.
Methods
Primary cell cultures from mouse pituitary glands were exposed to a PCBs mixture (Aroclor 1254) or dioxin-like (PCB-77, PCB-126) or non-dioxin-like (PCB-153, PCB-180) congeners. Apoptosis was assessed by Annexin V staining, DNA fragmentation, and TUNEL assay. The expression and activity of intrinsic and extrinsic pathways were evaluated by Western blot. Thyroid hormone receptor (TR), aryl-hydrocarbon receptor (AhR), and CYP1A1 antagonists were used to examine the mechanisms of PCBs action.
Results
Aroclor 1254 induced apoptosis of pituitary cells as well as an increase in the expression and activity of caspase-8 and caspase-3, whereas the expression and activity of caspase-9 was unmodified. PCB-180 affected the extrinsic pathways by an increase in the expression of TNF-α, TRAIL and TRADD whereas PCB-153 reduced the apoptosis through a decrease in the expression of TNF-α, FAS-L, TRADD, and FADD. The intrinsic pathway was not influenced by PCB-180 whereas PCB-153 affected it by an increase of PI3K-AKT and a reduction of the p38–p53 pathways. The anti-apoptotic phenotype of PCB-153 was counteracted by a TR or CYP1A1 antagonists, whereas the pro-apoptotic effect of PCB 180 was prevented by an AhR antagonist. In contrast, the dioxin-like congeners did not affect apoptosis. The apoptosis induced by Aroclor 1254 or PCB-180 was associated with a reduction in cell proliferation, whereas the decreased apoptosis due to PCB-153 increased cell proliferation by 30%.
Conclusions
Non-dioxin-like PCBs may modulate apoptosis and the proliferation rate of pituitary cells having pro- or anti-apoptotic effects depending on specific congeners.

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EP864

Circadian clock expression in anterior pituitary gland is altered in different thyroid conditions

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The hypo and hyperthyroidism alter the synthesis/secretion of pituitary hormones, which in normal conditions present fluctuations in serum concentration during the 24h period. An intrinsic pituitary circadian clock might be related to these oscillations; however, the possible interaction between thyroid hormonal conditions and circadian clock gene expression in anterior pituitary is still unknown. The purpose of this study was to investigate the expression of core circadian clock as Bmal1, Per2 and Clock, and *Tshb, Prl, Lhb and Dio2* as markers of thyrotroph, lactotroph, gonadotroph function and thyroid hormone action respectively, during hypo and hyperthyroidism in rats.
For this, male Wistar rats were divided in euthyroid, hypothyroid (thyroidectomized rats) and hyperthyroid (euthyroid animals treated for 5 days with T3: 1.5 μg/100g BW, twice a day) and euthanized every 3h, during 24h. The pituitaries were excised and the mRNA expression was evaluated by RT-qPCR, using *Rpl19* as internal control. One and Two-way ANOVA, as well as, cosinor analysis were used to evaluate the time-of-day-dependent differential expression for each gene/group and their interactions.
The expression of *Bmal1*, *Per2*, *Dio2, Prl* and *Lhb* presented a circadian rhythmicity in anterior pituitary of euthyroid rats. *Per2* and *Dio2* acrophases occurred around ZT 12, while *Bmal1, Lhb* and *Prl* were at ZT 0/24. In the hypo and hyperthyroid animals, the circadian pattern of *Per2, Prl* and *Lhb* was abolished. *Bmal1* expression lost its circadian pattern during hypothyroidism, while the hyperthyroidism reduced its acrophase and mesor values. In hypothyroid animals the acrophase of *Dio2* was advanced and mesor was higher than in euthyroid rats, while in hyperthyroidism its circadian pattern was lost.

Our study reveals that the expression of core clock components in anterior pituitary gland are altered during the hyper and hypothyroidism, which might contribute to the altered secretion of pituitary hormones observed in these pathological conditions.

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EP865

mTOR pathway: its role in regulating GH secretion in a rat pituitary adenoma cell line

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Acromegaly results from excess growth hormone (GH) secretion, due to a pituitary adenoma. Surgery is the first option recommended for treatment of GH secreting pituitary adenomas; medical therapy, mostly represented by somatostatin analogues (SSA), is most often used if surgery is not successful. Insulin-like Growth Factor-1 (IGF-1) physiologically reduces GH levels through an endocrine negative feedback loop. IGF-1 exerts its effects also through PI3K/Akt/mTOR pathway activation and regulates different cellular processes.

The aim of this study is to understand whether PI3K/Akt/mTOR pathway can influence IGF-1 feed-back in a rat pituitary adenoma cell line (GH3 cells). We used three inhibitors: Everolimus (mTOR inhibitor), NVP-BEZ235 (mTOR and PI3K inhibitor) and LY294002 (PI3K inhibitor) in the presence or in the absence of IGF-1. We evaluated cell viability by ATPlite Assay, GH secretion by ELISA and Akt phosphorylation by Western blot.

We found that cell viability was induced by IGF-1 (+30%) and reduced by Everolimus up to 30%; this effect was not counteracted by IGF-1. NVP-BEZ235 reduced cell viability and IGF-1 counteracted this effect. GH secretion was reduced by IGF-1 (40%); this effect was not affected by Everolimus, but was blocked by NVP-BEZ235. Moreover, IGF-1 induced Akt phosphorylation, that was enhanced by Everolimus and completely abolished by NVP-BEZ235. To validate these results, we assessed LY294002 alone and with IGF-1, confirming that IGF1 increases Akt phosphorylation while LY294002 arrest this effect.

These results show that IGF-1 is an important regulator of cell proliferation and GH secretion in pituitary cells and that PI3K/Akt/mTOR inhibitors may modulate IGF-1 signaling. This pathway has a role in IGF-1 negative feedback on GH secretion, through Akt inhibition. Therefore, mTOR pathway may represent a possible target for treatment of GH-secreting pituitary adenomas.

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EP866

Retrospective evaluation of pituitary tumours in a single tertiary care institution

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Introduction

We retrospectively evaluated all patients with pituitary tumours treated in our department from 1.1.1997–1.11.2014

Patients and methods

215 patients (124 females: 91 males, mean age 50,9 y.) were treated because of pituitary tumours. All patients underwent basal hormonal analysis and testing in order to check for hormonal activity. Pituitary masses were divided into groups concerning their hormonal status and were further classified according to gender, age at diagnosis, tumour size and the development of postoperative pituitary insufficiency when neurosurgical intervention was conducted.

Results

121 patients had hormonally inactive tumours (non-functional adenomas; 56.3%), 57 prolactinomas (26.5%), 17 growth-hormone secreting adenomas (7.9%), 16 Cushing's disease (7.4%) and 4 craniopharyngiomas (1.9%). Tumours with size <1 cm (microadenomas) were detected in 62 patients (28.8%) and >1 cm (macroadenomas) in 153 (71.2%) of all cases (rate 1:2,5). 98 patients (45.6%) were operated (87 transsphenoidal and 11 transcranial), of this group 34/90 (37.8%) with hormonally active tumours. Indications for surgery were an increased risk or manifestation of chiasma syndrome and/ clinical symptoms due to hormonal hypersecretion. Immunohistochemical stainings of the hormonally inactive tumours detected 18 gonadotrophic adenomas, 28 null-cell adenomas, 10 adenomas with other focal hormonal expression, 1 Rathke's cleft cyst, 2 cysts and 1 pituitary lesion because of hypophysitis. Complete (32 cases (32.6%)) or partial (33 cases (33.7%)) postoperative hypopituarism in minimum 1 pituitary axis was present in 65/98 (66.3%) of the operated patients.

Conclusions

Pituitary adenoma prevalence is rising due to widely available imaging procedures. The majority of the tumours in our cohort were macroadenomas and hormonally inactive. Tumour extirpation via transphenoidal or transcranial adenectomy resulted in functional pituitary impairment in 2/3 of the patients.

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EP867

HMGA2 as new biomarker of pituitary adenomas invasiveness?

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Proper classification of pituitary adenomas (PA) is an important area of research. Thus, developing of new biomarkers is essential to facilitate the early detection of PA, identify the drug response and predict recurrence reliably in all patients. The usual histological markers of tumor aggressiveness and/or invasiveness are often similar between recurring, regrowing, and stable tumors, and therefore are not reliable as prognostic parameters. To quantitate the levels of the HMGA2 gene expression we analysed 41 PA samples for the specific HMGA2 mRNA levels by a qPCR assay. We are evaluated 12 Somatotropinomas, 20 NFPA, 7 Corticotropinomas, 1 Gonadotropinoma and 1 Prolactinoma. Based on preoperative tomography computerized (TC) images the PA were classified as invasive or non-invasive. Aggressiveness is defined by clinical behaviour and tumours were considered aggressive when the Ki-67 index was $\geq 3\%$. Here, we show by qPCR that HMGA2 mRNA expression significantly correlates with invasiveness. HMGA2 expression levels were higher in non-invasive PA ($^{*}P=0.0154$) and significantly higher in non-invasive NFPA ($^{**}P=0.0087$). In addiction, we evaluated the possible relationship of Ki-67 labeling index with HMGA2 expression as a predictor of tumor prognostic. No significant association was found.

Keywords: Pituitary Adenoma, HMGA2, Invasiveness, Ki-67, Aggressiveness
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EP868

Serum proteases do not cleave prolactin to vasoinhibins at physiological pH

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Background
The prolactin/vasoinhibin axis constitutes a novel endocrine axis in which the generation, secretion, and actions of the pituitary hormones prolactin and vasoinhibins are under control of the hypothalamus, the pituitary gland, and of regulators in the target tissue microenvironment. Vasoinhibins are generated in the pituitary gland and in multiple target tissues through proteolytic cleavage of prolactin; it is not known wether they are also produced in the circulation.
Methods
Human serum or plasma and recombinant human prolactin (corresponding to protein data bank identification P01236) were incubated at 37 °C, alone and in combination, with a variation of pH, time, and buffer composition. The samples were resolved on sodium dodecyl sulfate polyacrylamide gel electrophoresis and Western Blotting was performed using polyclonal and monoclonal, epitope-mapped anti-prolactin and anti-vasoinhibin antibodies.
Results
Sodium dodecyl sulfate polyacrylamide gel electrophoresis and Western Blotting analyses demonstrated an anti-prolactin antibody immunoreactive band with an apparent molecular mass of 23 kDa, consistent with the presence of the recombinant prolactin-protein. Samples incubated throughout a time period ranging from 10 minutes to 24 hours at pH 7.4 did not demonstrate immunoreactive bands lower than 23 kDa. An anti-vasoinhibin immunoreactive band featuring an apparent molecular mass of 17 kDa was intermittently observed in samples incubated at pH 3.4.
Conclusion
Vasoinhibin generation by enzymatic cleavage of prolactin does not occur in human serum under physiological conditions. Thus, the generation of vasoinhibins seems to be restricted to the pituitary gland and the target tissue level. A limited proteolysis of prolactin, resulting in the generation of a prolactin-fragment with an apparent molecular weight of 17 kDa seems to occur at acid pH.

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EP869

Relationship between Insulin and somatostatin secretory response to Glucagon-like peptide-1 (GLP-1) and glucose concentration in perifused rat pancreatic islet cells

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Objective
The exogenous somatostatin inhibits insulin secretion in pancreatic cell and could lead to hyperglycemia. But, Glucagon-like peptide-1 (GLP-1) has insulinotropic actions despite stimulating somatostatin secretion in δ cell. So, we examined whether there is a time difference of insulin and somatostatin secretion after GLP-1 stimulation or secretion rate difference of insulin and somatostatin depending on GLP-1 concentration and glucose concentration inside the islets.
Methods
We isolated pancreatic islets from five 8-week-old male Sprague Dawley rats by collagenase digestion. The islets were incubated in RPMI1640 medium before experiments. The insulin and somatostatin were studied depending on glucose (2.7, 5.5 and 16.7 mmol as hypo-, normo-, and hyperglycemic condition respectively) and GLP-1 concentrations (0, 0.1, and 10 ng/ml) in perifused isolated rat pancreatic islet cells. Because of duplication laboratory settings, statistical analysis did not proceed and analyzed tendencies. The hormonal analysis was conducted using ELISA kit.
Results
At 2.7 mmol glucose, insulin and somatostatin did not respond to GLP-1 administration. At 5.5 and 16.7 mmol glucose, insulin and somatostatin secretion increased simultaneously as soon as GLP-1 administration. As GLP-1 concentration increased, so did insulin secretion but, somatostatin secretion was not affected by GLP-1 concentration. After a certain level of somatostatin was stimulated by GLP-1, somatostatin did not secreted any more. Whereas, both insulin and somatostatin secretion increased as increased glucose concentration. And somatostatin secretion decreased significantly compared with baseline after maximal secretion by GLP-1 stimulation.
Conclusion
The time difference of insulin and somatostatin secretion after GLP-1 stimulation was not observed. And there was no secretion rate difference of insulin and somatostatin depending on GLP-1 concentration. The somatostatin secretion rate were affected by not GLP-1 concentration but glucose concentration. The significant decline of somatostatin compared with baseline after GLP-1 stimulated somatostatin maximally was observed newly and additional research is needed in the future to prove that the fact might be associated with insulinotrophic action of GLP-1.

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Pituitary – Clinical

EP870

Association between serum IGF1 levels and liver fat content in patients with pituitary diseases

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Non-alcoholic fatty liver disease (NAFLD) is commonly associated with obesity, metabolic syndrome and type 2 diabetes. NAFLD is also seen in patients with endocrinopathies. However, the relationship between endocrinopathies and the development of NAFLD is not well known. Both GH and IGF1 are believed to be involved in the regulation of hepatic lipid metabolism.
Objective
In this study, we set out to determine whether liver fat content (LFC) was associated with IGF1 levels and with GH deficiency in people with pituitary diseases (PD).
Design, settings, and participants
Eighty eight patients with pituitary diseases and 74 healthy controls were included in this study. LFC was measured using MRI. Hepatic steatosis was defined as LFC $>5.5\%$.
Results
Patients with PD were older ($P=0.001$), had a higher BMI ($P=0.0005$) and higher ALAT level ($P=0.0002$) than healthy controls. LFC was significantly higher in people with PD than in controls (6.5% vs 3.2%; $P<0.001$). LFC was negatively associated with the IGF1 level. Fourteen patients with PD had GH deficiency. LFC was higher in PD patients with GH deficiency than in those without. The prevalence of steatosis (LFC $>5.5\%$) was higher in PD patients than in controls (36.3% vs 14.8%; $P=0.002$ respectively). The prevalence of steatosis was higher in PD patients with GH deficiency than in those without (12/14 (85.7%) vs 20/74 (27.0%); $P<0.001$). In multivariate analysis, which included patients and controls, the predictive variables for steatosis were age, BMI and IGF1 levels, whereas the presence of pituitary diseases and gender were not associated with steatosis.
Conclusions
Our data showed that LFC was strongly associated with IGF1 levels. These results suggest that steatosis associated with PD is probably a consequence of GH deficiency in patients with pituitary diseases. An evaluation of the interest of GH treatment in GH-deficient PD patients with NASH should be evaluated.

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EP871

Computer vision technology in the diagnosis of Cushing's syndrome – advanced studies with a cohort matched by body mass index

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Introduction
Cushing's syndrome (CS) is a rare disease characterized by clinical features that show overlap with the 'metabolic syndrome'. Pilot studies regarding the use facial image analysis software as a novel diagnostic tool in acromegaly and CS have shown promising results. Distinguishing CS patients from patients that show

similar features without true hypercortisolism remains a challenge in clinical practice. To address this particular problem, we evaluated the performance of this tool for CS with a larger cohort and included controls matched by BMI.
Methods
Eighty two (22 m., 60 f.) study subjects with confirmed CS and 98 (32 m., 66 f.) control subjects matched by age, gender and BMI were included. For the control group we screened patients with typical clinical signs (metabolic syndrome) but biochemically excluded CS. Standardized frontal and profile facial photographs were acquired using a regular digital camera. The images were analyzed with the software tool FIDA (facial image diagnostic aid). A grid of nodes was semi-automatically placed on relevant facial structures. Classification was done using a combination of Gabor wavelet transformation and geometrical analysis and a maximum likelihood classifier. Classification accuracy was calculated using a leave-one-one cross-validation procedure.
Results
The mean BMI and age of the study cohort, stratified by gender, did not differ significantly (*t*-test, $P > 0.05$). The correct classification rates were: 10/22 (45%) for male patients and 26/32 (81%) for male controls, 34/60 (57%) for female patients and 43/66 (65%) for female controls. The classification rates by etiology of CS were: Adrenal CS 3/8 (m), 7/13 (f); Cushing's disease 4/8 (m), 18/37 (f) and Iatrogenic CS 2/3 (m), 8/9 (f).
Conclusion
Regarding the advanced problem of detecting CS patients within a BMI-matched cohort, we have found a satisfying classification accuracy by facial image analysis. Classification accuracy would most likely be significantly higher in a study cohort with healthy control subjects. Further studies might pursue a different combination of nodes and equations in the analysis for improving the method.

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EP872

Endocrinologic outcomes of gamma knife radiosurgery for acromegaly: from an endocrine clinic

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Although surgical resection is the usual initial treatment for patients with acromegaly, it does not always lead to a remission. Gamma knife radiosurgery (GKRS) is an important additional strategy for unresected clinically active pituitary adenomas.
Objective
We evaluated retrospectively pituitary hormone status as well as the efficacy of GKRS for patients with acromegaly referred to our tertiary endocrinology clinic. Prognostic factors related to outcomes were also analyzed.
Method
In this study we reviewed 125 patients with clinically active acromegaly underwent GKRS at different neurosurgery clinics between 1999–2015. The median follow up interval was 72 months (range 12–192). Anterior pituitary hormones during follow up was recorded. Endocrine remission for acromegaly was defined as growth hormone level < 1 ng/ml and a normal insulin like growth factor 1 (IGF-1) level (age and sex adjusted) off growth hormone inhibiting drugs for at least 3 months. Endocrine control was defined as normal GH and IGF-1 levels under medication.
Results
One hundred and ten patients had undergone GKRS after transsphenoidal surgical adenoma resection, 15 patients had primary GKRS.Thirty seven patients (29.6%) developed a new pituitary axis deficiency; 16.8% ($n=21$) had hypothyroidism, 12% $n=15$) had hypogonadism. Although 11 (8.8%) had panhypopituitarism prior to radiosurgery, only 1 patient (0.8%) developed panhypopituitarism after GKRS. Other complication reported in one patient as visual loss.
Remission was observed in 20 (16%) patients at a median onset of 34 months after radiosurgery and endocrine control was achieved in 77 (61.6%) patients. Patients with lower IGF-1 and with tumors that were less invasive at the cavernous sinus before GKRS were associated better GH remission rates. Fourteen patients had repeat GKRS because of persistently elevated and clinically symptomatic GH, IGF-1 levels. The median follow up interval between gamma knife radiosurgeries was 48 months (range 12–120 months).
Conclusion
GKRS which is most often applied in clinically symptomatic acromegaly persistent after initial microsurgery was most effective when the tumor was less invasive at the cavernous sinus and when patient had lower IGF-1 levels before GKRS. Previous transsphenoidal surgery for invasive macroadenomas are corresponding risk factors for pituitary hormone deficiency.

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EP873

Comorbidities and treatment patterns among patients with acromegaly in Sweden : a register-linkage population-based study

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Introduction
Treatment of patients with acromegaly is complex, including surgery, pharmacotherapy and radiotherapy. The objective was to describe comorbidities and treatment patterns among patients with acromegaly in Sweden.
Methods
Population-based study including all patients with a first diagnosis of acromegaly due to a pituitary adenoma in Sweden between 1 Jul 2005 and 31 Dec 2013. Data was obtained via linkage of the National Patient Register, Swedish Prescribed Drug Register and Cause of Death Register.
Results
Predefined selection criteria identified 358 patients (48% men, mean age at diagnosis 50.0 [SD 15.3] years). Eighty-one percent had at least one comorbidity, which was 88% among patients diagnosed before 2010 and 73% if diagnosed $\geq$2010. Hypertension (40%), neoplasms outside the pituitary gland (30%), hypopituitarism (22%) and diabetes mellitus (17%) were the most common comorbidities. First-line treatment was initiated on average 3.7 (s.d. 6.9) months after diagnosis; 16% received no treatment for acromegaly during the follow-up period. Mean follow-up time from diagnosis to death or 31 Dec 2013 was 4.2 (s.d. 2.5) years. Among the 301 patients who received treatment, the most common first-line treatments were surgery (60%), somatostatin analogues (SSA) (21%) and dopamine agonists (14%). After primary surgical treatment, 63% received no second-line treatment during follow-up, while 24% received SSA initiated on average 14.0 (s.d. 14.7) months after surgery. The most common treatment after first-line SSA was surgery (58%), performed on average 5.3 (s.d. 5.4) months after SSA initiation. Overall, 10% had received growth hormone receptor antagonists. Radiation therapy was performed for 16% and 8% if diagnosed before 2010 and $\geq$2010, respectively.
Conclusions
Comorbidity in patients with acromegaly is very high. The most common first-line treatment in acromegalic patients in Sweden was surgery, with the majority not receiving any second-line treatment. SSA was the second most common first-line treatment, often followed by second-line surgery.

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EP874

Discrepant GH and IGF-I values in the evaluation of treated acromegalic patients; an ongoing challenge. A meta-analysis

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Purpose
Growth Hormone (GH) and Insulin-like Growth Factor 1 (IGF-I) are currently the principal biomarkers used to assess disease activity in acromegaly and any discrepancy between them renders interpretation of results inconclusive. The purpose of this study was to assess the frequency of discrepant results and identify parameters that might affect the emergence of this phenomenon.
Methods
A systematic review of Medline and Scopus was performed (1987–2013) followed by a meta-analysis to address the frequency of discrepant results between GH and IGF-I levels. Meta-regression was performed using the year of publication as a continuous variable and subgroup analyses included the different types of GH testing and GH assays used, as well as the results of patients treated with Somatostatin Analogues (SSAs) compared to those treated with non-pharmaceutical modalities.

Results
The analysis retrieved 39 eligible studies totaling 7071 patients**.** The pooled discordance rate between GH and IGF-I was 25.7% (95% CI: 22.3–29.4) and the predominant format was that of elevated IGF-I with normal GH levels [15.3% (95% CI: 12.5–18.7)]. No significant correlation between the discordance rate and the year of publication was shown, whereas, the use of ultrasensitive GH assays resulted in higher discordance rates (30.7%, 95% CI: 25.9–35.9 vs. 19.8%, 95% CI: 14.1–27.2, $P=0.04$). Patients receiving SSAs presented a discordance rate significantly higher than those not on SSA treatment (32.5%, 95% CI: 27.8–37.4) vs. (21.6%, 95% CI: 17.8–25.6, $P=0.001$)
Conclusions
Discrepancy between GH and IGF-I results is encountered in a quarter of treated patients with acromegaly, especially when using ultrasensitive GH assays or in patients receiving SSAs, a fact that the clinician should take into consideration when making clinical decisions.

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EP875

Gender aspects in the biochemical control of acromegaly in Austria: evaluation of 607 cases from the Austrian Acromegaly Registry

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The Austrian Acromegaly Registry is an initiative of the Austrian Society for Endocrinology and Metabolism. This database includes 607 patients (54% females) followed in twelve centers. Mean treatment period is 10.7 years (range 0–50 years), the total number of patient-years is 6470. Here we report gender-specific differences in the presentation, therapy and biochemical control of acromegaly in patients included in this registry.
Mean age at diagnosis was 46.7 years for females and 44.1 years for males. Younger age at diagnosis of acromegaly and male sex were associated with larger tumour size ($P=0.001$). Co-morbidities were found to be more prevalent in females, where hypertension was observed in 50% of the cases (45% in males), diabetes in 29% (24% in males) and both hypertension and diabetes in 20% (as compared to 15% in males). Mortality rates were 2.9% in males and 3.3% in females, but mean age at death was 63 years for men and 73 years for women.
Data on biochemical control were collected in 476 patients with acromegaly and disease duration longer than 9 months, who were last visited between 2003 and 2014. Disease control was evaluated by GH less than 1.0 ng/ml during an oral glucose suppression test and/or normal age- and gender-specific IGF-1. These outcome data were available for 414 patients, 55% were females. At the last visit, 71% of the patients were biochemically controlled. Female gender was a significant predictor of biochemical control ($P=0.011$), as 77% of females but only 64% of males showed normal IGF-1 and/or GH nadir during OGTT. Fifty percent of females and 62% of males with biochemically controlled disease receive concomitant medical therapy for acromegaly.
In summary, male patients with acromegaly are diagnosed at younger age and have larger tumors. Although the prevalence and co-morbidities of acromegaly are higher in females, both biochemical control of the disease and life expectancy are remarkably better in women.

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EP876

ACRO-POLIS study: differences of symptoms and comorbidities in 472 acromegalic patients according the sex of patients and sources of clinical data

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Introduction
Acromegaly is characterized by excessive secretion of GH and increased IGF-1 levels caused by benign pituitary adenoma. The ACRO-POLIS study describes symptoms and comorbidities of acromegaly at diagnosis in a large cohort of patients diagnosed between 2009 and 2014 in France.
Methodology
Observational, cross-sectional, multicentre study included adult patients with acromegaly diagnosed for less than 5 years. Data were collected retrospectively from patient medical files and from patients'questionnaires.
Results
472 patients were included. Mean ($\pm$S.D.) age was 51.9 ($\pm$14.3) years and 57.2% were female. GH- and GH/PRL-secreting pituitary adenomas were reported in 78.8% and 18.2% of patients, respectively. Most patients had a macroadenoma (80.5%). At diagnosis, mean ($\pm$S.D.) GH level and IGF-1 level were 18.7 ($\pm$30.1) ng/L and 295 ($\pm$160) %ULN respectively. Mean time between symptom or comorbidity onset and diagnosis of acromegaly was 5.1 ($\pm$6.75) years. The symptoms are mainly morphological manifestations, snoring and weight gain and were detected earlier in females than in males [enlargement of hands: 7.4 ($\pm$7.4) years vs. 5.6 ($\pm$6.3) years; enlargement of feet: 6.7 ($\pm$6.7) years vs. 5.8 ($\pm$7.0) years; snoring: 9.1 ($\pm$8.5) years vs. 5.9 ($\pm$6.7) years; weight gain: 6.6 ($\pm$5.9) years vs. 4.9 ($\pm$5.7) years]. Majority of signs were predominantly reported in the patient's questionnaires and less in the patient's medical records. The rates of important symptoms reported only in questionnaires are: snoring (40.4%), weight gain (50.2%), loss of libido (74.4%), rachialgia (61.7%), asthenia (35.8%), arthropathy (30.4%).
Conclusion
In ACRO-POLIS study, symptoms and comorbidities associated with acromegaly were different in terms of time to diagnosis between males and females. Furthermore, the study highlights the value of collecting data directly from the patient's questionnaire in complement with the patient's medical record.

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EP877

"The incidence of central adrenal insufficiency in euvolaemic hyponatraemia. Results of a large prospective study"

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Context
The syndrome of inappropriate antidiuresis(SIAD) is the commonest cause of hyponatraemia. Data on the aetiology of SIAD is mainly derived from retrospective studies, often with poor ascertainment of minimum criteria for correct diagnosis. Although central adrenal insufficiency(CAI) is known to cause euvolaemic hyponatraemia, the incidence of undiagnosed CAI in SIAD is unknown.
Objective
To establish the incidence of CAI in SIAD.
Design
Prospective, single-centre study from January 1st to October 1st 2015.
Patients
1323 admissions with hyponatraemia were prospectively evaluated; 573 (43.4%) classified as SIAD. Full ascertainment of the criteria for diagnosis of SIAD was obtained in 83% of patients.
Methods
Patients underwent a short synacthen test (SST) if 09:00 hour cortisol was <300 nmol/l. The diagnosis of CAI was stablished with symptoms of adrenal insufficiency and a 09:00 hour cortisol <100 nmol/l, or cortisol peak following SST <500 nmol/l.
Results
CNS diseases were the commonest cause of SIAD ($n=148.26\%$) followed by pulmonary diseases ($n=111.19\%$) malignancy ($n=105.18\%$) and drugs ($n=47.8\%$). 14/573 (2.4%) had CAI. 7/14 (50%) were related to recent exogenous glucocorticoid administration; 6 patients (42%) had new onset hypopituitarism; (pituitary apoplexy, $n=1$, ipilimumab induced hypophysitis, $n=1$, pituitary metastasis, $n=1$, traumatic brain injury (TBI), $n=1$, viral meningitis, $n=1$ and new diagnosis of empty sella syndrome, $n=1$). One other had CAI possibly due to previous TBI. 4 patients (28%) had a clinical diagnosis of acute adrenal crisis. Hyponatraemia resolved in 10/14 (71%) of patients following treatment with glucocorticoids, but 4 patients remained hyponatraemic at hospital discharge. In this subgroup, the underlying causes were possibly SIAD due to

bronchiectasis ($N=1$), COPD ($N=1$) metastatic malignancy ($N=1$) and Venlafaxine ($N=1$).

Conclusion

In this large, well-characterized, prospective cohort of SIAD patients, the incidence of CAI was 2.4%; undiagnosed primary pituitary disease occurred in 1% of patients. Screening for CAI is an essential component of the diagnostic approach in SIAD.

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EP878

Perioperative plasma cortisol levels during transsphenoidal operation of pituitary adenoma in ACTH sufficiency and deficiency

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Introduction

The demand of cortisol rises during stress and to avoid acute cortisol deficiency, patients undergoing transsphenoidal surgery at Skåne University Hospital (Sweden) receive peri- and postoperative substitution with hydrocortisone (HC), even at normal ACTH function. Some anesthetics are known to affect cortisol levels.

This study aimed to assess the perioperative cortisol plasma levels during transsphenoidal surgery in ACTH sufficient and deficient patients.

Description of methods/design

We studied 15 patients with transsphenoidal surgery for a pituitary adenoma. Out of 10 patients with normal ACTH function (morning *P*-cortisol >400 nmol/l and/or >550 nmol/l after Synacthen); 7 patients were not receiving HC substitution whereas the remaining 3 received the routine 50 mg iv HC. 5 patients with ACTH deficiency received the routine iv HC of 100 mg in the morning before surgery and with the additional 50 mg HC for an afternoon operation ($n=2$). *P*-cortisol was measured at the start and every 30 min during surgery (surgery duration 60–200 min). Propofol and remifentanil were used as anesthetics.

Results

Among 7 patients with normal ACTH function, *P*-cortisol levels were, at the start of surgery between 38–244 nmol/l and during the operation the levels decreased to 24–139 nmol/l. At the time point of intrasellar manipulation a distinct rise of the cortisol levels was noted in 6 of these 7 patients (to 350–628 nmol/l). Correspondingly, in the 3 ACTH-sufficient patients receiving 50 mg HC at the start of surgery, cortisol levels increased slightly, from 407 to 553, 719 to 822, and 1092 to 1180 nmol/l, respectively. In the 3 ACTH-deficient patients undergoing surgery in the morning cortisol levels fell slightly from very high levels. In the 2 patients who received additional 50 mg HC in the afternoon cortisol levels peaked at 1914 and 2384 nmol/l.

Conclusion

The low p-cortisol in the first phase of surgery in ACTH-sufficient patients without HC substitution is probably explained by anesthetics. When surgery reached the sella tursica, cortisol levels increased in 6 of 7 patients. In the ACTH deficient patients, pre-operative HC resulted in high cortisol levels without corresponding increase after intrasellar manipulation. Patients who did not receive HC substitution did not show any abnormal parameters during surgery. Supraphysiological cortisol levels were achieved after iv HC.

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EP879

Does vitamin D status correlate with cardiometabolic risk factors in adults with growth hormone deficiency?

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Introduction

Apart from being individually associated with cardiometabolic health, Vitamin D and growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis are reported to interplay, with a positive correlation between IGF-1 and 25-hydroxyvitamin D (25(OH)D). These findings raise questions about the role of vitamin D for the adverse cardiovascular (CV) risk profile in hyposomatotropism. Thus, the aim of our study was to investigate the association between 25(OH)D and metabolic syndrome (MetS), its components and other surrogate markers of CV risk.

Methods

This cross-sectional study included 129 adults with GHD, 41.9% with childhood-onset GHD. Each subject underwent routine biochemical blood testing, anthropometric (body mass index (BMI), waist circumference (WC), waist-to-hip ratio, percent body fat (PBF), visceral fat area (VFA), skeletal muscle mass) and blood pressure (BP) measurements. Other CV risk markers were examined in a subsample of the initial population - high-sensitivity C-reactive protein, adiponectin and asymmetric dimethylarginine ($n=88$); intima-media thickness of carotid arteries ($n=44$). Total serum 25(OH)D was used to assess vitamin D status and was measured by electro-chemiluminescence binding assay. Vitamin D status and GHD were defined according to the Endocrine Society Clinical Practice Guideline recommendations.

Results

Our data demonstrated significantly lower 25(OH)D levels among patients with MetS (11.8 ± 4.5 vs. 16.3 ± 8.1 ng/ml in those without MetS, $P<0.0001$). Serum 25(OH)D correlated negatively and weakly with anthropometric parameters (BMI, WC, PBF, VFA) and systolic BP.

Conclusion

The severe impairment of vitamin D status in hyposomatotropism and its association with adiposity and BP warrant 25(OH)D testing in GHD patients. Although the normalization of the vitamin D status has not been proven to improve CV outcomes in general population, it might have beneficial effects in GHD subjects, especially in those with obesity or hypertension. Patients with a combination of GHD, hypovitaminosis D and MetS show an adverse CV risk profile and need more active therapeutic care.

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EP880

Predictive factors of surgical outcomes in acromegaly: what's new in 2016?

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Introduction

In the era of personalized patient management in acromegaly, transsphenoidal surgery remains a treatment of choice in cases where surgical cure can be expected. In order to better target these patients and to assess the risk of persistence/progression disease, we evaluated clinical, hormonal, radiological and pathological predictors of surgical outcome in acromegaly.

Methods

A single-institution retrospective study from 2009 to 2015 was performed. From a cohort of 79 acromegalic patients operated by a single operator, 63 patients with complete pre- and postoperative work-up, magnetic resonance imaging (MRI) blinded evaluation and pathological analysis, with prognostic clinicopathological classification (J Trouillas et al.) were studied.

Results

Three month after surgery, remission rate defined by IGF-1 normalization and/or nadir GH/oral glucose tolerance test $<$ 1.2 mUI/l, was 50.8%. In univariate analysis, no biological parameter was predictive of poor outcomes. MRI-results: tumour diameter greater than 20 mm ($P<0.05$) and intracavernous extension (Knops $\geq$ 3) ($P<0.05$) were associated with a higher probability of not being cured. T2-weighted MRI signal was not associated with post-operative remission. Peroperative evaluation of infrasellar ($P<0.05$) and intracavernous invasion ($P<0.01$) were associated with a lower probability of cure. For pathological assessment, grade 2a and 2b tumors were predictive of non-healing ($P<0.01$). In multivariate analysis, 2a and 2b tumors, infrasellar and intracavernous invasion remained the major predictors of poor surgical outcome.

Conclusion

This study confirms that intracavernous invasion and tumour size seems to be the strongest parameters to predict surgical outcomes. Moreover, prognostic clinicopathological classification help to predict post-operative remission.

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EP881

Outcomes of surgically treated nonfunctioning pituitary adenomas

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Introduction
The sequelae of surgically treated non-functioning pituitary adenomas (NFPA) is an important area of study to help plan management. The aim was to study all Maltese patients who had a surgically treated NFPA and analyse the results of surgery, risk factors for tumour recurrence/regrowth and the role of postoperative radiotherapy.
Materials and methods
One hundred and seventy-five patients were identified as having a NFPA of whom 77 had underwent pituitary surgery. Detailed analysis of these patients was done including their demographic details, surgical details, post-surgical management, regrowth and recurrence patterns.
Results
63.6% of patients presented with visual field defects, 40.3% had headaches at presentation and 87.0% had chiasmal compression by their NFPA. Residual tumour postoperatively was evident in 67.5% of patients while 29.9% of patients had immediate postoperative radiotherapy. Recurrence /regrowth was documented in 18.2% of patients within a median time of 3.2 (IQR: 1.6–5.6) years. Factors that were found to be statistically significantly associated with a higher rate of regrowth using Kaplan-Meier estimates were the presence of residual tumour ($P=0.036$), presence of cavernous sinus invasion ($P=0.034$) and the lack of postoperative radiotherapy ($P=0.004$). Independent risk factors for tumour regrowth using multivariate Cox hazard analysis were absence of post-op radiotherapy ($P=0.010$) and cavernous sinus invasion ($P=0.020$).
Conclusion
By studying this cohort of patients we were able to characterise better the outcomes of NFPA management and outline risk factors which can effect prognosis.

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EP882

Metabolic state in ACTH insufficient & ACTH sufficient patients with hypopituitarism not treated for growth hormone deficiency (GHD): a comparative study

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Background
Inadequate glucocorticoid (GC) replacement may be associated with over-exposure to GC, which can adversely influence metabolic and cardio-vascular state of hypopituitary growth hormone deficient adult patients (A-GHD). In this study we compared metabolic profile of ACTH insufficient and sufficient patients in A-GHD not treated with GH.
Patients and methods
A cohort of 260 patients (age 48.6 ± 12 years and BMI 28.7 ± 6.6 kg/m^2) with hypopituitarism and A-GHD was divided according to ACTH status and analyzed for antropometric and metabolic parameters including lipid status and glucose matabolism. All ACTH insufficient patients were replaced with hydrocortisone (10–20 mg/day in divided doses), and for other hormone deficiencies adequately. None of the patients were treated with GH.
Results
In our cohort prevalence of ACTH insufficiency was 75.4%. ACTH insufficiency was more prevalent in males compared to females (59.7% vs 40.5%, $P<0.05$). Although our patients were overweight with adverse lipid profiles, no differences were found between the two groups in body weight, waist to hip ratio and lipid profile (total, LDL and HDL cholesterol, triglycerides and Lp a). Prevalence of metabolic syndrome defined according to NCEP (3/5) criteria was similar in both groups (33.9% vs 30.7% ACTH suff. vs ACTH insuff. $P>0.05$). Significant differences were found in glucose metabolism characterized by lower glucose leves at baseline (4.5 ± 0.9 vs 4.8 ± 0.8 mmol/l, $P=0.04$) and during oral glucose tolerance test (OGTT 75 g) peak (7.7 ± 2.0 vs 8.6 ± 2.1 mmol/l, $P=0.006$) and area under the curve values (753.3 ± 197.6 vs 851.2 ± 217.8 mmol/l.min $P=0.002$) calculated using trapezoidal rule. However insulin concentrations at baseline and during OGTT as well as HOMA IR were not significantly different between ACTH sufficient and ACTH insufficient GHD hypopituitary patients.
Conclusion
Adverse metabolic profile in patients with hypoptuitarism and GHD is not significantly influenced by ACTH deficiency state if it is replaced with low to moderate doses of hydrocortisone.

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EP883

Disease activity and lifestyle influence the occurrence of cardiovascular risk factors and cardiovascular events in acromegaly

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Context
Acromegalic patients have a high-risk cardiovascular profile. However, the determinants of cardiovascular risk factors and major cardiovascular events (MACE), which may develop after diagnosis of acromegaly, are not fully understood.
Objectives
To identify the predictors for systemic comorbidities and MACE, after diagnosis of disease. The role of therapy for acromegaly on the occurrence of such complications was also evaluated.
Patients and methods
Retrospective cohort study on 200 consecutive acromegalic patients. The following outcomes were evaluated: diabetes mellitus, arterial hypertension, hypercholesterolemia and MACE. Each patient was included in the analysis for a specific outcome if it was not present at diagnosis of acromegaly and further classified as: 1) in remission after adenomectomy (Hx), 2) controlled by somatostatin analogues (SSA) (SSAc) or 3) not controlled by SSA (SSAnc). Data were evaluated using Cox regression analysis.
Results
After diagnosis of acromegaly, diabetes occurred in 40.8% of the patients (Hx 27.3%; SSAc 40%; SSAnc 65%; $P=0.002$); lack of control of acromegaly was decisive for the onset of the outcome (HR = 3.32; $P=0.006$). Hypertension arose in 35.5% of the patients (Hx 33.3%; SSAc 36.8%; SSAnc 50%; $P=0.0172$). The strongest determinants of this outcome were age at diagnosis of acromegaly (HR = 1.059; $P=0.014$) and body mass index (HR = 1.05; $P=0.014$). Hypercholesterolemia occurred in 47.8% of the patients without differences among the 3 groups ($P=0.322$). Disease activity was a predictor of hypercholesterolemia (HR = 2.14; $P=0.004$). MACE were recorded in 12.7% of the patients (Hx 15%; SSAc 10.9%; SSAnc 13.6%; $P=0.247$). Age at diagnosis of acromegaly (HR = 1.09; $P=0.005$) and smoking habit (HR = 5.95; $P=0.001$) were associated with an increased risk of MACE.
Conclusion
After diagnosis of acromegaly**,** control of disease (irrespectively to the type of treatment) and lifestyle are predictors of the occurrence of cardiovascular risk factors and cardiovascular events.

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EP884

Hyperprolactinaemia causes and manifestation in outpatient practice

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Hyperprolactinaemia is a common endocrine disorder. Causes are related to physiological factors, pharmacological intervention and pathological conditions. There are a wide variety of drugs that can induce a significant hyperprolactinaemia frequently associated with clinical symptoms. The aim was to analyse clinical manifestation of hyperprolactinaemia in routine clinical practice.

Material and methods
We conducted retrospective review of medical records of patients with hyperprolactinaemia (serum prolactin concentration >1000 mIU/l) treated at Vilnius Antakalnio outpatient clinic in 2011–2014. Pregnant and lactating women and patients with macroprolactin were excluded. We recorded demographic data, medical history, LH, FSH, TTH, LT4, anti-TPO concentration and MRI results.
Results
We analysed data of 68 patients (4.4% male and 95.6% female). Mean age was 31.60±9.23 years. Mean prolactin concentration was 1448.75±526.78 mIU/l. Irregular cycles were observed in 48.5% of women, galactorrhoea in 20.6%, infertility in 20.6%. Headache was present in 17.6% of patients, body weight gain in 13.2%. The most frequent concomitant diseases were thyroid disorders (41.2%), mental illnesses, including usage of antidepressants or neuroleptics (14.7%) and polycystic ovary syndrome (7.4%). 76.4% of patients were treated with dopamine agonists (bromocriptine or cabergoline). 50.0% of the patients underwent MRI: pituitary microadenoma was diagnosed in 13 patients, macroadenoma in 2, empty sella syndrome in 1 and pituitary cyst in 1. MRI results of 17 patients didn't show any pathology. Patients with pituitary pathology were older than those with normal MRI results (35.35±9.41 vs. 27.88±8.14 years, $P=0.012$). There was no difference in prolactin concentration, frequency of complains, BMI, underlying diseases and hormone concentration between groups. In a group of patients without pituitary pathology anti-TPO was associated with prolactin level ($r=0.900$, $P=0.037$).
Conclusion
Main clinical manifestation of hyperprolactinaemia was menstrual irregularity, galactorrhoea and headache. In routine practice up to 50% of hyperprolactinaemia cases were associated with causes other than pituitary tumours.

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EP885

What is the outcome of nonfunctioning pituitary adenomas (NFPAs) after surgery and are there any factors to predict it: a multicenter study in Northern Spain

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Introduction
There is scarcity of data on the recurrence and/or progression (R/P) rate in nonfunctioning pituitary adenomas (NFPAs) after surgery and the risk factors that can predict this outcome. So the aim of this study was to analyze a large series of NFPAs with a long follow-up after surgery, focusing on the evaluation of R/P rate and the risk factors associated with it.
Methods
Retrospective cohort analysis of 164 patients with NFPAs from 3 different centers in Northern Spain who underwent surgery between 1987–2014. The main outcomes were R/P rate during follow-up using Kaplan-Meier estimator and the univariate and multivariate analysis of risk factors that could be involved with R/P.
Results
R/P was detected in 70 patients (43%) after surgery, over a median clinical follow-up of 8 years (1–27), the median time to R/P was 4.1 years. Recurrence-free survival was 65%, 49%, 42% and 32% at 5, 10, 15 and 20 years after surgery, respectively. The univariate analysis identified the following R/P risk factors: pituitary apoplexy and visual impairment at diagnosis; and as protective factor: RT after surgery in patients with subtotal resection (STR) but the multivariate Cox analysis only confirmed as independent factors: visual impairment (hazard ratio [HR] 2.1, 95% confidence interval [CI] 1.1–4.2; $P=0,02$) and RT in patients with STR after surgery (HR 0.4, 95% CI 0.21–0.89; $P=0.02$).
Conclusions
Long term follow-up in NFPAs after surgery is mandatory because R/P occurs in a large percentage of these patients and the risk does not disappear in the long term. Our study suggests that this follow-up has to be more rigorous in patients with visual impairment at diagnosis because they have the highest risk of R/P. RT could decrease this risk specially in those patients with subtotal tumor resection.

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EP886

Radiological vertebral fractures in patients with acromegaly treated with L-thyroxine

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Acromegaly is associated with skeletal fragility and high risk of vertebral fractures (VFs), but the determinants of such a risk are still under investigation and it is not clear whether replacement therapies of coexistent hypopituitarism may influence prevalence and incidence of VFs. In this cross sectional study, fourty acromegaly patients (24 M, 16 F; median age, 57 years; range, 25–72), 20 with active disease, were evaluated for the effects of replacement therapy of central hypothyroidism on radiological VFs. Seven patients had glucocorticoid deficiency, 14 had hypothyroidism and 25 were hypogonadal (5 men and one pre-menopausal woman were on replacement therapy). Patients were evaluated for morphometrical VFs and for bone mineral density (BMD) with DXA at lumbar spine, total hip and femoral neck. VFs were found in 15 patients (37.5%), without significant difference between patients with hypothyroidism and those without hypothyroidism (50.0% vs. 30.8%; $P=0.23$). Among patients with hypothyroidism, those with VFs showed higher serum FT4 (13.0 pg/ml, range: 7–17 vs. 9.7 pg/ml, range: 9–16; $P=0.02$) and daily levo-thyroxine (L-T4) dose (1.43 μg/kg, range: 1.29–1.58 vs. 0.92 μg/kg, range: 0.7–1.1; $P=0.009$). Serum FT4 and daily dose of L-T4 were not significantly associated with BMD at lumbar spine, femoral neck and total hip. VFs were also significantly associated with age of patients (odds ratio: 1.16; C.I. 95% 1.05–1.3), untreated hypogonadism (odds ratio: 5.8; C.I. 95% 1.4–24.2) and duration of active acromegaly (odds ratio: 1.21; C.I. 95% 1.01–1.4), whereas no significant associations were found with treated hypoadrenalism, sex, BMI and BMD at either skeletal sites. In conclusion, this study provides a first evidence that a relative overtreatment of central hypothyroidism may influence the fracture risk in patients with acromegaly, consistently with the pathophysiological hypothesis that thyroid hormone excess and GH hypersecretion may have additive negative effects on bone remodeling and skeletal health.

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EP887

Long-term (19-month) control of urinary free cortisol with osilodrostat in patients with Cushing's disease: results from an extension to the LINC-2 study

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Introduction
During the 22-week LINC-2 study, the potent oral 11β-hydroxylase inhibitor osilodrostat normalized UFC in 15/19 (78.9%) patients with Cushing's disease. Most common AEs were nausea, diarrhoea, asthenia, and adrenal insufficiency. This report describes 19-month results following an extension.
Methods
Patients who were receiving clinical benefit at week 22 could enter the extension. Efficacy/safety is reported for patients who entered the extension. Response was assessed exploratively by last-observation-carried-forward analysis for ongoing

patients at the specific time point. AEs are reported from core baseline until last patient reached month 19 (maximum follow-up = 27.5 months).
Results
16/17 patients (male:female = 5:11) who completed the core entered the extension. Response rate (UFC ≤ ULN [control] *or* UFC > ULN but > 50% decrease from baseline [partial control]) for these patients was 94% at week 22 (control: 94% [$n = 15/16$]; partial control: 0% [$n = 0/16$]) and month 19 (control: 81% [$n = 13/16$]; partial control: 13% [$n = 2/16$]). No controlled patients experienced 'escape' (UFC > ULN at ≥ 2 consecutive visits on maximum tolerated dose) during the extension. Blood pressure, weight/BMI remained stable throughout treatment. In patients with diabetes history ($n = 3$), mean ± S.D. FPG, HbA_{1c} decreased by 60.7 ± 39.3 mg/dl, 1.1 ± 0.6% from baseline to month 19. Two patients discontinued during the extension (AEs [increased ACTH (maximum = 1493 pmol/l), pituitary-tumour enlargement], $n = 1$; consent withdrawal, $n = 1$), one of whom after month 19. Most common AEs were increased ACTH ($n = 7$), adrenal insufficiency, diarrhoea, and nasopharyngitis ($n = 6$). In females, increases in mean ± S.D. testosterone from baseline were 2.7 ± 3.4 nmol/l at week 22 ($n = 10$), 0.8 ± 1.3 nmol/l at month 19 ($n = 9$). Hirsutism was reported in one female and acne in two, which emerged before week 22. One patient experienced ***QTc prolongation*** > 450 ms during the extension (494 ms), which was reversible on dose reduction.
Conclusions
UFC normalization was maintained for 19 months of osilodrostat treatment in 81% of patients with Cushing's disease. The long-term safety profile of osilodrostat was similar to that reported after 22 weeks.

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EP888

Evaluation of endothelial function and insulin sensitivity in patients with prolactinoma

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Objective
Hyperprolactinemia has been reported to be associated with endothelial dysfunction, abnormalities of carbohydrate metabolism and insulin sensitivity. The aim of this study was to evaluate carbohydrate metabolism and endothelial function of our patients in outpatient clinics.
Material and methods
In this cross-sectional study, currently or previously treated 87 hyperprolactinemic patients with PRL-secreting adenoma (fifty four with microadenoma and 33 with macroadenoma; 21 men, 66 women; aged 39,9 ± 8,8 years) and 55 healthy controls (twelve men, 43 women; aged 38.8 ± 10 years) of comparable gender and age with normal PRL values were included. Anthropometric parameters (body mass index (BMI), blood pressure and waist circumference) and serum glucose, insulin, lipid profiles were measured. Carotid intima media thicknesses (CIMT) were measured by using GE Logic 3 Expert Doppler Ultrasonography to evaluate endothelial function. Insulin resistance was calculated by using homeostasis model assessment of insulin resistance (HOMA IR) and insulin sensitivity index (ISI) Matsuda.
Results
No significant differences were observed in systolic and diastolic blood pressure measurements or BMI values between prolactinoma and control group ($> P = 0.05$). Serum lipid profile levels and waist circumference measurements were also similar, compared to control group (Low-density lipoprotein (LDL) ($P = 0.42$), triglycerides (TG) ($P = 0.15$), high-density lipoprotein (HDL) ($P = 0.48$), total cholesterol ($P = 0.17$) and waist circumference ($P = 0.94$)). There were no significant differences in CIMT values, HOMA and Matsuda index scores between prolactinoma and control groups (respectively ($P = 0.47$), ($P = 0.68$), ($P = 0.54$)).
Conclusion
In contrast to previous studies, BMD and CIMT measurements, insulin resistances and serum lipid levels in prolactinoma and control groups were similar in our study. This can be associated with that most of our patients are under treatment or were previously treated. Although our study results support the opinion that treatment with dopaminergic agents could improve BMD, endothelial function and insulin sensitivity in prolactinoma patients.

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EP889

Combined treatment with octreotide LAR and pegvisomant in patients with gigantism – acromegaly: clinical evaluation and genetic screening

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Pituitary gigantism is a rare condition caused by growth hormone secreting lesions, where treatment is usually challenging, especially in cases with genetic predisposition. Aim: We studied a gigantism cohort from Venezuela for genetic defects and their response to treatment. Subjects: 160 somatotropinoma patients were evaluated at the University hospital (from 1985–2015); eight (6M) were diagnosed with acrogigantism and underwent genetic analysis including aCGH for Xq26.3 duplications. Results: All patients had accelerated growth rates/tall stature at first evaluation. The mean age at diagnosis was 18.7 years (range 12–28). Among other frequent signs/symptoms at presentation were acral enlargement (7/8) and headache (5/8). All presented with growth hormone-secreting macroadenomas (all except one were invasive) with prolactin co-secretion seen in 4 cases. Six cases received primary medical treatment with the long-acting somatostatin analogue (SSA) octreotide LAR 20 mg/28 days for 6–12 months resulting in tumor control in 64%, in 2 patients SSA treatment was administrated after unsuccessful surgery (radiotherapy was also used in one case). Cabergoline was added in those with elevated prolactin levels. None of the patients had normalization of IGF-1 levels with SSA. Pegvisomant (20 mg daily) was added. And this combination resulted in a decrease of IGF-1 levels to normal ranges while tumor volume was stable in all patients. Regression of clinical symptoms was seen after 1–4 months of treatment including a decrease in growth velocity. Three novel AIP mutations were identified and none of the patients had Xq26.3 microduplications. Clinical characteristics at baseline and treatment responses were not different in patients with AIP mutations compared with AIP negatives.
Conclusions
Patients with gigantism have large and aggressive GH secreting pituitary lesions difficult to control with conventional treatment options. Prolactin co-secresion is frequent. Combined therapy (long-lasting SSA and pegvisomant) as primary treatment or after pituitary surgery and radiotherapy can permit the normalization of IGF-1 levels and achieve clinical improvement in these difficult to manage patients.

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EP890

High incidence of thyroid cancer among patients with acromegaly

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Introduction
Several studies have suggested that patients with acromegaly have an increased risk of thyroid, colorectal, breast and prostate tumors. We determined the prevalence of malignant neoplasms in patients with acromegaly in a single Greek Centre during the years 1995–2015.
Methods
We evaluated cancer risk in a cohort of 110 patients (M/F 48/62, age 58.63 ± 13.8 years, range 30–86) with acromegaly. Mean age at diagnosis of acromegaly was 46.37 ± 13.11 years old. A total of 42 patients had a microadenoma and 68 patients had a macroadenoma. Mean period of time since diagnosis of acromegaly was 12.26 ± 9.6 years. 108 patients were treated with somatostatin analogues. Only 2 patients were successfully treated with pituitary transsphenoidal surgery and received no medical treatment afterwards.

Results
From 110 patients, cancer was diagnosed in 26 patients. Thyroid cancer was the most common cancer and was diagnosed in 13 patients (11.8%) and among all other cancers there were 2 patients with gastric cancer, 2 patients with endometrial cancer, 1 patient with breast cancer, 1 patient with colon cancer, 2 patient with prostate cancer, 1 patient with myelodysplastic syndrome, 1 patient with renal cell carcinoma, 1 patient with lung cancer and 1 patient with pancreas carcinoma. The mean age of patients with cancer was not statistical significant when compared with the mean age of those without cancer. There was also no significant difference in disease duration, pituitary tumor size, or age at onset between them.
Conclusions
This study suggests that patients with acromegaly have an increased risk of thyroid cancer. In conclusion, each acromegalic patient requires hormonal, ultrasound evaluation of the thyroid and FNAB if required, when the diagnosis of acromegaly is made. It is particularly essential to diagnose the patients early and to rule out thyroid cancer.

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EP891

Non-alcoholic fatty liver disease in patients with biochemically cured Cushing's disease and non-functioning pituitary adenomas: role of adrenal insufficiency and growth hormone deficiency

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Objective
Nonalcoholic fatty liver disease (NAFLD) is a hallmark of the metabolic syndrome and has been shown to be an independent predictor of cardiovascular mortality. Although glucocorticoids and growth hormone are known to be implicated in its pathophysiology, it has only rarely been investigated in the context of patients with pituitary insufficiency or former cortisol excess.
Design
Case-control study, including patients with biochemically controlled Cushing's disease (CD) ($N=33$) and non-functioning pituitary adenomas (NFPA) ($N=79$).
Methods
NAFLD estimated by calculating the fatty liver index (FLI) including BMI, waist circumference, GGT and triglyceride levels.
Results
Although there was no difference in FLI between patients with NFPA and CD, we identified average daily hydrocortisone (HC) intake in those with adrenal insufficiency to be an independent predictor of FLI ($\beta=1.124$; $P=0.017$, even after adjusting from BMI and waist circumference. In line, those with a FLI >60 were also taking in average significantly more HC per day than those with a score <60 ($21.05\,mg \pm 5.9$ vs. $17.9\,mg \pm 4.4$; $P=0.01$). FLI was also the best independent predictor for HbA1c and fasting glucose levels (both $P=0.001$). Growth hormone deficiency and replacement therapy were not associated with FLI in either group.
Conclusion
While HC dosage affects FLI as an estimate of NFLD in patients with CD and NFPA, the benefit of GH replacement still needs to be determined. In contrast to reports in CD patients with active disease, NAFLD in those with biochemical control was not different from NFPA patients.

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Early water intake restriction to prevent inappropriate antidiuretic hormone secretion following transsphenoidal surgery: low BMI predicts postoperative SIADH

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Objective
The goals of this study were to assess the incidence of and risk factors for syndrome of inappropriate antidiuretic hormone secretion (SIADH) in patients following transsphenoidal surgery (TSS), and to validate the effectiveness of early prophylactic restriction of water intake.
Design
Retrospective analysis was performed for 207 patients who had undergone TSS, including 156 patients not placed on early prophylactic water restriction. Sixty-four patients received treatment for SIADH.
Methods
We compared the incidence of SIADH between patients with and without early water intake restriction, and analyzed various risk factors for SIADH using statistical analyses.
Results
BMI was significantly lower for patients with SIADH than for those patients without SIADH. Statistical analysis revealed that the threshold BMI predicting SIADH was 26. Serum sodium levels on postoperative days 5–10 and daily urine volumes on postoperative days 5–10 were significantly lower in patients with SIADH than in those without SIADH. Postoperative body weight loss on days 6, 8, 10, and 11 was significantly higher in patients with SIADH. The incidence of SIADH after starting prophylactic water intake restriction (14%) was significantly lower than the rate before early water restriction (38%; $P<0.05$).
Conclusions
SIADH is relatively common after TSS, and serum sodium concentrations and daily urine volumes should be carefully monitored. Patients with low preoperative BMI should be closely observed, as this represented a significant preoperative risk factor for SIADH. Early prophylactic water intake restriction appears effective at preventing postoperative SIADH.

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EP893

Evaluation of pituitary functions in patients with traumatic maxillofacial fractures: preliminary results

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Introduction
Traumatic brain injury (TBI) is a worldwide public health problem and has been recently documented as a cause of neuroendocrine dysfunction. It has been shown that hypopituitarism may develop nearly 10–20% of the TBI patients, and most common pituitary hormone deficiency after TBI is growth hormone deficiency (GHD). To date no study has evaluated the relation between isolated maxillofacial fractures and pituitary dysfunction. Therefore we aimed to investigate pituitary function in patients with traumatic maxillofacial fracture.
Methods and results
Thirty patients who had traumatic maxillofacial fracture at least 12 months ago (mean 33.6 months) were included in the study retrospectively. Twenty-six of 30 patients (86.7) were male and 4 patients (13.3%) were female, and mean age of the study group was 39.8 years (range; 18–63). None of the patients had loss of consciousness after head trauma and they did not hospitalized in intensive care unit.
The type of maxillofacial fractures were as follows: One patient had blow out, seven patients had Lefort 1–2, six patients had mandibula, three patients had nasal and thirteen patients had zygoma fractures. Basal hormone levels, Glucagon and 1 mcg ACTH stimulation tests were performed to investigate the pituitary functions. Four of 30 patients (13.3%) had isolated GH deficiency based on glucagon stimulation test (GST). Mean peak GH level after GST in patients with hypopituitarism (0.43 ng/ml) was significantly lower than the patients without hypopituitarism (6.7 ng/ml). Other anterior pituitary hormones were normal in all patients, and none of them had diabetes insipidus.
Conclusion
These preliminary results suggest that there is a substantial risk for hypopituitarism, GH deficiency in particular, during the chronic phase of traumatic maxillofacial fractures. However these findings need confirmation with further prospective studies with higher number of patients.

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Cardiac tissue Doppler echocardiographic evaluation of patients with prolactinoma treated with cabergoline

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Introduction and aim
There are few side effects of cabergoline which is used for medical treatment of prolactinoma. For this reason, cabergoline is considered as first-line therapy of prolactinoma. However, chronic administration of high dose cabergoline in patients with prolactinoma may be associated with valvular heart disease. The aim of this study is to evaluate left ventricular systolic and diastolic functions by conventional and tissue Doppler echocardiography in patients with prolactinoma who have been chronically treated with cabergoline.
Materials and methods
A total of 30 patients with prolactinoma who have been treated with cabergoline (mean age 33.4±8.5 years and body mass index (BMI): 28.1±7.8 kg/m^2) were included in this study. Thirty age- and BMI-matched (mean age 30.0±9.8 years; BMI: 26.8±6.4 kg/m^2) hyperprolactinemia patients without cabergoline treatment were also included, and 30 age- and BMI-matched healthy subjects (mean age 31.0±7.0 years; BMI: 25.2±2.9 kg/m^2) were assigned to control group. Cumulative cabergoline dose in patients with prolactinoma was calculated as 218 mg. Mean duration of cabergoline therapy was 121.9±98.5 weeks (range 52-468 weeks). All patients were evaluated by transthoracic and tissue Doppler echocardiography. Left ventricle systolic and diastolic functions and left ventricle, left atrium diameters were measured. All biochemical and hormonal analysis were performed by automatic analyzer.
Results
According to our data, serum prolactin levels were 35.5±39.5 ng/ml in prolactinoma group during cabergoline treatment, 58.3±40.5 ng/ml in hyperprolactinemia group without cabergoline treatment and 16.2±8.3 ng/ml in control group. Left ventricle systolic and diastolic functions parameters were normal among all of the study groups. However there was a positive correlation between cumulative cabergoline dose and deceleration time (DT) ($r=0.369$, $P=<0.001$) of mitral inflow signal. There was also positive correlation between tissue Doppler longitidual myocardial velocity associated with atrial contraction (Am) ($r=0.258$, $P=0.043$). Valvular regurgitation was determined in 11 patients (36.6%) in prolactinoma group, 7 patients (23.3%) in hyperprolctinemia group and 5 patients (16.7%) in control group. However the degree of valvuler regurgitation was mild and there was no significant difference between the groups.
Conclusions
Low-dose cabergoline in patients with prolactinoma is not associated with cardiac valvular dysfunction and also left ventricular systolic and diastolic dysfunction by conventional and tissue Doppler echocardiography. However, high cumulative cabergoline dose may relate to increase in DT and Am parameters that may be related to diastolic dysfunction in the future.

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EP895

Preoperative markers of Cushing's disease remission after transsphenoidal endoscopic surgery

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Purpose
Transsphenoidal endoscopic surgery (TSS) is the first-line treatment for Cushing's disease (CD). However, persistence and recurrence of hypercortisolism after TSS considered important problem. In this case search for CD remission predictors is actual.
Aim
To study the role of preoperative oral high-dose dexamethasone suppression test (HDDST) and pituitary MRI in the prognosis of CD remission after TSS.
Materials and methods
Fifty-nine patients with Cushing's disease (9 men, 50 women, mean age 40 years (15–72) underwent TSS were included. Before the TSS HDDST and pituitary MRI were performed in all cases. Postoperative examination was done one year after surgery. Remission criteria were: secondary adrenal insufficiency (the need for glucocorticoid replacement) or combination of normal midnight ACTH and serum cortisol levels, normal 24 hour urine free cortisol (UFC) excretion and serum cortisol suppression less than 50 nmol/l in 1-mg dexamethasone test. The optimal threshold value of serum cortisol suppression in the HDDST for prediction of CD remission after TSS was calculated by ROC-analysis.
Results
One year after surgery CD remission was confirmed in 39 patients, whereas in 20 patients hypercortisolism persisted. The optimal threshold value of serum cortisol suppression in the HDDST for prediction of CD remission after TSS was 72%. Test's sensitivity and specificity were 82% and 84%, respectively. The probability of wrong prediction was 17% ($P=0.0001$). In our study, the results of TSS did not correlate with MRI adenoma size.
Conclusion
According to our data serum cortisol suppression more than 72% in HDDST may be used as a prognostic criterion for CD remission after TSS.

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Hypertension in acromegaly patients with obstructive sleep apnea

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Purpose
Hypertension is an independent factor of cardiovascular morbidity in acromegaly patients. Obstructive sleep disordered breathing (SDB) is the most common respiratory impairment in acromegaly and is considered one of the mechanisms underlying the development of hypertension in this disorder.
Aim
To study blood pressure parameters and prevalence of hypertension in naïve acromegaly patients depending on the presence of moderate-to-severe obstructive sleep apnea.
Materials and methods
Forty-eight naïve acromegalic patients (11 men, 37 women, median age 53.5 (27–76) years) were recruited into the study. All subjects underwent clinical examination including office blood pressure measurement, full polysomnography, twenty-four blood pressure monitoring (24-hour BPM).
Results
SDB, namely obstructive sleep apnea, was found in 36 (75%) patients. Thirteen patients (36%) had mild, eleven (31%) - moderate and twelve (33%) showed severe OSA. The latter two groups (moderate-to-severe OSA, further referred as patients with OSA) were compared to patients without OSA (non-OSA). In patients with OSA office diastolic blood pressure was significantly higher than in patients without OSA ($P<0.03$). According to 24-hour BPM mean 24-hour, daytime and nighttime blood pressure were significantly higher in patients with OSA as compare to non-OSA subjects. The rate of office hypertension ($\chi^2=3.85$; $P<0.05$), mean 24-hour ($\chi^2=4.8$; $P=0.03$) and nighttime hypertension ($\chi^2=5.23$; $P<0.03$) was significantly higher in OSA group, while the frequency of daytime hypertension was similar in both groups.
Conclusion
According to the office measurement and 24-hour BPM the blood pressure parameters and prevalence of hypertension were higher in patients with OSA. According to our data, patients with newly diagnosed acromegaly should be recommended to undergo polysomnography study in order to detect ones at higher risk of hypertension development.

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EP897

Cabergoline treatment in prolactinoma may not relate with dyslipidemia

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Introduction and aim
The metabolic changes of lipid profiles in prolactinoma treated with cabergoline are not completely clarified. The aim of this preliminary study is to evaluate changes of lipid profile in both of patients with functional hyperprolactinemia and prolactinoma before and after cabergoline treatment.

Materials and methods
Twelve patients with prolactinoma who were treated with cabergoline (mean age 33.8±7.6 years and body mass index (BMI) 27.0±9.6 kg/m^2), 30 age- and BMI-matched (mean age 30.0±9.8 years; BMI 26.8±6.4 kg/m^2) patients with functional hyperprolactinemia, and 30 age- and BMI-matched healthy control subjects (mean age 31.0±7.0 years; BMI 25.2±2.9 kg/m^2) were included in this study. All venous blood samples after 12 hour overnight fasting period were taken before and after cabergoline treatment. All hormonal and biochemical analysis were performed by automatic analyzer.
Results
Our findings demonstrated that serum prolactin levels in prolactinoma were 139.9±111.9 ng/ml vs. 23.0±28.2 ng/ml before and after cabergoline treatment, respectively ($P=0.001$). On the other hand, serum mean prolactin levels was 58.3±40.5 ng/ml in hyperprolactinemia group without cabergoline treatment and 16.2±8.3 ng/ml in control group ($P=0.01$). Serum mean total cholesterol levels were found as 181.2±30.0 vs 184.1±26.7 mg/dl respectively, before and after treatment in prolactinoma group. Serum mean LDL-cholesterol levels in prolactinoma group were 102.8±25.4 vs 104.2±19.9 mg/dl before and after treatment. Serum mean HDL- cholesterol levels in prolactinoma group were 57.5±11.1 vs 59.1±15.8 mg/dl and serum mean triglyceride levels were 106.9±46.0 vs. 102.5±47.2 mg/dl before and after treatment, respectively. Before and after cabergoline treatment, no significantly differences were found between study groups in terms of serum lipid profiles such as total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels. In addition, all lipid parameters in prolactinoma group were not different from both of hyperprolactinemia group and their control group.
Conclusions
According to our preliminary results, we consider that cabergoline therapy does not impact on serum lipid levels in patients with prolactinoma. This study is still ongoing.

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EP898

Decreased skin capacitance and elasticity may be reversible after treatment of Cushing's syndrome

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Background
Acne, stria and decreased skin elasticity are dermatological features of Cushing's syndrome (CS). Although it is known that collagen mass in skin is decreased in CS and glucocorticoids play a role in acneiform skin lesions, the dermatological findings of CS has not previously been measured by reliable methods.
Objective
The aim of the present study was to measure skin elasticity, capacitance, sebum content, pH and temperature in CS before and after 12 months of treatment.
Methods
Twenty patients with CS and 11 healthy control subjects were included in the study. Skin properties were measured on dorsum of both hands by Cutameter, Corneometer CM825, Sebumeter SM810, Phmeter PH900 as non-invasive reliable measuring methods. Patients were treated for CS with surgery and they were reevaluated 12 months after.
Results
The sebum content, temperature and capacitance of the skin were found to be significantly decreased in patients with CS compared to healthy controls on dorsum of both hands at baseline. The skin capacitance in CS was found to be similar to healthy controls after treatment, however the increment was not found to be significant compared to baseline. The sebum and temperature of the skin did not show significant changes according to baseline and was still significantly lower than healthy controls. Although statistically not significant, the elasticity of the skin was lower in CS than in the controls. The elasticity of the skin was found to be significantly increased a year after treatment. There was no correlation of skin elasticity, capacitance, temperature and sebum content of the skin with morning or midnight cortisol, urinary free cortisol or ACTH levels at baseline.
Conclusion
This study revealed a hypothermic skin surface with decreased sebum secretion and capacitance and mildly decreased skin elasticity in CS. The decreased elasticity and capacitance of the skin may increase after treatment of CS.

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EP899

Surgical Treatment and outcome of TSH-producing pituitary adenoma

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Objectives
TSH-producing pituitary adenomas account for 1–2% of all pituitary tumors and there is debate wether transsphenoidal surgery or medical treatment should be recommended as first-line treatment. This study summarizes the authors surgical experience and puts it into context of literature concerning non-surgical treatment of TSHomas.
Methods
A retrospective analysis of 12 patients including imaging, laboratory testing, short-term and long-term parameters of remission and overall pituitary function.
Results
12 patients are presented, 3 are male, 9 are female, mean age is 40 years (16–56). Time from first symptoms to diagnosis was 92.5 months (12–180 months).
Preoperative blood draws revealed mean TSH-levels of 8.07 mU/l (range 0.95–43.65, s.d. 11.5), mean fT3 of 8.5 pmol/l (range 4.2–17.3, s.d. 3.2) and mean levels of fT4 of 25.7 pmol/l (range 18.7–33.1 s.d. 4.7). TSH-levels decreased to a mean of 0.69mU/l (range 0.03–3.018, s.d. 1) on postoperative day one and to 0.64mU/l (range 0.01–3.5, s.d. 1.1) between postoperative days 2 and 5 (table). Postoperative day 1 levels of fT3 and fT4 were measured at a mean of 3.68pmol/l (range 2.3–5.7, s.d. 1.2) and 21.6pmol/l (range 15.5–28.5, s.d. 4.1). A further decrease in fT3 and fT4 levels were observed during days 2 and 5 with fT3 reducing to a mean of 3.1 pmol/l (range 2-5.3, s.d. 0.98) and fT4 levels of 15.3 pmol/l (range 12.3–19.2, s.d. 2) Data on long term development of TSH, fT3 and fT4 were available for 9 out of 12 patients, showing levels of mean TSH of 1.8 mU/l (0.39–4.45, s.d. 1.16), mean levels of fT3 of 2.6 pmol/l (0.32–5, s.d. 2.0) and mean levels of fT4 of 16.07 pmol/l (1.7–19.5, s.d. 2). ACTH and cortisol levels were available in 10 out of 12 patients showing mean ACTH-levels of 6.6 pmol/l (2.8–12.1, s.d. 3.4) and mean cortisol levels of 356.8 nmol/l (158–893, s.d. 216.8).
Conclusion
We argue that transsphenoidal surgery for TSH-producing adenoma of the pituitary should always be considered as the treatment of choice. Even in patients harboring invasive tumors or giant adenomas remission following surgery is highly probable. Postoperative hypopituitarism is very unlikely if patients are referred to centers with high case load of pituitary surgery.

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EP900

Impact of the GH-receptor antagonist pegvisomant on mammographic breast density in postmenopausal acromegalic women

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Background
Acromegaly is a severe systemic condition characterized by elevated circulating levels of growth hormone (GH) and insulin-like growth factor I (IGF-I) and increased mortality and morbidity. The role of GH and IGF-I in mammary hyperplasia is well established and GH/IGF-I elevation has been hypothesized to favor neoplastic development. We recently demonstrated that premenopausal females with active acromegaly may display an increased mammographic breast density (MBD) compared with healthy matched controls. In the present study, we aimed to evaluate the impact of treatment with the GH-receptor antagonist pegvisomant (PEGV) on MBD in postmenopausal acromegalic patients.
Patients and Methods
patients (mean age 59 yrs) with at least one mammogram available were evaluated. A second and a third mammogram was available in 29 and 27 patients. Clinical and biochemical characteristics at the time of the first and last mammogram were recorded. Mammograms were evaluated using a validated software (MDEST) which provides a quantitative assessment of MBD on a percentage scale.
Results
At first radiological evaluation, 12 patients were treated with long-acting somatostatin analogues (LA-SSAs) combined with PEGV and 27 with LA-SSAs alone. MBD was slightly lower in patients treated with LA-SSA and PEGV compared with patients on SSA monotherapy (0.29±0.15% vs. 0.24±0.09%, n.s.). Interestingly, MBD significantly decreased in the 7 patients with moderate-high breast density, which started PEGV treatment after the first radiological

evaluation and performed a second and third mammogram in a 2 yrs time frame (0.43 ± 0.13% vs. 0.29 ± 0.8% vs. 0.26 ± 0.5%, $P = 0.01$).
Conclusions
The addition of PEGV to LA-SSA treatment in postmenopausal acromegalic patients with moderate-high MBD results in a significant decrease of MBD and could, therefore, reduce the risk of developing malignancy in these patients exposed to increased risk of breast cancer.

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EP901

High burden of illness at baseline in patients with uncontrolled acromegaly participating in the PAOLA study

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Background
The Phase III PAOLA study assessed the efficacy and safety of pasireotide LAR versus continued treatment with octreotide LAR or lanreotide Autogel in patients with uncontrolled acromegaly. The current analysis investigated overall baseline characteristics and response rates to pasireotide according to co-morbidities.
Methods
Patients were classified into five groups of co-morbidities related to acromegaly: glucose- ($n = 104$), endocrine- ($n = 127$), lipid-related ($n = 56$), vascular disorders ($n = 80$), and all other acromegaly-related disorders not included in these previous groups ($n = 111$). A sixth group consisted of patients without any acromegaly-related co-morbidity ($n = 17$). Baseline characteristics and efficacy were based on the total population ($N = 198$) and patients receiving pasireotide (N = 130), respectively.
Results
of patients had ≥1 co-morbidity, while 70%, 49%, and 24% had ≥2, ≥3, and ≥4 co-morbidities, respectively. The most common co-morbidities were endocrine related (64%; eg goitre and hypothyroidism), all other acromegaly related (56%; eg sleep apnoea and headache), and glucose related (53%, eg diabetes mellitus and impaired glucose tolerance), followed by vascular (40%, eg hypertension), lipid-related (28%, eg dyslipidaemia and hypercholesterolaemia), and without any acromegaly-related co-morbidity (9%). Across the five groups of comorbidities related to acromegaly, mean age (45.8–52.3 years), baseline insulin-like growth factor 1 (IGF-1; 2.2–3.1× upper limit of normal), and baseline growth hormone (GH) levels (9.0–12.4 μg/L) were similar. Across these same groups, pasireotide treatment reduced mean GH and IGF-1 levels from baseline to week 24 by 26.5–47.5% and 33.2–46.2%, respectively. Response rates to pasireotide (defined as GH < 2.5 μg/L and IGF-1 normalization at week 24) were similar (18.2–20.6%).
Conclusions
Most patients in the PAOLA study had multiple acromegaly-related co-morbidities at baseline. GH/IGF-1 response to pasireotide treatment was similar between groups of patients regardless of co-morbidity at baseline. Qualitative analysis of the effect of each co-morbidity on treatment outcome is ongoing.

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EP902

Craniopharyngiomas–35 years of experience in a central hospital's Endocrinology Department

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Introduction
Craniopharyngiomas are rare epithelial tumors of the sellar and parasellar region, with high survival rates but with frequent tumor recurrence or persistence.
Methods
Information collection from clinical records and review of the epidemiology, diagnosis, treatment and follow-up of patients with diagnosis of craniopharyngioma followed in an Endocrinology Department between 1980 and 2015. Statistical analysis using SPSS v. 22.0.
Results
Forty patients were included, 50% were male. Median age by diagnosis was 36 years (minimum 6, maximum 70). In respect to clinical manifestations at diagnosis, visual alterations were present in 77.5% ($n = 31$) and headache in 72.5% ($n = 29$). The majority of the tumors had sellar and suprasellar involvement (77.5%); cystic component was detected in 89.7% and calcifications in 47.5%. Initial surgical approach was transcranial in 74.4%, transsphenoidal in 25.6%. From the available neuropathology results ($n = 29$), 79.3% were adamantinomatous and 20.7% papillary. The average number of surgical interventions per patient was 2.03 (minimum 1, maximum 7). Eight patients (20.0%) were treated with radiotherapy. In the last neuroimaging evaluation, 47.5% of patients had residual tumor. Panhypopituitarism was detected in 6/30 patients preoperatively and in 23/39 in follow-up. All the isolated anterior pituitary deficits were also more frequent in follow-up. Weight gain was seen in 83.9% of patients. Prevalence of diabetes Mellitus, arterial hypertension and dyslipidemia also increased. Average follow-up time was 15.5 (±10) years. Six patients died, of whom four had been diagnosed between 6 and 14 years of age.
Conclusion
Despite the evolution in neurosurgical technique and the possibility of radiotherapy, craniopharyngiomas are still associated with high rates of tumor persistence and substantial morbidity. Optimization of the treatment of any endocrine and metabolic sequelae of the disease is essential in the management of these patients.

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EP903

Acromegalic cardiomyopathy: echocardiographic and CMR analysis

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Introduction
Acromegalic cardiomyopathy is characterized by myocardial hypertrophy and interstitial myocardial fibrosis at biopsy. We studied left ventricular hypertrophy -LVH- through echocardiography (-ECHO- 2-D standard echocardiography and Doppler analysis) and cardiac magnetic resonance (CMR) analysis. Myocardial fibrosis was studied with late enhancement technique (LE) and extracellular volume technique (ECV) at CMR.
Methods
25 patients -pts- (13 males) with an average age of 49.24 ± 11.96 yy, mean IGF-1 324(186-626) ug/L, 17pts with active disease, 9 pts had a newly diagnosed disease. Results of the CMR (on 24 pts) were compared with those of 20 controls -CTR- matched for sex and age.
Results
On ECHO: 10pts reported LVH (mean left ventricular mass index LVMi = 118.83 ± 26.32 g/m^2), 17 pts had first grade diastolic dysfunction (E/A = 0.81 ± 0.3). There was no correlation between the echocardiography data and IGF-1. On CMR: 5pts had LVH (median LVMi = 64.2g/m^2). Pts with LVH had higher IGF-1 levels than pts without LVH (Median = 801 μg/l vs 267 μg/l; $P = 0.01$); pts with active disease had higher LVMi values than non-active pts (Median = 70.2 g/m^2 vs 61g/m^2; $P = 0.007$); there was a significant correlation between IGF-1 and LVMi ($r = 0.63$; $P < 0.05$). LE was found in 9 pts. Pts's ECV was significantly elevated in comparison to CTR (pts = 24.05 ± 3.2% vs CTR = 19.99 ± 1.58% $P < 0.0001$). LVMi at CMR had a significant correlation with LVMi at echocardiography ($r = 0.5$, $P < 0.05$).
Conclusions
This study confirms that LVH and diastolic dysfunction are key features of acromegalic cardiomyopathy. Both macroscopic (LE) and interstitial fibrosis (ECV) are common findings in acromegaly.

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EP904

Subarachnoid haemorrhage results in poor quality of life independent of pituitary hormone concentrations

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Introduction
Subarachnoid haemorrhage (SAH) is associated with a mortality rate of 30% and the survivors face significant morbidity including fatigue, isolation, depression and sleep disorders; factors affecting general health related quality of life (QoL). QoL is also known to be decreased in pituitary-hypothalamic insufficiency and tends to improve after treatment. SAH has been suggested to be a common cause of hypopituitarism by some whereas not by others. We aimed to investigate if aneurismal SAH results in changes in QoL and if these changes relate to the concentrations of pituitary hormones.
Methods
We performed a cross-sectional evaluation including a subgroup with prospective follow-up. QoL measurements were performed at 12 months post-SAH in 62 patients with SAH and 30 healthy controls. Twenty-six of the patients were followed prospectively (3-, 6-, and 12-months) post-SAH. Full anterior pituitary assessments, including stimulation tests for growth hormone and adrenal insufficiencies, were performed on collected blood samples at all time points. QoL evaluation was assessed by using two generic questionnaires, the euroQoL-5D (EQ-5D) and Nottingham Health Profile (NHP) and one specific of growth hormone deficiency (GHD), the Quality of Life Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA).
Results
Post-SAH patients scored significantly lower on all QoL questionnaires (NHP, EQ-5D and QoL-AGHDA) when compared to controls 12 months post-SAH (all patients), as well as at 3-, 6-, and 12 months (prospective subgroup). Pituitary hormone levels at 12 months were found to be within the normal range. No correlations between QoL measurements and pituitary hormone levels were found, and there were no significant differences in QoL between patients with the lowest and highest hormone levels, respectively ($P > 0.08$ for all comparisons).
Conclusion
SAH is associated with long term worsened QoL, but it appears to be independent of pituitary hormone concentration, and thus rather a consequence of the SAH *per se*.

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EP905

Incidental finding of "Empty Sella" and prevalence of endocrine disturbances – a systematic review

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Neuroimaging techniques have improved over the last years; hence an "empty sella" is more often incidentally diagnosed. The term "empty sella" describes a missing pituitary gland in the sella turcica. Up to now, it is not known if routine endocrine assessment is necessary in patients with primary empty sella syndrome (PES) without clinical suspicion or history of neuroendocrine disorders.
We performed a systematic literature research using the search term "empty sella" in the databases PubMed/MEDLINE and Web of Science. Studies published between 1995 and 2015 were included according to the PRISMA four-phase flow diagram. A cross-sectional quality appraisal tool was used to assess quality of studies. Only studies in which endocrine diagnostics were performed properly according to published guidelines were included into our analysis.
A total of 615 studies were identified. We excluded all reviews, pediatric studies, animal studies and case reports (less than $n = 3$ patients). Only 25 studies addressed the question of prevalence of neuroendocrine disturbances in PES; only 4 studies referred to an incidentally diagnosed PES. The pooled prevalence rate of hypopituitarism was $50.5\% \pm 21.6\%$. Isolated pituitary insufficiency was less frequent than impairment of two or more pituitary hormonal axes ($22.0\% \pm 13.2\%$ vs. $31.5 \pm 20.5\%$). Growth hormone deficiency was reported to be the most frequent disorder irrespective of grade of empty sella (partial or complete) or number of pituitary deficiencies. Reported prevalence of ACTH-insufficiency varied from 9 to 37.5%. Panhypopituitarism seems to be rare (reported prevalence from 0% up to 19%); likewise hyperprolactinemia (mean prevalence $12.9\% \pm 6.3\%$) or diabetes insipidus (reported prevalence from 0% to 5%). Overall, gender and BMI seem to be associated with the prevalence of PES, as $77.6\% \pm 11.4\%$ of all patients were female and the mean reported BMI was 29.1 ± 0.3 kg/m^2.
Data on an incidentally diagnosed empty sella in asymptomatic patients are scarce. Based on our data and on expert opinion, we recommend performing routine neuroendocrine diagnostic in patients with an incidental finding of "empty sella".

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EP906

Quality of life in patients with acromegaly and the effect of somatostatin analogues

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Objective
Quality of life is currently considered a major factor in the assessment of disease outcome. The aim was to assess quality of life in acromegaly and the effect of somatostatin analogues on it.
Design
This study included 101 patients with acromegaly, mean age 59.51 ± 1.35 years (mean ± S.E.M.), with a disease duration of 12.88 ± 0.96 years. All subjects completed the Acromegaly Quality of Life Questionnaire (AcroQoL) which is a disease-specific questionnaire for patients with acromegaly. It contains 22 questions with five possible responses. Each response is scored from 1 to 5 and the maximum score is 110 whereas the minimum score is 22. A group of 27 patients were treated initially with a somatostatin analogue s.c. in 3 divided daily doses and subsequently long acting somatostatin analogues, whereas 72 were treated with long acting somatostatin analogues as a primary medical treatment.
Results
Quality of life as assessed by AcroQol was found to be impaired in acromegaly. The administration of somatostatin analogues was found to improve quality of life in acromegaly. Acromegalics showed a mean total AcroQoL score of 53.22 ± 1.87 (mean ± S.E.M.) before treatment. Total AcroQol after treatment was 73.59 ± 2.97 for patients who initially received somatostatin analogues 3 times daily ($n = 27$), and 86.15 ± 1.37 for all the patients who received long acting somatostatin analogues once per 28 days (27 patients who first received short acting and 72 patients who received long acting somatostatin analogues as a primary treatment) ($P < 0.001$)
Conclusions
Quality of life is impaired in acromegaly. The administration of somatostatin analogues is related with better quality of life. Long acting somatostatin analogues improve quality of life more than short acting somatostatin analogues.

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EP907

Serum N-terminal pro brain natriuretic peptide level in patients with prolactinoma who were treated with cabergoline

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Introduction and aim
Cabergoline, a long-lasting dopamine-agonist, is generally considered to be the safety drug for the treatment of prolactinoma. But, use of long time and high dose cabergoline may be a cause of cardiac valvulopathy in patient with prolactinoma. In present study, we aim to determine serum N-terminal probrain natriuretic peptide levels in patients with prolactinoma who were treated with cabergoline.
Materials and methods
Thirty patients with prolactinoma who applied to our endocrinology outpatient clinic (mean age 33.4 ± 8.5 years and body mass index (BMI): 28.1 ± 7.8 kg/m^2), 30 age- and BMI matched (mean age 30.0 ± 9.8 years; BMI: 26.8 ± 6.4 kg/m^2) patients who were determined another cause of hyperprolactinemia except

prolactinoma, and age- and BMI matched healthy individuals (mean age 31.0 ± 7.0 years; BMI: 25.2 ± 2.9 kg/m^2 were included in the study. Cumulative cabergoline dose was calculated in patients with prolactinoma who have received prior cabergoline therapy. Anthropometric measurements were performed. Blood pressure was measured in accordance with its thecnic. Serum samples for NT-pro BNP levels were stored −20° C. All biochemical and hormonal analysis were performed by automatic analyzer.

Results

We found that serum NT-pro BNP levels were not significantly different between study groups (63.9 ± 39.8 pg/ml in prolactinoma group, 47.3 ± 31.2 pg/ml in hyperprolactinemia group and 57.2 ± 28.3 pg/ml in control group, $P = 0.160$). Mean cumulative cabergoline dose (CCD) were calculated as 218.1 ± 252.5 (range 52–1248 mg). However, we did not determine any correlations between serum NT-pro BNP levels and cumulative cabergoline dose, and between serum NT-pro BNP and prolactine levels. There was only a positive correlation between CCD and systolic blood tension ($r = 0.213$, $P = 0.044$).

Conclusions

According to our findings, cabergoline treatment does not influence serum NT-pro BNP levels in prolactinoma patients. Advanced studies which were included more patients with prolactinoma need to clarified this topic.

Keywords: Prolactinoma, cabergoline, NT-proBNP.

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EP908

Vitamin D status of adults with growth hormone deficiency

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Introduction

Vitamin D and growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis are reported to interplay at both endocrine and paracrine levels, with a positive correlation between IGF-1 and 25-hydroxyvitamin D (25(OH)D) in healthy subjects. Hyposomatotropism is among the conditions predisposing to lower vitamin D status due to several direct and indirect mechanisms. Thus, the aim of our study was to evaluate vitamin D status in a representative sample of adults with GH deficiency (GHD) and to investigate the association between serum 25(OH)D and age, gender and onset of hyposomatotropism.

Methods

This cross-sectional study included 129 adults (aged 42.1 ± 16.6 years, 70 males) diagnosed with GHD (41.9% with childhood-onset GHD (COGHD)) in the Clinical Centre of Endocrinology in Sofia, Bulgaria. Total serum 25(OH)D was the vitamin D metabolite used to assess vitamin D status and was measured by electro-chemiluminescence binding assay. Vitamin D status and GHD were defined according to the Endocrine Society Clinical Practice Guideline recommendations.

Results

Major part of the patients was diagnosed with vitamin D deficiency (79.1%, $n = 102$) and another 14.7% ($n = 19$) had vitamin D insufficiency. 25(OH)D levels >30 ng/ml were found in only 6.2% ($n = 8$) of the subjects. Mean 25(OH)D levels (15.1 ± 7.6 ng/ml) did not differ between men and women (15.7 ± 7.2 vs. 14.5 ± 8.1 ng/ml, $P = 0.387$) and correlated negatively and weakly with age ($r = -0.256$; $P = 0.003$). In the AOGHD subgroup, however, mean serum 25(OH)D was significantly lower compared with COGHD participants (14.0 ± 7.2 vs.16.8 ± 8.0 ng/ml, $P = 0.039$).

Conclusion

Data from our study demonstrated considerably high prevalence of hypovitaminosis D in GHD adults, with lower 25(OH)D concentrations among the subgroup with AOGHD. Therefore, 25(OH)D testing is highly recommended in patients with hyposomatotropism. Normalization of vitamin D status might have beneficial effects in GHD subjects, especially considering the additive effects of vitamin D and GH replacement.

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EP909

Renal function in acromegaly – experience from a portuguese centre

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Introduction

The Nephron is a known target organ of the Growth Hormone/Insulin-like factor-1 axis. They influence glomerular and tubular function having an important physiological role in water and electrolyte balance, especially in Acromegaly. The aim of the study was to investigate renal function in acromegalic patients during active disease and remission and evaluate hormonal impact on renal function markers.

Methods

A retrospective, longitudinal, observational analysis was performed regarding 52 acromegalic patients. Variables such as creatinine, glomerular filtration rate (GFR), IGF1/GH and the remainder pituitary hormones were evaluated. Descriptive statistical methods were used and the results are presented as mean and standard deviation. Pearson correlations and student *T*-test were used to analyze numerical data.

Results

52 acromegalic patients (69.2% females) with a mean age of 57 years were eligible to the study. The underlying etiology was a pituitary macroadenoma in 78.9% and 19.2% were treated with Radiotherapy. Disease control was achieved in 71.2%. Statistical significant correlations were found between IGF-1 and creatinine and eGFR (P 0.001 and 0.003 respectively). Patients in remission had a lower mean eGFR (79 vs 89 mL/min/1.73 m^2). Degree of elevation of IGF1 from the upper normal range (expressed in %) was correlated with eGFR, creatinine and metabolic parameters (Fasting blood glucose and glycated hemoglobin) with statistical significance.

Conclusion

The current study demonstrates consistently a possible positive correlation between IGF1/GH axis and renal function markers. Despite being a retrospective study, the sample size may further support the relevance of the GH/IGF1-renal axis in Acromegaly.

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EP910

High mean platelet volume in prolactinoma treated with cabergoline

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Introduction and aim

Mean platelet volume (MPV) is a new important indicator of platelet activity in atherosclerosis. Elevated MPV is associated with the presence of more metabolically active platelets. The aim of our study is to evaluate whether change of MPV value is associated with cabergoline treatment in patients with prolactinoma.

Materials and methods

Thirty patients with prolactinoma (mean age 33.4 ± 8.5 years and body mass index (BMI): 28.1 ± 7.8 kg/m^2), and 30 age- and BMI matched healthy control subjects (mean age 31.0 ± 7.0 years; BMI: 25.2 ± 2.9 kg/m^2 were recruited in our study. Cumulative cabergoline (CCD) dose was calculated. The MPV value was evaluated before and after cabergoline therapy and was compared to control group. Anthropometric measurements were performed. Patients have hematological and other endocrinologic diseases including diabetes mellitus were excluded from the study. All complete blood count, biochemical and hormonal analysis were performed by automatic analyzer.

Results

According to our findings, serum prolactin levels in prolactinoma before and after the cabergoline treatment were significantly different (128.0 ± 99.7 vs 35.5 ± 39.5 ng/ml, $P = 0.0001$, respectively). Mean cumulative cabergoline dose were calculated as 218.1 ± 252.5 mg. We found that the mean pre-treatment MPV values in prolactinoma group were lower than post-treatment MPV values (8.9 ± 0.8 and 9.6 ± 0.8 fL, $P = 0.0001$, respectively) and lower than control group (8.9 ± 0.8 and 9.8 ± 0.9 fL, $P = 0.0001$, respectively). There was no correlation both between post-treatment MPV and CCD. Moreover, there were not any relationships between MPV and both prolactin levels before and after the treatment.

Conclusions

The cabergoline treatment in prolactinoma may relate high MPV value independent to cumulative cabergoline dose and prolactine levels. The future study need to clarify this increment of MPV during low dose cabergoline therapy.

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EP911

Serum cortisol in the early post operative period after transphenoidal surgery to predict adrenal insufficiency

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Adrenal insufficiency is a common complication of transsphenoidal surgery (TSS) for pituitary adenoma. It is very important to identify patients requiring glucocorticoid replacement, minimising risks of adrenal insufficiency.
Aim
To assess the performance of early (3° day) post-TSS 08:00 a.m. cortisol measurement to detect and exclude secondary adrenal insufficiency.
Methods
We selected patients undergoing TSS in our hospital during 12 months and performed a 3° day postoperative 08:00 a.m. cortisol measurement and cortisol ± Synachten 6 months post-surgery. All patients received perioperative glucocorticoid replacement (First and second days postsurgery) unless basal cortisol was > 10 microg/dl and cortisol after Synachten > 23 microg/dl previous to surgery. We excluded patients with previous diagnosed and treated adrenal insuficiency. In patients with 3° day cortisol lower than 10 microg/dl we maintained glucocorticoid treatment until reevaluation with cortisol/Synachten 6 months post-surgery.In patients with 3° day cortisol higher than 10 microg/dl glucocorticoids were discontinued.
Results
Data were reviewed from 20 patients (9 males, mean age 52.8 years), 18 with macroadenomas, 8 patients with cushing disease. Patients with adenomas no cushing: all patients with 3° day cortisol > 15 microg/dl had normal cortisol/Synachten 6 months post-surgery. 2 patients with 3° day cortisol between 10 and 15 microg/dl had adrenal insufficiency 6 months postsurgery. 1 patient with 3° day cortisol < 10 microg/dl mantained adrenal insuficiency 6 months postsurgery. Cushing disease: all patients with 3° day cortisol > 10 microg/dl had not adrenal insuficiency 6 months postsurgery, all except one with recurrence. All patients with 3° day cortisol < 10 microg/dl had not recurrences, all except one with adrenal insufficiency.
Conclusion
A 3° day post-TSS cortisol > 15 microg/dl is a safe cutt off to discarge adrenal insufficiency. In cushing disease, a level < 10 microg/dl predict a low likelihood of recurrences.

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EP912

A neurosarcoidosis case with pituitary stalk involvement manifesting as hypogonadism and hyperprolactinemia

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Sarcoidosis is a multisystem granulomatous disease of unknown cause. The prevalence of neurosarcoidosis is about 5–15%. Hypothalamo-pituitary sarcoidosis is even rarer (< 1% of cases evaluated for sellar and stalk lesions).
Case Report
A 33-year-old man presented to urology department with erectile dysfunction which started six months ago. Hormonal evaluation revealed gonadotropin deficiency and hyperprolactinemia (Total testosterone: 30.5 ng/dl, LH: 2 mIU/ml, FSH: 1.9 mIU/ml, PRL: 32.2 ng/ml). His sellar MRI showed uniformly thickened pituitary stalk and gadolinium-enhancement of leptomeninges, posterior limb of internal capsule, base of third ventricle, suprasellar- perioptic regions, cerebellar hemispheres and pineal gland.
His medical history uncovered that he was diagnosed as pulmonary sarcoidosis four years ago for which he didn't receive any specific therapy and was lost of follow-up. He was diagnosed with deep venous thrombosis of lower extremity 4 months ago. Patient was put on anticoagulation therapy.
Bilateral hilar and mediastinal adenopathy was detected on thorax CT. The *endobronchial ultrasound*-guided transbronchial needle aspiration of hilar lymph node showed noncaseating granulomas consistent with sarcoidosis. These findings suggested a diagnosis of neurosarcoidosis with pituitary stalk involvement. This patient was treated with an initial dose of methylprednisolon (1 mg/kg/day) which was then tapered and azathioprine (150 mg/day) was added two months later because of partial response. Testosterone replacement was also initiated. MRI abnormalities regressed partially after 6 months of treatment accompanied by prolactin normalisation without any change in gonadotropin deficiency.
Conclusion
The pituitary involvement is usually associated with severity of sarcoidosis and hypogonadism is the most frequent manifestation. Sarcoidosis is also significantly associated with thrombosis risk as our case. Glucocorticoid and immunosuppressive therapy may improve MRI findings but effect on hormonal dysfunction seems to be limited. Physicians should be aware of hypothalamo-pituitary involvement of sarcoidosis since earyl treatment may rescue pituitary functions.

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EP913

An attempt to prepare local Guidelines for Management of Syndrome of Inappropriate ADH Secretion (SIADH) in a District General Hospital in the UK

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Aim
To establish the local Guidelines for management of SIADH.
Methods
The European and NIH Guidelines are considered.
Discussion
Diagnosis: Patients admitted with hyponatraemia are first assessed clinically for their hydration status. Those who are euvolaemic should have their urine sodium checked (if < 30 mmol/l, hypothyroidism is suspected and if > 30 mmol/l either SIADH or Addison's disease is suspected). Hypothyroidism and Addison's disease are first excluded biochemically. The diagnosis is established with serum sodium < 130 mmol/l, serum osmolality of < 275 mOsmol/kg and urine osmolality of > 100 mOsmol/kg, with normal renal function and the patient on no diuretic.
Management: 1) Fluid restriction to around 750 ml daily. 2) Investigation and treatment of cause (CXR, CT Thorax, Abdomen and Pelvis, CT head and stopping drugs like diuretics, antidepressants and antipsychotics, if possible). 3) Oral Tolvaptan (vasopressin receptor-2 antagonist) 7.5–15 mg can be initiated daily as inpatient. Plasma sodium is monitored at 6, 12, 24 and 48 hours and thereafter daily. Free fluid intake is recommended when on Tolvaptan. 4) Demeclocycline 600-1200 mg/day (if available). Renal function should be monitored. 5) Urea in dosages of 10–40 g/day causes osmotic diuresis and enhanced water excretion. This form of treatment is cost effective and corrects hyponatremia slowly, by 2–3 mmol/l/day. 6) In acute emergencies (on ITU): 3% hypertonic saline is to be used at the dose of 150 ml over 20 minutes and can be repeated according to 2014 European Guidelines. The infusion should stop when the symptoms improve or the serum sodium increases 10 mmol/l in total or its concentration reaches 130 mmol/l, whichever occurs first. The combination of intravenous saline and a loop diuretic may sometimes be helpful.
Conclusion
Plasma sodium rise should not exceed 10 mmol/l/day and 18 mmol/l in 48 hours. In refractory cases, haemodialysis, CVVH and SLEDD may be helpful in specialist centres.

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EP914

The association between adenoma size classification and the hormone hypersecretion in acromegaly

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Introduction
Acromegaly is a chronic disease caused by growth hormone (GH) oversecretion. A pituitary macroadenoma is found in mostly of cases, but the secretion pattern of GH and insulin-like growth factor 1 (IGF-1) and the natural history of somatotropinomas are heterogeneous. The objective of the present study was to evaluate the relationship between tumor size, GH and IGF-1 levels in patients diagnosed with acromegaly.

Methods
A cross-sectional, observational, descriptive study was carried out in acromegaly patients ($n=25$) attending our Neuroendocrinology Outpatient Clinic at the local university hospital. Patients' anthropometric data, biochemical investigations and adenoma size by MRI at diagnosis were recorded. Basal GH and IGF-1 blood levels (chemiluminescent immunometric assays) were obtained; IGF-1 relative to the upper limit of the normal range (IGF-1_ULN) and the mean standard deviation scores (IGF-1_SDS) were calculated from each patient. ROC curves analysis were performed to determine the discriminative ability of GH, IGF-1, IGF-1_ULN or IGF-1_SDS in predicting the presence of a GH-secreting Macroadenoma (≥ 10 mm). The results were expressed as sensitivity (S) and specificity (Sp).
Results
Based on the tumor size MRI classification, 76% of the tumors were macroadenomas (1.85 ± 1.08 cm maximal diameter; mean $\pm$ S.D.). The biochemical variable IGF-1 exhibited the highest area under the curve (AUC $=0.88$, $P<0.01$) with a cut-off point of 703.6 ng/ml (S $=88\%$; SP $=83\%$). IGF-1_mean and IGF-1_ULN presented cut off of 4.2 and 2.8, respectively with identical AUC values (0.80); $P=0.03$, S $=82\%$, SP $=83\%$. GH level's cut-off was 4.520 ng/ml (AUC 0.73, $P=0.11$; S $=94.12\%$; SP $=50\%$). The most specific cut-off value for IGF-1 to discriminate between micro and macroadenomas was 1681 ng/ml (SP $=100\%$).
Conclusion
The basal GH level could not discriminate adenoma sizes, while IGF-1 values were able to indicate the presence of macroadenoma. The absolute IGF-1 blood concentration was more effective than relative values.

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EP915

Prolactin measurements improve the diagnostic accuracy of inferior petrosal sinus sampling

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Introduction
Inferior petrosal sinus sampling for ACTH is the current gold standard test for the differentiation of pituitary Cushing disease from the ectopic ACTH syndrome. Early studies with İPSS reported a diagnostic sensitive and specificity approaching 100%, additional experience has shown a false negative rate of 1-10%. This has been due to either technical problem with unsuccessful petrosal sinus catheterization or anomalous venous drainage of the pituitary. The measurement of other anterior pituitary hormones may be useful during İPSS to improve the accuracy of the procedure.
Objective
The aim of the study is to increase the accuracy of the inferior petrosal sinus sampling procedure and reduce the false negative rate through the addition of prolactin as a marker of pituitary venous outflow as well as validate this adjunct to the test process.
Method
İn this retrospective cohort study, we reviewed 33 patients who had undergone IPSS for the investigation of ACTH dependent hypercortisolism at Marmara university hospital between 2011-2015. Plasma ACTH and Prolactin levels were measured both centrally and peripherally. The normalized ACTH/prolactin inferior petrosal sinus/peripheral ratio was then calculated to asses the accuracy of the sampling procedure.
Results
Thirty-three patients with confirmed ACTH dependent cortisol excess underwent investigation with İPSS. Thirty-two patients initially had a positive İPSS result (i.e. a basal central/peripheral ACTH ratio >2, and >3 post CRH). When the corrected prolactin data were used, one patient was additionally found to have positive result suggestive of pituitary Cushing's. The prolactin normalized ACTH IPS/peripheral ratios were all >0.8 in patients proven Cushing's disease.
Conclusion
Normalizing the İPS/peripheral ratios with prolactin helps to improve the accuracy of the results and reduces the false negative rate.

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EP916

Acromegaly: is there a need for colorectal cancer screening?

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Objective
Acromegaly is characterized by chronic hypersecretion of growth hormone (GH) with increased concentration of IGF-1. There have been controversial debates over the question whether elevated GH levels indicate high risk of developing colorectal neoplasm. There is no clear guideline indicating the need for colorectal cancer screening for acromegalics. We evaluated the colonoscopic findings in our series of patients to analyze the prevalence of risk. Should patients with acromegaly undergo screening for colorectal cancer?
Methods
Full-length colonoscopy was performed on 24 patients within one week after transsphenoidal surgery. The study includes 13 male and 11 female aged 27–62 years. We analyzed the colonoscopic findings - taking histological, hormonal and clinical data into account.
Results
All of the patients were asymptomatic prior to colonoscopy. None of the patients had a positive family history of colorectal cancer. 3 patients showed normal findings, 3 patients were diagnosed with diverticulosis, 2 patients showed inflammatory lesions, 1 patient showed parasite infestation. 8 patients were detected with multiple polyps. 7 patients showed premalignant adenomas. In this respect IGF-1 levels and duration of disease were similar to those with no precancerous lesions. Mean time between symptom onset and diagnosis was estimated as 10 years.
Conclusion
In our series we could detect a high prevalence of premalignant tubulovillous adenomas (7/24) and hyperplastic polyps (8/24) in patients with acromegaly. The results suggest the necessity for routine colorectal cancer screening in this group of patients.

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EP917

The role of p16 and MDM2 gene polymorphisms in tumorigenesis and characteristics of prolactinoma

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Introduction
Prolactinomas are thought to arise from the proliferation of a mutated pituitary stem cell which is subjected to the growth stimuli of several permissive factors, although the pathogenetic mechanisms underlying the tumorigenesis still remain unclear. The present study aimed to investigate the role of p16 (540C $\rightarrow$ G and 580C $\rightarrow$ T) and MDM2 (SNP309T $\rightarrow$ G) gene polymorphisms in tumorigenesis and characteristics of prolactinoma.
Methods/Design
74 patients with prolactinoma and age- and gender-matched healthy subjects were enrolled in the study. Serum prolactin levels were measured by enzyme linked immunosorbent assay. DNA was extracted from peripheral blood samples then p16 and MDM2 polymorphisms were determined by polymerase chain reaction-restriction fragment polymorphism and agarose gel electrophoresis.
Results
p16 540C $\rightarrow$ G genotype distribution was found as CC:66.2%, CG:28.4%, GG:5.4%; p16 580C $\rightarrow$ T genotype distribution was found as CC:82.4%, CT:17.6%, TT:0% and MDM2 genotype distribution was found as TT:31.1%, TG:47.3%, GG:21.6% in patients with prolactinoma. Tumor diameter before treatment was correlated with prolactin levels before treatment and percentage of prolactin decrease with treatment ($P<0.001$ $r=0.719$, $P=0.034$ $r=0.256$, respectively). Tumor diameter after treatment was correlated with prolactin levels ($P<0.001$ $r=0.569$). CC genotype (homozygote wild type) frequency is higher without statistical significance in both p16 540C $\rightarrow$ G and p16 580C $\rightarrow$ T polymorphisms among prolactinoma patients. The number of patients with tumor size decreased more than 50% in homozygous genotype (TT + GG) carriers of MDM2 SNP309T $\rightarrow$ G is significantly higher than in heterozygous genotype (TG) carriers ($P=0.003$, OR: 0.18, CI: 0.06–0.58).
Conclusion
This study showed that p16 and MDM2 polymorphisms do not play an important role in tumorigenesis, but some genotypes of these polymorphisms could be associated with follow-up characteristics of prolactinoma. Further studies are needed to clarify the underlying mechanisms of the tumorigenesis in order to define prognostic factors and facilitate appropriate treatment choices for patients with prolactinoma.

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EP918

Clinical proofs for necessity of macroprolactinemia screening

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Prevalence of macroprolactin in serum (>40%) can be a cause of asymptomatic hyperprolactinemia. However, there is still lack of evidence how to manage with symptomatic patients with macroprolactinemia.

We analyzed clinical data and monomeric prolactin levels in 85 women of reproductive age with hyperprolactinemia: NonTumor hyperprolactinemia (NT, $n=31$), MIcroadenomas (MI, $n=32$), MAcroadenomas (MA, $n=22$). Prolactin levels 1716 [1150; 2700] mIU/l; 2974 [1190; 3665] mIU/l and 3546 [1312; 48209] mIU/l, accordingly.

Prevalence of macroprolactin in serum was found in 16/31 (51.6%) NT, 9/32 (28.1%) MI, and 2/22 (9%) MA (a relative amount macroprolactin was 79 [75; 88] %). Among patients with macroprolactinemia normal levels of monomeric prolactin were found in 10/16 NT, 4/9 MI and 1/2 MA; all patients with normal monomeric prolactin levels had total prolactin levels <5000 mIU/l; only 6 NT and 4 MI were asymptomatic, other patients had menstrual irregularities and/or infertility and non-hyperprolactinemic reasons for these clinical symptoms were found after investigations.

Biological activity of hyperprolactinemic sera (as a proliferative response of Nb2 rat lymphoma cells) was evaluated *in vitro* in 8 patients with predominance of monomeric prolactin and in 5 patients with macroprolactiemia. Ratio 'Prolactin Immunoreactivity/Prolactin Bioactivity' varied 0.88–1.1 and 1.46–2.26 in these subgroups accordingly. Hence lower biological activity of hyperprolactinemic sera with the predominance of macroprolactin was proven.

Thus in cases of macroprolactinemia normal monomeric prolactin levels (with proven low biological activity of serum) can coexist with menstrual disorders and/or infertility due to other reasons, and mimic true hyperprolactinemic conditions. Some of patients with macroprolactinemia also had pituitary incidentaloma. To avoid misinterpretation of clinical and hormonal data we support assessing for macroprolactin in all patients with total prolactin levels <5000 mIU/l regardless of symptoms.

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EP919

Cardiovascular effects of obstructive sleep apnea syndrome (OSAS) on acromegaly

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Introduction

Acromegaly is known to be associated with obstructive sleep apnea syndrome (OSAS) in about 60–70% of the cases. Both OSAS and acromegaly are thought to be responsible from cardiovascular diseases and endothelial dysfunction. The aim of the present study was to investigate the role of OSAS on cardiovascular effects of acromegaly.

Materials and Methods

25 patients with acromegaly and 7 healthy volunteers were enrolled into the study. Cardiac and endothelial functions were evaluated with echocardiography (ECHO), carotis intima-media thickness (CIMT), aortic stiffness and flow mediated dilatation (FMD). All subjects were performed polysomnography (PSG). Patients were categorized into 3 groups according to their apnea-hypopnea index (AHİ). AHİ of <5 was accepted as normal, >15 as OSAS and between 5-15 as borderline.

Results

10 (40%) patients were found to have OSAS, 7 (28%) had borderline AHİ and 8 (32%) patients were normal. No differences were found between acromegaly and healthy controls in means of CIMT, aortic stiffness and ECHO parameters. FMD was found to be lower in acromegalic patients (8.9 ± 4.7%) than in healthy controls (18.8 ± 2.2%). FMD, CIMT, aortic stiffness and ECHO parameters were found to be similar in 3 acromegalic groups. No correlation was found between AHI and FMD, CIMT or aortic stiffness.

Conclusion

Acromegaly leads to endothelial dysfunction. Presence of OSAS in acromegalic patients does not seem to cause further deterioration of cardiovascular or endothelial functions.

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EP920

Fatigue and subjective complaints in patients with active and controlled acromegaly: a cross sectional multi-center study

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Introduction

Acromegalic patients (AP) often report fatigue and chronic subjective complaints. We aimed to investigate in more detail these aspects in AP, dependent on disease activity, age, gender, medication and pituitary insufficiency (PI).

Patients/methods

Cross sectional, 124 patients (M/W 51/73, age 58.3 ± 14.7 years, 49/75–active/controlled disease). The patients completed the Multidimensional Fatigue Inventory (MFI-20) and the Giessen Subjective Complaints List (GBB-24), after written informed consent. Age, gender, IGF-1 concentrations, comorbidities, treatment modalities and PI were documented.

Results

The MFI-20 inventory showed higher age- and gender-specific values on all fatigue subscales compared to controls (general and mental fatigue, decreased motivation and decreased activity), except physical fatigue, which was obviously higher only in patients under 60 years of age. No differences were observed between patients dependent on disease activity, age, gender and PI. The GBB inventory showed more gastric, joint and general complaints in patients with a disease duration >10 years. In this group, patients were older (62.2 ± 13.6 vs. 53.3 ± 14.4 years); however, 14/67 had an active disease compared to 35/57 patients with a disease duration ≤ 10 years ($P<0.001$). Patients with PI exhibited more exhaustion ($P=0.01$), gastric ($P=0.005$), joint ($P=0.02$) and general complaints ($P=0.006$) compared to patients without PI. Patients who needed chronic medication for disease control had higher scores for exhaustion than patients without medication ($P=0.03$). Interestingly, there were no significant differences between patients with active and controlled disease or between patients with one or more PIs. Even if complaint scores were higher in patients after more than one pituitary surgical intervention or after sellar radiotherapy, the differences did not reach significance.

Conclusions

AP display more fatigue than healthy controls. Chronic subjective complaints are more pronounced in patients with a disease duration >10 years, PI and medication for disease control, irrespective of the hormonal activity status.

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EP921

Quality of life, neurocognitive status and frequency of hypopituitarism following brain injury

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Background

Post traumatic Hypopituitarism (PTHP) is common, its prevalence is about 30%.

Aim
The aim is firstly to assess the frequency and predictive factors of hypopituitarism 3 and 12 months following Brain injury (BI) in a simple of 133 victims of moderate to severe BI in two neighbors' hospitals in the east of Algiers. Secondly is to evaluate the quality of life and neurocognitive status of this cohort.
Method
Hypopituitarism, evaluation of quality of life and neurocognitive status were searched in 133 victims of moderate to severe BI.
Result
Mean age was 32 years with male predominance. Traffic accident was the most frequent cause of BI. The frequency of PTHP at three months after injury was 44% with 31.5% of corticotrop failure, 18% of GH deficiency, 6.8% of gonadotropin deficiency, 6.8% of hypoprolactinemia, 1.5% of thyrotrophic deficiency and 3.8% of hyperprolactinemia. Predictive factors of occurrence of PTHP was skull base fracture, duration of intubation and coma and initial traumatic imaging. The prevalence of PTHP at twelve months after injury was 34.5% with 25% of corticotropic failure, 17.2% of GH deficiency, 8.6% of gonadotropic deficiency, 5.17% of hypoprolactinemia, 0.9% of thyrotrophic deficiency and 8.6% of hyperprolactinemia. Predictive factors of Twelve months PTHP was the duration of intubation and coma and polytraumatism. Among the patients with PTHP at three months 50.8% still in hypopituitarism. 14.8% of non PTHP patients at three months developed PTHP at 12 months. 40.67% of patients with hypopituitarism at three months have recovered their pituitary functions at 12 months. A link was found between PTHP and impairment of quality of life at 3 months and one year using AGHDA and SF-36 scales. PTHP patients have more neurocognitive disorders using NRS-R scale than non hypopituitaric patients at three months but not at 12 months after the injury.

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EP922

Clinical characteristics of giant pituitary adenomas

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Our Pituitary Tumour Registry includes data about 346 patients with pituitary macroadenomas: 142 non-functional adenomas (NFA) including 18 (12.7%) giant, 62 macroprolactinomas – 6 (9.7%) giant, 141 somatotropinomas – 6 (4.3%) giant. We analysed clinical features of these 30 giant pituitary tumors (<40 mm at least one of the sizes): 18 NFA (11 Females; 7 Males), 6 prolactinomas (3 Females; 3 Males), 6 somatotropinomas (3 Females; 3 Males). Patients with giant NFA were of the same age as others with NFA, however patients with giant prolactinomas and somatotropinomas were 10–15 years younger than mean age of their group.
According to MRI data pituitary sizes were: NFA – sagittal 28–56 mm (35 [31; 43] mm); vertical 23–51 mm (42 [33; 45] mm), frontal 26–62 mm (42 [36; 46] mm); prolactinomas – sagittal 40–62 mm (43.5 [41.5; 59] mm), vertical 25–65 mm (46 [37; 56] mm), frontal 30–62 mm (50 [32; 58] mm); somatotropinomas – sagittal 23–67 mm (53 [39.5; 65.5] mm), vertical 30–61 mm (49.5 [40; 54], frontal 34–60 mm (47 [37; 60] mm).
Pituitary tumour volumes were: NFA 16,998–68,753 mm^3 (Median 28,190 [21,143; 44,896] mm^3); prolactinomas 16,876–130,760 mm^3 (48,091 [30,331;97,843] mm^3; and somatotropinomas 19,644–124,501 mm^3 (51,209 [36,703;102,207] mm^3). The most often observed tumour growth directions were supra-latero-infrasellar ($n=19$, 63.3%), and supra-latero-sellar ($n=6.20\%$). Chiasm compression visualized on MR-images in 24 (80%) patients (18 NFA, 3 prolactinomas and 3 somatotropinomas).
Main complains were visual impairment (18 patients, 60%) and headache (12 patients, 40%), and most often "first referred" specialists were ophthalmologist and neurologist in 15 (50%) and 11 (36.7%) cases, accordingly. Hypopituitarism before any treatment was found in 10 (33.3%) cases (7 NFA, 1 prolactinoma, 2 somatotropinomas), all tumors had vertical size >40 mm and significant suprasellar extension.
Thus, age <50 y.o. and tumor volume $>70{,}000$ mm^3 were predictors of hormonal activity of giant adenoma; vertical size >40 mm and suprasellar extension were predictors of hypopituitarism; ophthalmologist and neurologist should be aware of giant adenomas.

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EP923

Recurrent meningitis secondary to medically induced CSF leakage in the setting of a pituitary macroprolactinoma

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A 49 year old gentleman was diagnosed with a pituitary macroprolactinoma at Leicester Royal Infirmary (LRI) (Baseline prolactin 8000 mU/l). He was treated with Cabergoline 0.5 mg twice/week. He developed CSF rhinorrhoea shortly after treatment was commenced and was listed for repair under the neurosurgical team at Queen's Medical Centre (QMC). Six weeks later, while visiting Wales, he was admitted to Bangor hospital with headaches and vomiting. CSF cultures were positive for pneumococcus so he was treated with a 10 day course of Ceftriaxone. He continued on cabergoline and this was associated with persistence of his CSF leak. He was discharged without prophylactic antibiotics with a plan for his CSF repair to be done 6/52 later at QMC in Nottingham. He was re-admitted to the LRI 3 weeks later with similar headaches and vomiting and was treated for recurrent meningitis with Meropenem despite negative cultures on CSF. He improved clinically, but he continued to experience a significant CSF leak. Two weeks later, he had a trans-sphenoidal repair of the sella using abdominal fat and fascia. This procedure as was unsuccessful, 4 weeks later, he underwent a second endoscopic repair with a vascularized nasoseptal flap and was discharged with no further problems.
Discussion
CSF rhinorrhoea may occur in the setting of pituitary adenomas, following a favourable response of invasive prolactinomas to initiation of dopamine agonist therapy. This risk might be even greater with cabergoline than with other dopamine agonists, due to the high sensitivity of prolactinomas to cabergoline. CSF leakage can occur within days of treatment and even minimal tumour shrinkage may lead to the development of a CSF fistula. Thus, we advise monitoring these patients closely and to actively forewarn them of this complication and the risk of life threatening meningitis. In this situation, prophylactic antibiotics to prevent meningitis remain controversial. Surgical intervention via a trans-sphenoidal approach is the *recommended initial treatment for definitive repair of the CSF leak.*

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EP924

Coexidence of neuroendocrine tumor of the lung and pituitary adenoma – pitfalls in diagnosing acromegaly - case report

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Acromegaly is caused by growth hormone-secreting adenoma in more then 95% cases. Ectopic secretion of GH-RH is a rare cause of acromegaly accounting for less than 1% of all cases. The most frequent source of ectopic GHRH is bronchial carcinoid. Clinical and biochemical findings are similar in both conditions. A distinction of pituitary vs extrapituitary acromegaly is important in planning effective management and both reasons should be considered in the diagnostic process.
Case report
An 80-year-old woman with the clinical features of acromegaly (hypertension, congestive heart failure, osteoarthritis of the knees, carpal tunnel syndrome, enlargement of mandibule, hands and feet) was admitted to the Endocrinology Unit for further evaluation. The lab test confirmed acromegaly. The pituitary tumor was not found on MRI. The hypothesis of acromegaly secondary to ectopic GHRH secretion was propounded. The lung tumors ($9\times9\times6$ mm and 5 mm) were detected in CT scans. There was no confirmation of lung or pituitary pathology in somatostatin receptor scintigraphy. PET-CT revealed a presence of higher expression of somatostatin receptors in 10th segment of left lung. The lung tumor was successfully removed (histologically NET). The postoperative IGF1 level was still elevated with no GH suppression during the OGTT. The MRI of the pituitary was repeated and finally pituitary tumor was found ($3.5\times7\times4.5$ mm anterior lobe). The patient was successfully operated and biochemically cured.
Conclusions
Despite the rare occurrence of acromegaly, it shoild always be considered during the diagnosis. Only detailed evaluation may facilitate prompt diagnosis and recovery from this destructive disease.

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EP925

Macroprolactinemia: prevalence and clinical characteristics in a cohort of hyperprolactinemic patients assessed for macroprolactinemia

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Macroprolactin is a collective term for a heterogenous group of high molecular mass forms of prolactin with minimal bioactivity *in vivo*. Objective: to determine prevalence of macroprolactinemia (macroPRL) and clinical characteristics of patients with hyperprolactinemia (hyperPRL) who underwent assessment for macroPRL in Endocrinology outpatient clinic.
Methods
We reviewed the medical records of 54 patients who were evaluated for macroPRL between 04/2010-10/2015. MacroPRL was evaluated by PEG serum precipitation (prolactin recovery $\leq$40%-macroPRL, 40–60%-inconclusive $\geq$60%-absence of macroPRL).
Results
Fifty four patients (49 women; 5 men) underwent assessment for macroPRL: 21 (38.9%) had macroprPRL, 29 (53.7%) monomeric hyperPRL and 4 (7.4%) were not conclusive. Among premenopausal women with macroPRL the most common complaints were: galactorrhea (23.5%), menstrual irregularities (29.4%), infertility (29.4%), while among those with true hyperPRL they were found in 45%, 50%, and 15% respectively. No symptoms were reported in 22.2% of patients with macroPRL and 14.8% with true hyperPRL. Three male patients had macroPRL and symptoms: erectile dysfunction, infertility or galactorrhea. Two men with true hyperPRL presented: erectile dysfunction with gynecomastia and headaches with visual disturbances. Six patients with macroPRL had performed pituitary image studies before assessment of macroprolactin: 1 microadenoma with deviation of the pituitary stalk and 3 not conclusive. Twenty two patients with true hyperPRL underwent image studies: 7-normal findings, 2-microadenoma, 2-macroadenoma, 4-not conclusive, 1-extra-pituitary infra-sellar lesion. Comments: in our study high prevalence of macroPRL (38.9%) was observed. Symptoms were common in macroPRL and true hyperPRL groups and the number of asymptomatic patients was similar. It confirms that it is not possible to distinguish macroPRL from true hyperPRL on the basis of clinical characteristics and laboratory screening is required. Assessment for macroPRL should be a part of initial evaluation of hyperPRL, not only reserved to asymptomatic patients. If macroPRL is not recognized it results in misdiagnosis, unnecessary imaging and treatment.

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EP926

Pituitary tuberculosis: a cause of giant cell granulomatous hypophysitis presented with hypopituitarism

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Introduction
Giant cell granulomatous hypophysitis is a rare chronic inflammatory disorder of the pituitary gland. It is generally presents with a clinic of sellar mass lesion with pituitary insufficiency. Histologically it is characterized by composites of histiocytes, plasma cells and giant cells with or without areas of necrosis. Tuberculosis is a very rare cause of secondary granulomatous hypophysitis. We report a case presented with hypopituitarism symptoms due to tuberculosis etiology and pathology revealed non-caseating giant cell granulomatous hypophysitis.
Case Report
A 51-year-old female admitted to our clinic with symptoms of mild headache and lethargy. Laboratory findings revealed TSH: 2.28 μIU/ml (normal, 0.34–5.6) fT_3: 2.08 pg/ml (normal, 2.5–3.9) fT_4: 0.56 ng/dl (normal, 0.61–1.12). The laboratory findings were suggest the central hypothyroidism. Gonadotropin levels were consistent with menopause. Basal cortisol level was found 2 μg/dl. Serum sodium and potassium levels were in normal range. Insulin tolerance test was performed for evaluation of the peak levels of cortisol and GH response. Peak GH and cortisol levels found 0.43 ng/ml and 14.75 μg/dl, respectively. Afterwards a diagnosis of pituitary hormone deficiency was made. Steroid was initially started and later on levothyroxine therapy was added. MRI showed a significant enlargement in adenohypophysis. Transsphenoidal biopsy of sella was done for the diagnosis. Pathology showed multinucleated giant cells characterised noncaseating granulomatous inflammation. Stain for acid fast bacilli and fungal etiologies were negative. The evaluation of etiology and differential diagnosis of granulomatous hypophysitis was done. Tuberculosis was diagnosed. The patient was started to receive antitubercular therapy including Pyrazinamide, Streptomycin, Isoniazid and Rifampicin for first 3 months, after that continued with Isoniazid and Rifampicin for 9 months.
Discussion
Pituitary tuberculosis should be considered in the differential diagnosis of granulomatous hypophysitis. The early and quick diagnosis is an important concern because the disease may be reversible with anti tubercular therapy.

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EP927

Results of transsphenoidal surgery and somatostatin analogues therapies and their combination in acromegaly

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Introduction
Data on transsphenoidal surgery (TSS) and effect of somatostatin analog therapy (SSA) in acromegaly different among medical centers. We analyzed the data on TSS, SSA and their combination in acromegalic patients of Moscow region.
Design
In this study 117 acromegalic patients (25 males and 92 females, 55.0 (IQR 44 – 62) years) were eligible for participation, of whom 34 were newly-diagnosed aromegaly (NA group) (macroadenoma (macro)- 80%), 35 primary treated with SSA group (macro −60%), 29 after TSS group, (macro −73%), 19 SSA after TSS (macro – 95%). In 34 NA patients we assessed efficiency after 6 months of SSA (23 patients) (macro −78%) and TSS (10 patients) (macro −70%). We also assessed efficiency of SSA therapy after 6 months in 10 patients (macro −100%) without control of acromegaly after TSS (SSA + TSS).
Results
In micro adenoma cases number of patients with controlled phase of acromegaly was comparable between TSS and SSA groups (47% and 43%). In macro adenoma cases controlled phase of acromegaly was greater in TSS and TSS + SSA groups in compare with SSA group (43%, 40 and 35% accordingly). Among NA patients, who started treatment of SSA or underwent TSS the %ULN of IGF-1 greater decreased in TSS group than in SSA group ($P<0.05$) (from 172 (83.7–238.1) to −22.6 (−36.7–23.7)% ($P<0.05$) and from 227 (136–342)% to 30.7 (3.0–118.4)%, accordingly, ($P<0.05$)). In group TSS + SSA the %ULN of IGF-1 decreased from 158.5 (53.7–215.8)% to 1.4 (−11.7–34.5)% accordingly, ($P<0.05$). The controlled phase of acromegaly in macro- and micro adenoma cases was reached in 40% and 50% after primary SSA treatment, in 57% and 100% after primary TSS, accordingly, and in 50% in SSA + TSS.
Conclusion
The primary TSS lowered IGF1 values more efficiently and allowed to reach control of disease in compare with primary SSA treatment, especially in macro adenoma cases in acromegalic patients.

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EP928

Bone metabolism in acromegaly

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Aim
To evaluate calcium and bone metabolism in a monocentric series of acromegaly patients (pts), treated with pegvisomant (PEG) alone or in association to long acting somatostatine analogs.
Patients and methods
All pts with at least 24 consecutive months PEG treatment (alone or in combination with SSA) were enrolled. All pts had been tested at least twice/year

for biochemical acromegaly-disease evaluation and annually for calcium metabolism and for bone metabolism though serum test. In all the cases, BMD of femoral neck and lumbar spine was measured by DXA. Measurements were made at the time of the spinal X-ray. Fractured vertebrae (VF), were excluded from the lumbar BMD analysis. A quantitative morphometrical assessment of VFs in the T4–L4 region had been performed using a dedicated morphometrical software (Spine-X Analyzer, ICAM Diagnostics, Milan, Italy).
Results
A total of 24 pts met the inclusion criteria. 8 were male (33.3%). Mean age at acromegaly diagnosis was 39.3 years. 11 pts had a biochemically controlled acromegaly (45.8%). PEG treatment was prescribed in 5 cases as monotherapy. A total of 16 VFs were documented and occurred in 8 pts. Mean spine BMD was 1.09 and mean femoral BMD was 0.9. VF, spine and femoral BMD are not influenced in our series from gender, GH receptor isoform expression, secondary hypogonadism, menopause, bone metabolism markers and hormonal replacement treatment for hypogonadism, hypoadrenalism and hypothyroidism. We found that biochemically acromegaly status strongly correlated with VF: a higher number of VF were observed in not biochemically controlled acromegaly pts. Moreover, active acromegaly status correlated with a 10-folds higher risk of VF ($P=0.012$, OR: 10.12 95%IC 1.47–69.9). Moreover, in male acromegalic pt, VF correlated also with lower serum testosterone ($P=0.02$) and SHBG value ($P<0.001$). In female acromegaly pts we failed to find any correlation between gonadic status and VF. In conclusion, our study confirm the risk of VFs in acromegaly and suggest that fracture risk is higher in not biochemically controlled acromegaly pts, particularly in males with low testosterone value.

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EP929

Clinical management of pituitary teratomas and safety of rhgh replacement therapy: a case report

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Teratomas comprise 0.5% of all intracranial tumors. 15 cases of sellar teratoma have been described in the last 24 years (yrs). A 29-yrs female pan-hypopituitaric patient (pt) was admitted to our Pituitary Unit. At 6-yrs age, for polyuria and growth delay, an endocrine evaluation revealed diabetes insipidus and hypopituitarism. Cranial contrasted-MRI (cc-MRI) showed pituitary stalk thickening and a low intensity suprasellar lesion. Histological examination (HE) was suggestive for germinoma. Conventional radiotherapy was performed. After 6 months (mts) for disease-progression, a second biopsy was performed and HE was suggestive of 3th ventricle choroid plexus papilloma. Pt underwent radical neurosurgical resection. HE was conclusive for mature teratoma. At 10-yrs age, pt weight was 38 Kg (90th percentile), height was 124 cm (3rd percentile) and growth velocity was 3 cm/yr (<3rd percentile). Clonidine test suggested an impaired GH secretion. cc-MRI didn't documented teratoma recurrence (rec). After 3 disease-free survival yrs, rhGH replacement therapy (rhGH-RT) was started. Every 6 mts, endocrinological and neuroradiological evaluation were scheduled. At 18-yrs age, cc-MRI evidenced a falx cerebri lesion. rhGH-RT was discontinued. Pt underwent neurosurgery. HE documented an atypical meningioma. 1-yr post-surgery cc-MRI confirmed tumor radical resection. rhGH-RT was re-started. Every 6 mts, endocrinological and neuroradiological evaluation was scheduled. At 27-yrs age, cc-MRI showed meningioma rec. Pt underwent second radical neurosurgery. HE documented transitional meningioma with strong immunohistochemical positivity for GH receptor. rhGH-RT was discontinued. At admission in our department, laboratory tests confirmed panhypopituitarism, cc-MRI was negative for teratoma and meningioma rec. We confirmed the rhGH-RT discontinuation. To our knowledge, our case is the first describing rhGH-RT safety in a pt with teratoma history. Teratomas should be taken into account in the diagnosis of pituitary region tumors for allowing patients to benefit of correct treatment and later of a complete hormonal replacement therapy.

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EP930

Pituitary apoplexy induced remission in a macroadenoma Cushing Disease

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Introduction
Pituitary macroincidentalomas are rare, being found in only 0.2%–0.3% of the patients that undergo imaging studies for an unrelated reason. The majority of them are non-functioning adenomas.
Case Report
Woman, 77 years-old, with type 2 diabetes mellitus, hypertension and primary hypothyroidism. She was referred to Endocrinology due to a pituitary incidentaloma (18 mm of maximal diameter, with extension to the cavernous sinus and to the optic chiasm) diagnosed in a CT scan that was performed due to syncopal episodes. The patient also reported sporadic headaches and visual acuity loss. No endocrinopathy stigmata were found on physical examination. Laboratory study revealed a high late night salivary cortisol, a high ACTH and a positive 1-mg overnight dexamethasone suppression test (6.2 μg/dl). An elevated plasmatic cortisol in the low dose dexamethasone suppression test (29.2 μg/dl) confirmed the diagnosis of Cushing Syndrome. One week after the diagnosis, the patient presented to the Emergency Department (ER) with severe headaches, nausea, vomits and psychomotor impairment. Blood tests shown severe hyponatremia (114 mEq/l). Despite the ER head CT scan revealed no significant alterations, the patient was given 100 mg of hydrocortisone and she was hospitalized due to the clinical suspicion of a pituitary apoplexy. The hormonal study revealed panhypopituitarism (serum cortisol 12 μg/dl; ACTH 41.3 ng/l; TSH 0.04 μUI/l; FSH 2.14 mU/ml; LH 0.23 mUI/ml; prolactin 4.6 ng/ml) and the pituitary MRI demonstrated features of tumoral haemorrhage, confirming the apoplexy hypothesis. She maintained glucocorticoid therapy with symptomatic improvement and progressive correction of the sodium levels.
Conclusions
Pituitary apoplexy is rare but it can be a serious health issue if not promptly recognized. In this particular case, the apoplexy led to hypercortisolism resolution. Thus, if the revaluation MRI shows significant tumoral shrinking, the patient will no longer have surgical indication.

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EP931

Diabetes insipidus as a predictor of weight gain in craniopharyngeoma patients

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Craniopharyngeoma patients have reduced quality of life and increased cardiovascular mortality because of severe obesity present in about 50% of patients. In the present study we analysed postoperative body mass index (BMI) in craniopharyngeoma patients depending on the presence of the diabetes insipidus (DI).
We retrospectively analyzed 19 craniopharyngeoma patients (male:female = 12:7, age 31.2 years, range 9–67) treated at our Department since 2001. The majority of patients underwent transcranial surgery (18/19), 10/19 underwent complete debulking and 9/19 underwent incomplete resection followed by radiotherapy of residual tumor. BMI was measured before and after the treatment. All patients were evaluated for the presence of DI. Median BMI before the treatment was 26.4 kg/m^2 (17.7–40.8) and it increased significantly after the surgery (30.6 kg/m^2 (23.2–46), $P<0.0001$). Before the treatment only one patient had DI whereas postoperatively 13/19 patients developed DI. Postoperative BMI of the patients with DI was significantly higher compared to those without DI (31.5 kg/m^2 (27.1–46) vs. 27.45 kg/m^2 (23.2–31.6), $P=0.012$).
Craniopharyngeoma patients that developed postoperative DI had significantly higher BMI suggesting a predictive role of postoperative DI in the development of hypothalamic obesity.

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EP932

"What's the best approach to perioperative, immediate post op and 6 week post op cortisol assessment and replacement in patients undergoing transsphenoidal pituitary surgery?"

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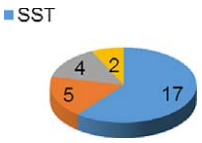
Introduction
There is great variation in management of perioperative cortisol management in patient's undergoing pituitary surgery across UK Hospitals. We evaluated safety and effectiveness of standards followed in ARI. The aim of audit was to confirm safety, improve knowledge and change practice for better patient care if needed based on information gained from the available data.
Description of methods/design
We evaluated 30 patients who have undergone pituitary surgery from 01/01/13 to 31/12/14 for Pituitary adenoma (functioning or non functioning) excluding Cushing's disease in ARI. Data was gathered from paper notes and using electronic record system about perioperative, immediate post op and 6-week post op cortisol assessment.
Tools for pre-operative HPA Axis Assessment



Results and conclusion
1. Short synacthen test is effective tool in assessment of perioperative cortisol sufficiency. 2. If SST is not available, basal cortisol can be used but a higher safety bar needs to be used. 3. Early morning cortisol monitoring is important in post op patients deemed steroid sufficient. 4. All patients discharged home without steroid immediately post op remained steroid sufficient at 6-week assessment (100% safety). 5. 50% of patients receiving steroids post surgery were able to discontinue them after 6-weeks review. 6. Some variability in interpretation of SST (often taking into account clinical features and variation of different assay's used in hospitals). 7. Patients with borderline results need steroid cover for intercurrent illness.
Outcome
Developing leaflet for patients needing intercurrent steroid cover.

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EP933

Obstructive hydrocephalus and intracranial hypertension caused by a giant pituitary non-functioning adenoma

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Introduction
Patients with large non-functioning pituitary macroadenomas often have symptoms due to varying degree of hypopituitarism and/or mass effect on visual structures, while presentation with hydrocephalus is extremely uncommon.
Case report
We describe an 82-year-old man who was referred to the Neurology department of our hospital because of rapidly progressive memory loss. The patient was in good health until ten weeks earlier, when he insidiously began to develop memory impairment, headaches and progressive asthenia. Ophtalmic examination revealed bitemporal hemianopia and bilateral papilloedema. The contrast enhanced CT scan of head revealed a well-defined enhancing mass in the sella and suprasellar region extending into the lumen of the 3rd ventricle producing obstructive hydrocephalus. Magnetic resonance imaging (MRI) confirmed the sellar mass with supra and parasellar extension compatible with pituitary macroadenoma ($6\times2.6\times2.6$ cm) associated with active hydrocephalus. Endocrinologic evaluation confirmed panhypopituitarism, therefore, hormone replacement therapy was immediately instituted. At the same time, surgical resection was planned but the patient and his family refused both surgical excision and external drainage.
Conclusions
Obstructive hydrocephalus as a late complication of adenomas or after pituitary surgery has been described, but the initial clinical manifestation of a pituitary adenoma with symptomatic hydrocephalus is rare.

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EP934

The outcomes of the transsphenoidal adenomectomy in patients with acromegaly

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Introduction
Acromegaly is a chronic disorder caused by growth hormone (GH) hyperproduction which leads to significant morbidity and mortality primarily due to cardiovascular and respiratory complications. Pituitary adenoma is the main cause of GH's hyperproduction. By current guidelines transsphenoidal surgery (TSS) is the first-line treatment in acromegaly patients.
Aim
To evaluate the results of TSS in acromegaly patients 6 months after surgery.
Materials and methods
65 patients (48 women and 17 men), mean age 51.2 ± 11.8 years (range 25–72 years) were enrolled into the study. Majority of our patients (75%) had macroadenomas. Only sixteen patients (25%) had microadenomas. All TSS were performed by one neurosurgeon. 6 months after surgery a nadir serum GH within 2 hours after 75 g of oral glucose and IGF-1 were estimated. Remission of acromegaly was considered as: nadir serum GH <0.4 μg/l after an oral glucose load and age-normalized serum IGF-1 value.
Results
Acromegaly remission was confirmed in 17 (26.1%) patients. Remission was established in 56.2% (9 out of 16) patients with the pituitary microadenomas. Among patients with macroadenomas remission was proved in 16.3% (8 out of 49) cases. Patients with the persisting disease have demonstrated significantly higher initial basal GH level ($P<0.006$).
Conclusions
According to our data TSS was effective in 26.1% cases. The rather low remission rate was associated with macroadenomas predominance in our study group. Microadenoma presence and low initial basal GH value increased the probability of remission.

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EP935

A rare case of ulcerative colitis coexisting with lymphocytic hypophysitis

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Background and aim
Lymphocytic hypophysitis is heterogeneous inflammatory processes of the pituitary gland and may cause isolated hormone deficiency, but rarely occurs as panhypopituitarism. We aim to present a rare case of ulcerative colitis coexisting with lymphocytic hypophysitis.
Case report
A 42-years old woman with ulcerative colitis was applied for our department of internal medicine with hypoglycemia. Her capillary blood glucose levels were found 22 and 33 mg/dl without typical hypoglycemic symptoms. She complained from weakness, anorexia, weight loss, secondary amenorrhea and chronic diarrhea for three months. She was diagnosed with ulcerative colitis 11 years ago and was treated with meselazine tablets and enema. Oral steroid therapy was started in 2014 and doses were gradually tapered and stopped. Her physical examination revealed pulse rate of 55 per minute, blood pressure of 90/60 mm Hg with pale skin. No other abnormal finding was found on physical examination. Secondary hypothyroidism and secondary adrenal insufficiency were considered according to endocrinological examinations. Prolonged 75 g oral glucose tolerance test was also performed, hypoglycaemia was not observed during the test. Pituitary magnetic resonance imaging showed findings consistent with

lymphocytic hypophysitis. Present laboratory and imaging findings suggested the presence of lymphocytic hypophysitis. She was initially treated with hydrocortisone and then L-thyroxine replacement therapy. After the treatment, we observed markedly improvement her signs and symptoms such as weakness, anorexia and hypoglycemia.
Conclusions
Although some autoimmune diseases may be together, coexistence of ulcerative colitis and lymphocytic hypophysitis is rarely situation. These patients should be followed in terms of autoimmune polyglandular syndrome.

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EP936

Mesocorticotropinoma- associated Nelson's syndrome: 28 years of follow-up

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Introduction
Nelson's syndrome (NS) is an exceptionally rare condition diagnosed sometimes after bilateral suprarenalectomy for Cushing's disease (CS) involving rapid enlargement of a pre-existing ACTH-secreting pituitary tumor. The clinical picture varies from hyperpigmentation, headache and visual disturbance to diabetes insipidus and hypopituitarism if the hypothalamic-pituitary portal system is disrupted or normal pituitary tissue is destroyed by the adenoma. The primary treatment for Nelson's syndrome is trans-sphenoid surgery.
Material and Method
This is a case report revealing the medical history and endocrine profile of a male with NS.
Case data
A 65-year old male patient, who had undergone total bilateral suprarenalectomy in 1987, for refractory CS is admitted in 2015 for periodic check-up a NS. In 1988 he received external radiation-therapy for the pituitary ACTH-secreting mesadenoma. In 2003, pituitary MRI performed pointed an 8/10/12 mm-sized mass of oval shape, with intra-sellar expansion. In 2010 a progressive form of NS was diagnosed based on ACTH level of 1250 pg/ml (N: 7.2-62.3 pg/ml) with increasing levels of 2000 pg/ml within 4 years and treated with radiation-theraphy. The eye exam was normal.
On admission, the associated conditions are hypothyroidism after total thyroidectomy for benign nodular goiter, diabetes mellitus and high blood pressure. He has been treated with daily Levothyroxine, Prednison, Fludrocortisone and oral anti-diabetic agents. The ACTH level continues to be high (of 715 pg/ml) but decreased compared to previous admissions. Close imagery, endocrine, ophthalmic follow-up is necessary.
Conclusion
The therapeutically resources in mild forms of Nelson's syndrome involves pituitary radiotherapy if surgery is not an option. Despite the current rarity of the condition is has a potential aggressive behavior and close monitoring is required including 28 years after bilateral adrenal remove as seen in this case.

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EP937

Trial design of a phase III, multicentre, randomised, double-blind, placebo-controlled, 48-week study to evaluate the safety and efficacy of osilodrostat in patients with Cushing's disease

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Background
Osilodrostat is an oral inhibitor of 11β-hydroxylase (CYP11B1), the enzyme that catalyses the final step in cortisol biosynthesis. In a 22-week, phase II study, osilodrostat treatment normalised mean urinary free cortisol (mUFC) in 78.9% (15/19) of patients with uncontrolled Cushing's disease and was well tolerated. The present phase 3 study is designed to confirm the safety and efficacy of osilodrostat in patients with uncontrolled Cushing's disease.
Methods
Patients: Adults with Cushing's disease (persistent, recurrent or de novo Cushing's disease, if not surgical candidates) with mUFC $>$ 1.3 times upper limit of normal (ULN). Design: A pivotal, phase III, global, multicentre, randomised study to enrol 69 patients. Period 1 (week 0–12): double-blind, placebo-controlled; patients will start receiving either osilodrostat 2 mg bid or placebo 2 mg bid (2:1 randomisation). Dose adjustments to normalise UFC or address safety issues, ranging between 1 mg qod and 20 mg bid are allowed. Period 2 (week 13-48): single-arm, open-label; patients on placebo or osilodrostat dose $\geq$ 2 mg bid during week 12 will begin period 2 with osilodrostat 2 mg bid, those on $<$ 2 mg bid will continue with their most recent dose. Dose escalation is permitted up to 30 mg bid. Endpoints: Primary: Proportion of randomised patients with a complete response (mUFC $\leq$ ULN) at week 12. Key secondary: Proportion of patients with mUFC $\leq$ ULN at week 36 for patients who have received osilodrostat treatment at any time. Others: Safety and tolerability; changes in cardiovascular and metabolic parameters, bone mineral density, and quality of life.
Conclusion
The present study design combines a 12-week placebo-controlled period, which allows blinded, placebo-controlled assessments with an open-label period to allow long-term evaluation of efficacy and safety of osilodrostat in patients with Cushing's disease.

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EP938

Tolosa Hunt syndrome involving the pituitary: a case report

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Introduction
Tolosa Hunt syndrome (THS) is described as unilateral orbital pain associated with paresis of one or more of the third, fourth and/or sixth cranial nerves caused by a granulomatous inflammation in the cavernous sinus, superior orbital fissure or orbit. Pituitary gland is rarely involved in this syndrome. Herein we represented a case with hypophysitis with Tolosa Hunt who was operated with the suspicion of pituitary adenoma.
Case
A 63-year-old female patient with diabetes history admitted to our clinics with the complaints of weight gain and headache. In the physical examination, BMI was 40 kg/m^2 and there was buffalo hump, central obesity and acanthosis nigricans. With the suspicion of Cushing syndrome, biochemical screening was performed with low dose dexamethasone suppression test and free cortisol in 24-hour-urine collection. Serum cortisol after 1 mg dexamethasone suppression was 2.2 μg/dl whereas free urinary cortisol was normal. For exclusion of pseudocushing, we performed 2 days 2 mg dexamethasone suppression with CRH and the result was equivocal (cortisol after CRH: 1.5 μg/dl). Her ACTH value was 20 pg/ml, and high dose dexamethasone test result was consistent with Cushing's disease. In the CRH test there was %300 increase in ACTH and %100 increase in cortisol after the administration of CRH. In the pituitary MRI, a lesion 1.8 cm in size was reported. While the evaluation was going on, the severity of headache was increased and ophtalmoplegia developed. The patient underwent endoscopic transsphenoidal surgery. The histopathology of the lesion was consistent with granulamatous reaction with caseous necrosis. Tuberculosis and sarcoidosis was excluded by PPD, thorax CT, lumbar puncture and analysis of the cerebrospinal fluid, mycobacterium tuberculosis PCR and the culture of the pathology specimen. The final diagnosis was Tolosa Hunt.
Conclusion
Tolosa Hunt is a very rare cause of hypophysitis and panhypopituitarism. It should be considered in the differential diagnosis of a sellar mass.

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EP939

Clinical features of thyrotropin secreting pituitary adenomas

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Introduction
Thyrotropin-secreting pituitary adenomas (TSHomas) are a rare cause of hyperthyroidism and represent $<1\%$ of all pituitary adenomas. The majority of TSHomas (70%) secrete TSH alone, while mixed adenomas are not infrequent.
Design
Herein, we reported the findings of six patients with TSHoma (mean age 44 yr, 4 female, 2 male). Mean TSH value was 15.1 mIU/L (3.3–38.0) who were followed-up in our department.
Results
Symptoms of hyperthyroidism were the initial findings in all these patients. Three of them recieved high dose antithyroid drugs for hyperthyroidism, Because of unresponsiveness, radioactive iodine ($n=1$) or thyroidectomy ($n=2$) was performed as a definitive treatment for hyperthyroidism before the correct diagnosis of TSHoma. The diagnosis delayed for 3–11 years. Four of the patients secrete TSH alone, while three of them were mixed adenomas [TSH, growth hormone (GH) ($n=1$); TSH, GH and prolactin ($n=1$); TSH, prolactin ($n=1$)]. Five of the cases had macroadenoma invading sphenoid and/or cavernous sinuses, and two of them also showed compression on optic tractus, one patient had microadenoma. The primary therapeutic approach was transsphenoidal surgery. İmmunohistochemically, GH, prolactin and TSH positivity was evident in two patients and one also showed diffuse Pit1 positivity. One patient showed positivity, for TSH and prolactin and another showed focal immunostaining for GH and FSH.
No remission was noted in four patients and medical therapy with somatostatin analogues (SSAs) and thereafter cabergoline were started. Radiotherapy was performed for one patient postoperatively. Hormonal control was achieved in all treated patients.
Conclusion
The delayed diagnosis of TSHoma usually cause inappropriate treatment of hyperthyroidism. Transsphenoidal surgery should be the first line treatment. If remission is not achieved medical therapy with SSAs and cabergoline and also radiotherapy should be options.

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EP940

A novel case of pituitary metastasis presented as the syndrome of inappropriate antidiuretic hormone: an unexpected association

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Introduction
Although the syndrome of inappropriate antidiuretic hormone (SIADH) has connection with various malignant tumors, the pituitary metastasis of malignant tumors are generally associated with diabetes insipidus.
Case report
A 59 years old male patient presented to emergency service with frequent syncope attacks, nausea, loss of appetite and fatigue that began 2 weeks prior to admission. Marked obtundation was found on physical examination. The patient had not any history or symptom consistent with lung disease. However, other physical examinations including vital signs were normal. Serum sodium was 100 mEq/l, potassium 4.6 mEq/l, creatinine 0.81 mg/dl, urea 29 mg/dl, uric acid 2.1 mg/dl, glucose 101 mg/dl, TSH: 0.01U/l (0.4–4), free T4: 0.94 ng/dl (0.9–1.8), free T3: 1.7 pg/ml (1.8–3.8), FSH: 0.3 mIU/ml, LH: 0.1 mIU/ml, total testosterone <20 ng/dl (230–400), cortisol: 6 mcg/dl, ACTH: 6 pg/ml, IGF-1: 68 ng/ml, urine sodium 126 mmol/l and plasma osmolality was 240 mOsmol/kg, on laboratory examination. The patient was diagnosed as panhypopituitarism and SIADH. The low serum cortisol levels did not respond to short synacthen test. A pituitary mass of $30\times16\times18$ mm in size was found on pituitary MRI. A complet right side vision loss was present on visual field examination. The patient underwent pituitary surgery. The histopathological and immunohistochemistry results revealed SCLC metastasis. A mass of 41×36 mm in size was determined on the apicoposterior segment of the left upper lung lobe on chest CT and widespread metastasis was found on FDG/PET CT, including pituitary gland. The result of lung needle biopsy was consistent with small cell lung cancer. The SIADH in this case was thought to be associated with SCLC. The patient died two months after first diagnosis.
Conclusions
Although associated with low survival rates, the presence of metastasis should always be thought in elderly and middle aged patients diagnosed with non-functioning pituitary tumors, irrespective of clinical presentation.

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EP941

The relationship between pituitary hormone levels and magnetic resonance imaging findings in diabetes insipidus patients

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Introduction
Diabetes insipidus (di) is a water metabolism disorder caused by antidiuretic hormone pathologies. In this study, we evaluated, retrospectively, pituitary hormone profiles and pituitary magnetic resonance imaging (mri) findings of patients with di.
Material and methods
After local ethic committee approval, 300 patients were evaluated retrospectively. Patients with a history of pituitary surgery and/or radiotherapy were excluded. Luteinizing hormone (lh), follicule stimulating hormone (fsh), estradiol (e2), prolactin (prl), total testosterone (tt), thyroid stimulating hormone (tsh), free thyroxine (ft4), free triiodothyronine (ft3), creatinine, sodium, potassium levels and mri findings were recorded. Totally data of 34 patients were evaluated. Spss 20.0 was used for statistical analysis.
Results
24 female (%70.6) and 10 male (%29.4) patients were included into the study. Potassium levels were found significantly related with fsh ($P=0.011$), lh ($P=0.030$) and posterior pituitary brightness loss in mri ($P=0.027$). Ft3 was significantly associated with pituitary height ($P=0.015$) and posterior pituitary brightness loss ($P=0.027$). Moreover, ft4 was found significantly related with pituitary stalk thickness ($P=0.025$) and posterior pituitary brightness loss ($P=0.007$). Glucose, urea, creatinine and urinary osmolality were found significantly different between male and female patients. Urea, creatinine, glucose and urinary osmolality values were found higher in men by comparison women.
Conclusıon
Hormonal levels, biochemical levels and imaging techniques are used together for the diagnosis of di. The interrelation between these tests should be taken into consideration while evaluating patients who are suspected as di because the pathologies of the laboratory tests can sometimes give clues about the pathologies of the imaging studies.
Keywords: diabetes insipidus, pituitary hormones, pituitary magnetic resonance imaging

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EP942

A rare case of acromegaly concomitant with pancreatic adenocarcinoma

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Background and aim
Acromegaly is a rare endocrine disease and is associated with an increased prevalence of colorectal cancer and pre-malignant tubular adenomas, and also may be associated with other organ malignancies such as breast and thyroid. We report a rare case of acromegaly concomitant with adenocarcinoma arising from pancreas.

Case report
A 52-year-old man who was diagnosed with acromegaly two years ago referred our outpatient clinic. After diagnosis, transsphenoidal surgery was performed. Surgery was not reduced serum growht hormone (GH) and insulin-like growth factor 1 (IGF-1) to normal, therefore somatostatin analog treatment was started. After this treatment, glucose-suppressed GH concentration was <1.0 ng/ml and serum IGF-1 concentration normal for age and gender. He was admitted to out-patient clinic with abdominal pain about 1 month ago. Abdomen CT showed that 44X26 mm mm mass lesion in the body and tail of the pancreas and multiple metastatic lesions in the liver. Upper gastrointestinal endoscopy and colonoscopy showed that erosive gastritis and polyps in the colon, respectively. After these imaging studies, endoscopic ultrasound-guided needle aspiration biopsy was performed to the mass lesions in the tail of the pancreas. Pathological examination revealed a adenocarcinoma arising from the pancreas.
Conclusions
The patients with acromegaly have an increased risk of benign and malignant neoplasms, These situation may be related with increased circulating levels of IGF-1 because of proliferative and anti-apoptotic activity of IGF-1.It is important to consider pancreatic adenocarcinoma in the presence of acromegaly.

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EP943

Complete pituitary regression with immunosupressive treatment in a patient with ANCA negative wegener granulomatosis

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Introduction
Wegener granulomatosis is a necrotizing granulomatous small-vessel vasculitis. It typically affects the upper respiratory tract, lungs, and kidneys but can involve virtually any organ including the pituitary. Pituitary involvement in wegener granumatosis is rare.
Case
A 50-year-old woman was admitted to the hospital with severe dyspne for 2 years and stridor for a month. During her hospitalization, her sodium level was noted to be persistently high. A further workup revealed a consistently low urine osmolality in the presence of high serum osmolality suggesting partially diabetes insipidus. Her baseline laboratory data showed Na 164 mEq/l (135–145 mEq/l), serum osmolality 351 mOsm/kg (285–295 mOsm/kg), and urine osmolality 232 mOsm/kg. The results were consistent with partial CDI. Her serum sodium level was corrected with increased free water intake and did not require desmopressin. Anterior pituitary functions were normal at presentation. MRI revealed enlargement of the whole pituitary, including the stalk, with heterogeneous gadolinium enhancement and a disappearance of the high signal intensity of the posterior pituitary. (Figure 1). Computed tomography showed thickened mucosa of the nasal sinus and multiple small nodular lesions in the lung. A nasal sinus biopsy revealed a pauci-immune focal segmental necrotizing sinusitis. She was diagnosed with wegener granulomatosis. Serology revealed negative ANCA, and the C-reactive protein (CRP) was elevated. No abnormalities were noted upon urine examination. Intravenous pulse methyl-prednisolone 1000 mg was administered for 3 days and then cyclophosphamide was given at a dose 1000 mg monthly for 3 months. A repeat brain MRI 4 months later showed complete resolution (Figure 2).
Conclusion
We think that pituitary enlargement in wegener granulomatosis can disappear totally with immuno supressive agents in some patients.
Keywords: wegener granulomatosis, pituitary mass, immuno supressive agents
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EP944

The prevalence of metabolic syndrome in adult patients with long-standing hypopituitarism who receive adequate supplemental therapy

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Introduction
Hypopituitarism is characterized by the absence of pituitary hormones. Depending on what pituitary hormones are missing and what is the etiology of hypopituitarism, its clinical manifestation varies. Apart from evident symptoms and signs of hypopituitarism due to hormonal insufficiencies, several studies reveal that long-standing hypopituitarism, including particularly absence of GH, is related to higher risk of metabolic syndrome.
Objective
The aim of the study was to asses the prevalence of metabolic syndrome (MS) in patients with long-standing pituitary hormones deficiency who receive adequate supplemental therapy, including GH treatment.
Material and methods
12 patients (5 males, 7 females), aged 18–40 years, with hypopituitarism who did receive GH supplemental therapy under the care of Chair and Department of Endocrinology Medical University of Lublin (Poland) from 01.01.2011 to 31.12.2015 were enrolled into the study. 9 patients had panhypopituitarism, 2 patients had isolated GH deficiency, 1 patient had deficiency of GH and gonadotropins. The recognition of MS among examined patients was based on criteria of IDF/NHLBI/AHA-2009.
Results
5 patients (41.7%) met criteria of metabolic syndrome. All these patients had panhypopituitarism with diabetes insipidus diagnosed in 4 of them. The 4 patients with diabetes insipidus had the most severe obesity. None of the patients with isolated GH deficiency or with GH and gonadotropins and GH deficiency met MS criteria.
Conclusion
Despite adequate supplemental therapy, panhypopituitarism is a risk factor of obesity and MS suggesting the role of other factors (hypothalamic leisure?) in the development of the above metabolic complications.

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EP945

Sudden global health impairment in a male patient– could it be hypohysitis?

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Introduction
Hypophysitis is a chronic inflammatory condition of the pituitary gland which typically presents with hypopituitarism and a pituitary mass. The disease is rare, with an estimated incidence of 1/9000000. Most reported cases are in women during peripartum period and only approximately 15% of reported cases occur in males.
Case report
Male patient, aged 57, smoker, with a history of hypertension, just returned from India, presented with anorexia, important asthenia, somnolence, weight loss (5 kg in 2 months), decreased blood pressure (110/80 mmHg without treatment), and fever. Investigations for a parasitosis were negative and the ultrasonographical detection of a nodular goiter determined an endocrinologic consultation. The diagnosis of secondary hypothyroidism (TSH $=0.102$ μIU/ml, fT4 $=0.558$ ng/dl) together with the clinical picture raised the supposition of a pituitary insufficiency, confirmed by the multiple hormonal deficiency: FSH $=1.22$ mIU/ml, LH $=0.477$ mIU/ml, testosterone <0.026 ng/ml; morning cortisol <1 μg/dl with low ACTH (19.7 pg/ml); IGF1 $=80.3$ ng/ml (81–225 ng/ml). Pituitary MRI detected a globular, convex and inhomogeneous aspect of the pituitary gland, with increased dimensions: 9.7/17.9 mm and normal sellar floor, suggestive for hypophysitis. Corticotherapy was started with rapid improvement (clinical and biological in 1 month and imagistic in 2 months).
Discussions
Lymphocytic hypophysitis is a rare disease, especially in men. Secondary adrenal insufficiency is one of the earliest manifestations and can become life threatening. Although spontaneous remission is possible, in these cases, as it was in our patient, treatment is preferable. The rapid good evolution sustained the diagnosis which can often be made on the basic clinical, biological and imagistic features, pituitary biopsy not being always necessary for effective management of the disease.

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EP946

Coincidence of subarachnoidal hemorrhage and pituitary apoplexy

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Pituitary apoplexy is a rare and life-threatening disorder often requiring emergency neurosurgical intervention to preserve vision and prevent cerebral herniation syndrome. Infarction or hemorrhage of an enlarged pituitary gland or pituitary tumor is the most common cause of pituitary apoplexy. Early recognition of this disorder is essential for preventing permanent visual loss or death; however, pituitary apoplexy often mimics subarachnoid hemorrhage, which in some cases may delay definitive diagnosis.
44 years old male patient was admitted to Emergency outpatient clinic with intense headache. He was discharged from the hospital after an administration of analgesic injection. But his mental status started to deteriorate at home and there were complaints of of blurring of vision with diplopia and drooping of the left eyelid. His headache was also persisting with same intensity. History of the patient revealed celiac disease. During second admission to the hospital, the patient was pale, pulse was 110/min, and blood pressure recorded was 90/50 mmHg. On examination, ptosis was present on left side, periorbital swelling was also observed. Restriction of medial/upward movement of both eyes were present. Pupils were bilateral equal and normally reacting to light.Visual acuity was 0.4 on right and 0.05 on the left side. The rest of the neurological examination and review of other systems were normal. Laboratory investigations were compatible with panhypopituitarism. The patient was started on hydrocortisone and thyroid hormone replacement therapy. Magnetic resonance imaging (MRI) established diagnosis of pituitary apoplexy and subarachnoid hemorrhage due to acute hemorrhage of a $32 \times 20 \times 32$ mm sized pituitary adenoma. MR angiography did not establish an artery aneurysm. His status and hemorrhage recovered with the treatment given. He is going to be operated for the pituitary adenoma.
Multidisciplinary evaluation of these patients will determine diagnosis and the most appropriate emergency treatment plan and long-term management strategies.

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EP947

A case of acromegaly presenting with lacrimal gland hypertrophy

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Introduction
Acromegaly is a chronic endocrine disorder caused by excess growth hormone (GH) secretion. Hypersecretion of GH causes increased IGF-1 secretion from the liver which in turn leads to a series of multisystemic complications including somatic overgrowth and multiple comorbidities.
Case report
Thirty-nine-year-old female patient was seen in ophthalmology outpatient clinic with the complaint of a mass inside the right upper eyelid. On ophthalmologic examination a 10x10 mm mass was noted inside the lateral part of the right upper eyelid and an orbital magnetic resonance imaging (MRI) was planned with a preliminary diagnosis of lacrimal gland cyst/tumor. MRI revealed a $16 \times 8 \times 10$ mm pituitary mass expanding the sella, extending to the right cavernous sinus deviating infindibulum to the left. The patient was referred to the endocrinology outpatient clinic. On medical history her periods had stopped one month ago. When questioned she mentioned that she was snoring during sleep and her shoe size had increased from 38 to 39. On physical examination she had prognatism, deep nasolabial folds and a conjuctival mass inside right upper eyelid was noted. On laboratory evaluation, her IGF-1 level was 275 (normal range: 66–240) ng/ml. On 75 gram oral glucose load, fasting and 2-hour plasma glucose level was 97 and 126 mg/dl, respectively, while baseline and 2-hour serum GH level was 1.98 and 1.05 ng/ml, respectively. The patient had pituitary adenomectomy and immunohistochemical analysis of the pathology specimen was compatible with GH-secreting pituitary adenoma.
Conclusions
Hypersecretion of GH may cause somatic overgrowth and these patients may present with several different clinical or metabolic features. Regarding eye involvement in acromegaly there is a previous report of a patient with restrictive extraocular myopathy and another report with epiphora and proptosis. This is the first case report in English literature regarding lacrimal gland hypertrophy as a presenting complaint in acromegaly.

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EP948

Frequency and predictive factors of acute adrenal insufficiency following brain injury

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Background
Biological diagnosis of adrenal insufficiency (AI) is very difficult in the setting of critical illness like in traumatic brain injury (TBI), and the cut off defining AI need more precision.
Aim
The aim is to assess the frequency and predictive factors of AI in a simple of 277 victims of moderate to severe BI in two neighbors' hospitals in the east of Algiers.
Method
Between November 2009 and December 2013, 277 patients victims of moderate to severe TBI aged from 18–65 years old were included.During the acute post injury period (0–7 days), the measurement of serum cortisol has been done in all patients at 8–9 pm. TBI subjects were defined as having AD using three cut offs: 83 nmol/ (the value that indicate severe AI usually admitted by endocrinologists), 276 nmol/l (the value indicating AI in critical illness according to the consensus statements from an international task force by the American college of critical care medicine), 414 nmol/(the value admitted by Hannon and al which indicate AI in victims of TBI). Variables studied were: age, severity of BI, duration of intubation and coma, pupillary status,presence of hypotension and anemia (Hb$<$ 9 dg/ml). CT findings were classified according to Marshall Classification, the presence of skull base fracture was assessed. The presence of insipidus diabetes, the kind of medications used for sedation has been assessed in intubated patients. The outcome was evaluated by the GOCS.
Result
Mean age was 32 years with male predominance. Traffic accident was the most frequent cause of brain injury The frequency of acute AD was 2.8% 20.21% and 35.37% respectively for cortisol levels of 83 nmol/l.276 nmol/l and 415 nmol/l respectively. Predictive factors for its occurrence was the acute diastolic blood pressure, prescription of Pentobarbital, acute insipidus diabetes, skull base fracture and the presence of intraparenchymal hematoma but at different levels of cortisol.

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EP949

High monocyte/HDL-cholesterol ratio in men with hypogonadotrophic hypogonadism

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Aim
In a previous study, we demonstrated elevated mean platelet volume in isolated hypogonadotrophic hypogonadism (IHH) is associated with high cardiovascular risk. Monocyte count/HDL-cholesterol ratio (MHR) is a new inflammatory marker showing cardiovascular risk. The purpose of this study is to evaluate (MHR) in men with hypogonadotrophic hypogonadism.
Method
This study includes 31 men with isolated hypogonadotrophic hypogonadism without previous treatment (mean age 22.5 ± 7.2 year; BMI 21.6 ± 4.9 kg/m^2) and 44 healthy men who have similar age and BMI (mean age 22.9 ± 6.4 years; BMI (19.5 ± 3.2 kg/m^2). HH was defined as total testosterone being below 229 ng/dl because of the absence or inadequacy of hypophyseal gonadotropins Hormonal biochemical and hematological parameters were measured by automatic analyzer after 12 h fasting.
Results
In our data, we detected statistically significant differences in total testosterone level (mean total testosterone levels 43.9 ± 43.9 ng/dl in HH group vs 524.6 ± 275.1 ng/dl in control group, respectively, $P=0.000$).
There was no statistically a significant difference between HH group and control group(mean HDL-C 49.3 ± 16.6 mg/dl in HH group vs 46.7 ± 8.3 mg/dl in control group, respectively, $P=0.7$), monocyte count (mean monocyte count 0.5 ± 0.3/mm^3 in HH group vs. 0.6 ± 0.2/mm^3 in control group, respectively, $P=0.2$)

and MHR (mean MHR 0.015 ± 0.014 in HH group vs 0.081 ± 0.4 in control group, respectively, $P = 0.57$). MHR also was not correlated with hematological parameters and total testosterone.
Conclusions
HH may not be a parameter that can be used for evaluation of monocyte count/HDL-cholesterol, cardiovascular risk in men.

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EP950

Ketoconazole in Cushing's disease management

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Background
Transphenoidal surgery is still the best initial therapy for Cushing's disease (CD), with a high probability of cure and few risks or complications. However, pharmacotherapy has a role as primary or adjunctive therapy: when surgery is delayed, in case of postoperative persistence or recurrence of hypercortisolism, or while waiting for radiotherapy effectiveness. Ketoconazole, a steroidogenesis inhibitor, is nowadays the main drug used to CD control by reducing cortisol levels, with potent antisecretory efficacy in majority of cases, and relatively rare major side effects (anaphylaxis and fulminant hepatitis), but its use remains controversial.
Objective
The present study aims to assess the efficacy and tolerance of ketoconazole in CD and evaluate the benefit/risk balance.
Patients and methods
We reviewed ten present cases of CD treated with ketoconazole in our center, with a mean follow-up of 16 ± 15.3 months (0.25–40). Clinical assessment included age, gender distribution, BMI, blood pressure, levels of serum cortisol and ACTH, urinary free cortisol (UFC), hepatic function, lipid profile, glucose and HbA1c levels, hypokalemia and GI tolerance.
Results
The mean age of the participants was 43.7 ± 13.01 years, 80% females, with a BMI of 29 ± 6.2 kg/m^2. Eight patients (80%) are receiving the drug for 3–40 months, with a mean final dose of 500 ± 270.8 mg. One patient suspended treatment after 1week due to GI intolerance and another one after 13 months due to an infectious intercurrence. At the last follow-up, 60% of patients had normal UFC levels, 50% had at least a 50% decrease and 10% had unchanged UFC levels. Increase in liver enzymes was generally mild and reversible (90%), with 1 (10%) case of major increase. No fatal hepatitis was observed.
Conclusion
Ketoconazole is a safe and efficacious drug in CD, but has the potential hepatotoxicity that requires careful selection of patients and subsequent clinical and biochemical monitoring.

Keywords: Cushing's disease, ketoconazole, steroidogenesis inhibitors, hypercortisolism

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EP951

Primary empty sella syndrome-is it familial?

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Introduction
Empty sella syndrome is a condition in which sella turcica is partially or completely filled with CSF resulting in a displacement of normal pituitary gland. Primary empty sella is due to inherent weakness of diaphragm sella or to an increase in intracranial pressure which promotes herniation of arachnoid membranes in to pituitary fossa. More common in middle aged obese female and headache is the most common presenting symptom. It may be associated with one or more pituitary hormone deficiency.
There no familial association in the aetiology of empty sella has been described in the literature. We would like to present cases of mother and daughter who presented with primary empty sella.
49-years-old lady with a background of type 2 diabetes, obstructive sleep apnoea, asthma, osteoarthritis, obesity presented to neurologists in 2009 with a history of recurrent headaches, no history of head injury. In her family there was a history of strokes and migraine. Neurological examination was normal. MRI of the brain revealed primary empty sella. A GnRH test revealed normal gonadotropin axis. Insulin tolerance test has revealed growth hormone deficiency. She has been commenced on growth hormone replacement. Six years after commencing the growth hormone replacement, a glucogan stress test has revealed a subnormal cortisol response.
34-year-old daughter (a neuropsychologist) of the above lady presented to the endocrine services with a history of weight gain, hair loss. She had a background of renal stones, endometrial polyp. Partial empty sella was diagnosed on MRI done when she participated in research. Pituitary dynamic function test have revealed growth hormone deficiency with hypothalamo–pituitary–adrenal axis and gonadotropin axis intact.

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EP952

A case of post-traumatic ACTH deficiency followed by Cushing syndrome prediagnosis

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Pitüitary ACTH deficiency is one cause of secondary adrenal insufficiency. Genetic factors, autoimmunity, infiltrative disease, cranial trauma can cause ACTH deficiency. Hyperpigmented skin lesions are expected in primary adrenal insufficiency while they are very rare in secondary adrenal insufficiency. Striae are characterized by linear smooth bands of atrophic appearing skin. They are mostly associated with obesity, pregnancy, hypercortisolism/Cushing syndrome. Striae are not an expected finding in hypocortisolemia. A 34-year-old male patient, referred to the endocrinology clinic for the evaluation of red-purple colored striae on both armpits. The case self-reported that the skin lesions appeared ~4 months ago and spread over time, and occurred also on his abdomen. He did not have history of any chronic disease or drug therapy; but had cranial operation twice 12 years ago due to a car accident, and an arterial embolization procedure due to internal carotid artery aneurysm a year later. On his physical examination was normal. Hematologic, biochemical, and hormonal tests were measured. Plasma ACTH (1.6 pg/ml) and cortisol (0.18 μg/dl) levels were low. For evaluation of HPA axis, cosyntrophin, TRH and LH–RH tests were conducted. The patient responded to TRH (basal: 2.86 μIU/ml, max: 10.43 μIU/ml) and LH-RH (basal: 3.25 mIU/ml, max: 12.30 mIU/ml) stimulation tests. However, in the standard ACTH stimulation test, adrenal gland could have a suboptimal cortisol response (basal: 0.22 μg/dl; max 8.30 μg/dl). There were no abnormalities on the adrenal and pituitary MR images. However, secondary defects due to cranial trauma were seen in cranial MR. Based on the laboratory and MR examinations, the case was considered a posttraumatic ACTH deficiency case that developed as a result of head trauma and intracranial operations. We presented case of posttraumatic ACTH deficiency with hypocortisolemia after we investigated suspect hypercortisolemia/Cushing syndrome due to striae.

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Steroid metabolism + action

EP953

Sex hormones and sleep in men and women from the general population: a cross-sectional observational study

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Introduction
To date, associations between sex hormones and sleep were mainly investigated in small and selected patient-based samples. Thus, we examined a comprehensive panel of mass spectrometry-measured sex hormones and various sleep characteristics in a population-based sample of healthy men and women from the general population.
Methods
We used data from 204 men and 213 women of the cross-sectional Study of Health in Pomerania TREND, who underwent cardiorespiratory polysomnography. Associations of total and free testosterone (TT, fT), androstenedione (ASD), estrone (E_1), estradiol (E_2), DHEAS, sex hormone-binding globulin (SHBG), and E_2/TT ratio with sleep measures (including total sleep time, sleep efficiency, wake after sleep onset (WASO), apnea-hypopnea index (AHI), insomnia severity index, epworth sleepiness scale (ESS), and Pittsburgh sleep quality index) were assessed by sex-specific multivariable regression models adjusting for age, waist circumference, hypertension, smoking, physical inactivity, and alcohol consumption. Sensitivity analyses were performed with stratification by diagnosis of depression and menopausal status (women).
Results
In men, associations of TT (β-coefficient per s.d.: 0.62; 95% CI: 0.46–0.83), fT, SHBG, and E2/TT ratio with AHI in age-adjusted analyses were rendered non-significant after multivariable adjustment. In multivariable analyses, ASD (β-coefficient: 1.37; 95% CI: 1.03–1.82) and SHBG were associated with ESS. In women, only age-adjusted models showed an inverse association of SHBG with AHI (β-coefficient: 0.55; 95% CI: 0.38–0.78). Multivariable analyses showed positive associations of DHEAS with WASO (β-coefficient: 0.16; 95% CI: 0.03–0.28) and of E2 (β-coefficient: 1.04; 95% CI: 0.37–1.72) and E2/TT ratio with ESS.
Conclusion
Consistent with previous findings, the present cross-sectional population-based study observed sex-specific associations of testosterone and estrogen with sleep disturbances and poor sleep quality. However, multivariable-adjusted analyses confirmed the relative impact of body composition, health-related lifestyle, and comorbidity on the association between sex hormones and sleep.

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EP954

First generation testosterone assays are influenced by sex hormone binding globulin concentrations as evidenced during oral contraceptive use and pregnancy

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Introduction
The quality of testosterone assays has been a matter of debate for several years. Known limitations of testosterone immunoassays are the cross-reactivity with other steroids and a high variation in the low concentration range. We hypothesized that one of the additional limitations of testosterone immunoassays is an ineffective displacement of testosterone from its binding protein.
Methods
Thirty samples from women not using oral contraceptives (OAC), 30 samples from women using oral contraceptives, and 30 samples from pregnant women were used to measure testosterone by an ID-LC-MS/MS method and by six commercially available testosterone immunoassays (Unicel, Architect, Centaur, Cobas, Immulite and Liaison). In addition, SHBG was measured by immunoassay (Architect).
Results
The 1st generation immunoassays (Unicel, Centaur, Immulite and Liaison) showed inaccurate testosterone results in the method comparisons with the ID-LC-MS/MS method (R between 0.61 and 0.86) and for some assays (Unicel and Liaison) also a very poor standardization (slopes of 0.59 and 0.67, respectively). On average, SHBG concentrations were lowest in women not using OAC and highest in pregnant women and overall ranged from 18.5 to 633 nmol/l. In the 1st generation immunoassays, but not in the 2nd generation immunoassays, we observed an inverse relationship between SHBG concentrations and deviations in testosterone from the ID-LC-MS/MS results.
Conclusion
First generation testosterone immunoassays are influenced by SHBG concentrations which leads to inaccurate results in samples from subjects with high or low SHBG concentrations, respectively. Laboratory specialists, clinicians, and researchers should be aware of this limitation in 1st generation testosterone immunoassays which are still used worldwide.

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EP955

Testosterone therapy in female-to-male transsexuals: effects on gonadotropins, prolactin, gonadal steroids and menstrual cycle

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Introduction and objectives
Testosterone therapy (TT) in female-to-male transsexuals (FMT) usually causes cessation of menses within the first few months. However the changes in the hormonal profile are not well known. We set out to analyze the hormonal changes and menstrual evolution in a cohort of FMT who began TT.
Methodology
Retrospective observational study with no control group in a cohort of 34 FMT patients who started TT following a standard protocol (target doses were 50 mg transdermal daily or 250 mg parenteral biweekly) comparing routine hormonal laboratory data before and after 6–12 months. A menstrual calendar was also requested from the patients.
Results
Age was 27 ± 6 years and BMI 26.7 ± 3.1 kg/m^2. As expected, treatment increased free testosterone (0.51 ± 0.18 to 15.5 ± 5.2 ng/dl, $P < 0.001$, paired *t*-test) and reduced 17-β-estradiol (118.3 ± 39.4 to 37.9 ± 14.1 pg/ml, $P < 0.001$). LH and FSH were also reduced (33.7 ± 13.4 to 1.7 ± 0.7 mIU/ml, and 9.9 ± 4.5 to 1.7 ± 0.7 mIU/ml, both $P < 0.001$), while PRL was not significantly changed (16.6 ± 6.8 to 17.5 ± 7.6 ng/ml, $P = 0.155$). After the first, second, third, fourth, fifth and sixth month, 82, 38, 15, 6, 3 and 0% of the patients maintained menses, although 9% of the patients reported minor spotting and/or abdominal pain after the sixth month.
Conclusions
Routine TT in our FMT cohort markedly reduced the circulating gonadotropins but did not totally suppress ovarian function along the first year (17-β-estradiol was in normal range for cisgender males but not suppressed) and did not cause hyperprolactinemia. Over 90% of the patients had ceased menstruation after 3 months and all of them after 6 months, except for minor disturbances. Medroxyprogesterone acetate injections are recommended if menses persist, but none of our FMT patients needed them.

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EP956

An estrogen receptor signaling pathway is involved in 3,3′-diindolylmethane-induced inhibition of cell migration of MCF-7 breast cancer caused by triclosan via the regulation of epithelial- mesenchymal transition

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Triclosan (TCS) is an endocrine-disrupting chemical and has a potential to increase progression of hormone responsive cancers as does 17β-estradiol (E_2). 3,3′-diindolylmethane (DIM), a phytoestrogen, has been known to have anticancer activity. In this study, we examined the anti-proliferative and anti-epithelial-mesenchymal transition (EMT) effects of DIM on TCS or E_2-induced EMT of MCF-7 breast cancer cells, which express estrogen receptors (ERs). In MTT assay, TCS (10-4-10-7 M) induced growth of MCF-7 cells compared to a control (DMSO) like E_2 (a positive control, 10–9 M), which was antagonized by addition of ICI 182,720 (10-8 M), suggesting that the cell proliferation effect induced by TCS appears to be mediated by an ER-dependent manner. On the contrary, DIM (20–50 μM) significantly reduced the increased viability of MCF-7 cells induced by TCS or E_2. In a scratch assay, TCS enhanced migration of MCF-7 cells like E_2, but co-treatment of DIM or ICI 182,720 reduced the migration ability of TCS and E_2 to a control level. Next, we measured TCS or E2-induced

alterations in mRNA and protein expression levels of EMT related markers, i.e., N-cadherin, N-cadherin, snail and slug by reverse transcription (RT)-PCR and western blot assay. mRNA and protein expression of E-cadherin was declined while N-cadherin, snail, and slug expressions were increased by TCS or E_2, indicating that TCS induced EMT process in MCF-7 cells like E_2. Differently, DIM was shown to adversely affect the expression of EMT markers induced by TCS or E_2. Taken together, these results present that DIM effectively inhibits the cell growth and EMT process of MCF-7 cells increased by TCS or E2. Based on these *in vitro* results, *in vivo* effect of TCS and DIM on tumor growth and EMT process will be examined in a xenografted mouse model transplanted with MCF-7 breast cancer cells.

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EP957

Similarity and differences of maximal and sub-maximal endurance exercise in increase the serum testosterone and DHT concentrations in healthy males

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Introduction
Physical exercise exerts several effects on endocrinological homeostasis and, in particular, sprint exercise elicits the largest testosterone response per unit of work, while in response to prolonged endurance exercise testosterone levels will typically decline. In contrast to a large amount of paper about the modification of testosterone during physical exercise few study evaluated how DHT was influenced by a single bout of aerobic exercise.
Design
Twelve healthy trained male volunteers involved in non-competitive team sports were included and performed maximal exercise test (MAX) and sub-maximal exercise test (sMAX) at the individual anaerobic threshold (IAT). One week before starting the experimental phase, each volunteer underwent a MAX started with a 1-min warm-up without any added load then the workload was increased 30 w every 3 min until exhaustion. This test was used also to evaluate the IAT and the maximal oxygen uptake (O_{2max}). The sMAX consisted of pedaling 30 min at IAT workload. Blood collections were performed immediately before (0-pre) starting each exercise test, immediately after stopping exercise (0-post), and at +15, +30, and +60 min during recovery. Following each blood collection the serum was separated and stored at −30°C until it was assayed for total testosterone (TT) and DHT.
Results
TT increased significantly after MAX and sMAX from 0-post and remain elevated till +60. DHT concentration increase significantly after MAX (from 0-post) and remain elevated during all recovery (to +60).
Conclusion
Due to the lack of parallelism increase between TT and DHT in both type of exercise, we could exclude that the increase of DHT is related to a conversion of Testosterone by 5 alpha reductase after MAX and we suggest that steroids increases could represent a specific adaptive response to physiological needs related to the intensity of aerobic exercise.

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EP958

Resting state functional connectivity is affected by testosterone treatment in female-to-male transgender persons

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Background
Several resting state networks have been described in literature. Today, it is still unclear whether these networks are stable or can be influenced by sex hormones. Transgender persons offer a unique opportunity to study these hormonal influences.
Objective
To examine the effects of cross-sex hormone treatment in transgender persons on two resting state networks involved in cognition and emotion, the default mode network and executive network.
Methods
Resting state functional magnetic resonance imaging and sex hormone levels were analyzed in 21 female-to-males, 13 male-to-females, 17 untreated control men and 12 untreated control women (all participants were aged ≥17). Measurements were done at baseline, when endogenous gonadal stimulation in the transgender participants was suppressed by a gonadotropin-releasing hormone analogue, and four months after the start of cross-sex hormone treatment (testosterone in female-to-males and estradiol in male-to-females). Independent component analysis was used to evaluate the effect of cross-sex hormones.
Results
Within the default mode network, female-to-males showed increased functional connectivity in the right postcentral gyrus four months after starting testosterone treatment. In the male-to-females and both control groups no differences in functional connectivity in any of the two networks were observed.
Conclusions
Functional connectivity within the default mode network appears to be affected by testosterone treatment in female-to-male transgender persons.

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EP959

Effect of estradiol on the development of hypoxic pulmonary hypertension (O_2=13%, 10%, 6%) and blood hematocrit in the female ovariectomized rats

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Objective
The role of sex in pulmonary hypertension (PAH) is not fully known. The majority of animal studies have suggested a protective role of female sex hormone in PAH. But women of various ages are more subjected to PAH compared with male. The aim of current research was to test the hypothesis that the level of oxygen in the inspired air can influence on the effect of estradiol on the development of experimental PAH in female rats.
Methods and design
Female gonadectomized Wistar rats were divided into 6 groups, three from which were injected subcutaneously during 4 weeks with 1,2-propandion (vehicle, 200 mkl/rat/day, C.); and three groups with estradiol (15 mkg/kg/day E_2). The procedures followed the FELASA/ICLAS guide for use of laboratory animals. PAH was induced by exposure to hypobaric hypoxia in all 6 groups. 2 groups (C13, E13) had hypoxia with 13% O_2, 2 groups (C10, E10) – 10% O_2 and 2 groups (C6, E6) – 6% O_2. Rats were housed in a hypobaric chamber 10 h/day, 2wk. Right ventricular systolic pressure (RVSP) was measured as indices of PAH. Blood hematocrit (Hmt) were measured using a blood analyser Gemalait 1280.
Results
Chronic estradiol administration in groups with 13% O_2 caused a decrease of RVSP in group E13 on 14.6% compared with C13 ($P<0.05$). In groups 10% O_2 estradiol did not caused any change in the group of E10 vs. C10. E_2 increased degree of RVSP in group E6 vs C6; (54.8±1.4 vs 46.3±1.1 mm Hg; $P<0.01$). E2 decreased Hmt in all groups in the same extent.
Conclusions
Effect of estradiol on the development of hypoxic pulmonary hypertension in the female ovariectomized rats depends on the degree of hypoxia (O_2 13%, 10%, 6%). Decreasing effect of estradiol on the levels of Hmt does not correlate with the effect estradiol on the development of hypertension.

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EP960

17β-estradiol or triclosan-induced epithelial-mesenchymal transition and migration of MCF-7 breast cancer cells were reversed by kaempferol, a phytoestrogen

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As a phytoestrogen, kaempferol plays a chemopreventive role inhibiting cancer formation and progression. In this study, chemopreventive activity of kaempferol was examined by measuring its effect on growth, epithelial-mesenchymal transition (EMT), and migration of MCF-7 breast cancer cells increased by 17β-estradiol (E2, a positive control) or triclosan (TCS), an endocrine-disrupting chemical (EDC). As an EDC, TCS is known to interfere estrogen receptor (ER) dependent pathway in MCF-7 cells expressing ERs. In MTT assay, TCS (10^{-4}–10^{-7} M) or E2 (10^{-9} M) induced cell growth of MCF-7 cells, which was reversed to a control level by co-treatment of ICI 182,780 (10^{-8} M), an ER antagonist, or kaempferol (50 uM). In a wound-healing scratch assay, TCS enhanced migration of MCF-7 cells like E2, but co-treatment of kaempferol or ICI 182,720 decreased the migration ability of MCF-7 cells to a control level. In RT-PCR and western blot assay, we examined the effect of TCS and DIM on mRNA and protein expression of EMT-related markers such as E-cadherin, N-cadherin, snail and slug. TCS induced the increased expression of EMT promoting markers such as N-cadherin, snail and slug but down-regulated the expression of E-cadherin, an epithelial marker inhibiting EMT process. On the contrary, kaempferol was shown to reverse the expression pattern of EMT-related markers induced by TCS or E2. In conclusion, kaempferol effectively suppressed growth, EMT, and migration ability of MCF-7 breast cancer cells increased by E2 and TCS.

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EP961

Increase in insuline-like growh factor levels during cross-sex hormone treatment in transgender persons

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Background
Sex steroids probably stimulate growth-hormone secretion during puberty, which in turn contributes to the development of gender specific body characteristics. Hypothetically, adequate growth hormone levels in transgender persons are also important to achieve the best therapeutic results. The influence of cross-sex hormone treatment (CHT) at growth-hormone production in adult transgender persons is not yet elucidated.
Objective
To investigate the influence of CHT on growth-hormone production by the determination insulin-like growth factor (IGF-1) levels.
Methods
This prospective study includes 89 transgender persons, 43 male-to-female individuals (MtF's) and 46 FtM's (age $\geq$18) who started with CHT between March 2015 and December 2015. MtF's were treated with cyproterone acetate in combination with estradiol transdermally or orally. FtM's were treated with testosterone transdermally or intramuscular. Serum IGF-1 and IGF binding protein 3 (IGFBP-3) levels were determined at baseline and after three of CHT. IGFBP-3 was determined to calculate the IGF-1/IGFBP-3 ratio to estimate the availability of free IGF-1. IGF-1 was measured using an automated immunoassay (Liaison, DiaSorin) and IGFBP-3 using an ELISA (DRG).
Results
In MtF's mean IGF-1 levels increased from 31 nmol/L to 36 nmol/L (16%, 95CI: 11% to 20%) between baseline and three months of CHT and the mean IGF-1/IGFBP-3 ratio with 25% (95CI: 17% to 32%). At baseline two MtF's had elevated IGF-1 levels (i.e. levels above the upper limit of their age-specific reference range), which increased to 14 MtF's after three months of CHT. In FtM's mean IGF-1 levels increased from 39 nmol/L to 43 nmol/L (10%, 95CI: 6% to 15%) and mean IGF-1/IGFBP-3 ratio with 28% (95CI: 21% to 37%). The number of FtM's with elevated IGF-1 levels increased from nine at baseline to 19 after three months of CHT.
Conclusions
In both MtF's and FtM's IGF-1 levels increased moderately during the first three months of CHT.

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EP962

Effects of sex steroid hormone on regulation and localization of the calcium related genes in rat esophagus

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Calcium ion is important for physiological functions in all tissues and organs, and is essential for many vital functions. Calcium in lumen is absorbed to cytosol, and Calbindin-D9k binds calcium. It can remove calcium to extracellular through PMCA1 and NCX1. However, in the rat esophagus, the calcium related gene regulations and localizations were not well documented. We evaluated calcium related genes including Calbindin-D9k, PMCA1, and NCX1. Immature rats were daily treated for three days with estradiol, progesterone and vehicle as control. To evaluate the pathway, antagonist groups were treated with ICI 182,780 and RU486 before 30min ahead on hormone administration. The mRNA level of Calbindin-D9k, PMCA1, and NCX1 were quantified by qPCR, protein level and localization of Calbindin-D9k, PMCA1, and NCX1 in the esophagus were identified by immunofluorescence. Calbindin-D9k expression was increased by E2 and not altered by P4. ICI decreased Calbindin-D9k expression induced by E2, but no effect was observed in RU compare with P4. PMCA1 expression was shown as opposed to the Calbindin-D9k expression. PMCA1 mRNA was decreased by E2 and not altered by P4. ICI recovered PMCA1 expression inhibited by E2. Similarly, NCX1 mRNA expression was decreased only by E2. Calbindin-D9k and PMCA1 were mainly localized in mucosa layer. The main site of the NCX1 expression was muscularis externa. Calcium related gene expressions were affected by steroid hormones in esophagus similar with previous studies. Study for regulation factor for Calcium related genes other than steroid hormone is further needed.

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EP963

How does energy intake influence the levels of certain steroids?

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Introduction
The influence of steroid hormones on food intake is well described. However, there are only a few studies on the effect of food intake on steroid levels.
Methods
The study involved eight non-smoker women (average age 29.48 ± 2.99 years; average BMI 21.3 ± 1.3 kg/m^2); they did not use any kind of medication affecting steroidogenesis. We analysed the influence of four various stimuli on the levels of steroid hormones and melatonin. During their follicular phase of menstrual cycle, each woman had an oral glucose tolerance test (OGTT), intravenous glucose tolerance test (IVGTT), a standard breakfast and psyllium (a non-caloric fibre). The samplings were performed fasting in the morning, at 20, 40, 60, 90, and 120 minutes.
Results
Cortisol declined during each test, which is a physiological decline in the morning hours. In all tests (except of the application of the non-caloric fibre, psyllium),

however, this decline was modified. After the standard breakfast there was an increase in cortisol at 40th minute. The OGTT and IVGTT tests led to a plateau in cortisol levels. Testosterone levels showed no relationships to tested stimulations. After the initial decline there was an increase in DHEA after all stimuli.
Conclusion
Despite the fact that we performed the tests in the morning hours, when steroid hormone levels physiologically start to change due to their diurnal rhythm, we still found that food intake influences some of the hormone levels.

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EP964

Endocrinological approach of individuals with gender dysphoria (transsexuality): experience of a large center

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Introduction:
Gender dysphoria (GD) is featured by significant difference between the individual's expressed gender and the gender others would assign him or her, with marked distress in social and occupational functionality, according to DSM-V classification. We report the experience in the clinical evaluation and the results of hormonal therapy and sex reassignment surgery in a hospital center.
Methods:
It was conducted a retrospective analysis of 85 patients with GD, referred for clinical and psychological evaluation, hormone therapy and sex reassignment surgery (SRC) at the *Genitourinary and Sexual Reconstruction Unit of* Coimbra Hospital and University Centre (Portugal).
Results:
Since 2004, a total of 85 patients, 47 female-to-male (FTM) and 38 male-to-female (MTF) were evaluated. The number of patients seeking treatment has increased substantially in the last 5 years. Age at initial endocrinology evaluation: 29.29 ± 11.60 years, significantly lower ($P < 0.001$) in the FTM group.
These patients had a high prevalence of mental health and psychiatric problems, over 30% ($N = 26$) and other important associated pathology were evaluated (multinodular goiter, neoplasia, diabetes, karyotype alterations and infectious diseases).
Sixty-three patients (74.1%) started hormonal treatment without significant complications (prior self-medication in 12.9%). Thirty-seven patients (43.5%) undergone sex-reassignment surgery, without significant differences between MTF and FTM groups ($P = 0.264$) however waiting time for surgery was higher in the last one. Surgical complications in 30% ($N = 14$) of operated patients (urethral fistula in 4 patients who underwent phalloplasty).
Conclusions:
It was found that 55.3% of patients pretended sex reassignment therapy from FTM. Most of the patients (74.1%) performed hormonal therapy without significant complications, so we can conclude that testosterone and estradiol treatment in physiological levels are effective and safe in female and male transsexual patients. Although 30% of operated patients had post-surgical complications, we consider that with increased clinical and surgical experience, long-term outcomes for transsexual persons should improve.

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EP965

Correlation among DNA methylation status and LINE-1 expression in rat brain

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Abstract withdrawn.

Thyroid (non-cancer)

EP966

What does matter for AUS/FLUS: size, sex or age?

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Background
The clinical attitude to the treatment of Bethesda System Category III lesions has been under controversy. Our aim was to analyse three variables and to establish a possible predictive value for carcinoma in patients with AUS/FLUS nodules.
Methods
Retrospective study of 671 thyroid fine-needle aspirations (FNAs) classified as AUS/FLUS between January 2012 and June 2015. Size, sex and age were analysed, using SPSS.
Results
671 (14.8%) FNAs were initially classified as Bethesda's category III, in a database of 4549 FNAs from 3696 patients. 195 patients underwent surgery. The risk of malignancy for operated patients was 29.7%. Nodule mean size was 24.4mm. Nodules were bigger in men than in women (27mm/24mm). The median size for histologically benign nodules was 26.5mm while malignant nodules had a median of 25mm. Follicular carcinomas were larger than papillary carcinomas (34mm/26.8mm). The histologic follow-up revealed a prevalence of malignancy for women (30.7% vs 24.1%) and for younger ages. The median for histologically benign nodules was in the 6th decade while for carcinomas was in the 5th.
Conclusion
Age was the only variable with predictable value for carcinoma in AUS/FLUS. The probability of carcinoma reduces 3% per year according to a multifactorial analysis. Patients over 70s have 5 times less probability of carcinoma than those under 40s. According to that, the authors suggest that surveillance may be enough for patients over 70s with AUS/FLUS nodules.

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EP967

Clinical features and outcomes of thyroid storm: a retrospective study

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Thyroid storm (TS) is a rare but life-threatening manifestation of thyrotoxicosis.
Objective
To describe the clinical features and outcomes of patients admitted for TS according to Burch-Wartofsky's score (BW).

Methods
A retrospective review of subjects admitted to a single hospital from 2009 through 2015 was conducted.
Results
15 cases were identified. Etiology: autoimmune ($n=8$), factitious ($n=3$), amiodarone-induced ($n=3$), undetermined ($n=1$). Manifestations at admission were: cardiovascular ($n=8$), fever ($n=3$), delirium ($n=2$), diabetic ketoacidosis ($n=1$) and hypokalemic paralysis ($n=1$). Eleven had previous history of thyroid disease (7 hyperthyroidism, 4 hypothyroidism). Hipokalemia (hk) was found in 8 cases and precipitating factors in 12. Thyroid hormone levels did not correlate with the severity of thyrotoxicosis according to BW. One patient died from sepsis. Late hospital discharge was found in 4 patients ($P=0.01$): 3 required antithyroid drugs withdrawal (febrile neutropenia, cholestasis, digestive intolerance) and the other received a heart transplant.
Conclusions
We found 4 cases of TS per 10000 admitted. The most common etiology was autoimmune. Cardiovascular manifestations were predominant. Precipitating factors were identified in 80% of patients. Unusual findings were high consumption of iodine, hk, factitious thyrotoxicosis and a prior history of hypothyroidism. Mortality rate was 6.6%. Treatment with antithyroid drugs was associated with a significant shorter time of hospitalization. This review adds data to the few previous reports and provides useful information for the management of TS, a rare and acute disease that requires high clinical suspicion in order to improve patient survival.

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EP968

Mean platelet volume (MPV) and platelet distribution width (PDW) in euthyroid woman with Hashimoto's Thyroiditis

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Objective
Hashimoto's thyroiditis (HT) is extremely common, particularly among women. Mean platelet volume (MPV) and platelet distribution width (PDW) are the measure of platelet size. We aimed to investigate MPV and PDW levels in euthyroid woman with HT.
Methods
This was a retrospective study in which the data were obtained from a computerized patient registry database. We evaluated 145 women with HT and 60 matched healty controls, who applied to our outpatient clinic of the internal medicine and endocrinology department. Anti-thyroid peroxidase (anti-TPO) and anti-tiroglobulin (anti-TG) antibody were positive in all patients. Serum thyroid-stimulating hormone (TSH),free thyroxine, free triiodothyronine, platelet count (PC),platelet mass (PM), MPV, and PDW were measured. PM was calculated by multiplying MPV and PLT. All subjects iron, total iron binding capacity, ferritin, vitamin B12 and folic acid were evaluated.
Results
There were no significant differences in age between the study and the control groups. Anti-TPO and anti-TG levels were significantly higher in the study group ($P<0.001$).Although serum TSH was within the reference value, which was higher in the HT ($P<0.009$).Mean MPV,PDW and PM were significantly higher in the HT ($P<0.001$).Analysis of subgroups indicated that TSH,MPV and PDW levels were significantly higher in the levothroxine replacement patients in the HT than no levothroxine replacement patients in the HT.There were positive corelation between PDW and anti-TPO levels ($r=0.217$, $P=0.01$). MPV was positive correlated with anti-TPO and anti-TG levels ($r=0.175$, $P=0.03$; $r=0.407$, $P<0.001$,respectively), also PM was positive correlated with anti-TPO and anti-TG levels ($r=0.168$, $P=0.04$; $r=0.250$, $P=0.006$, respectively).
Our results suggest that even if in euthyroid state, patients with HT have higher MPV, PDW,PC, and PM levels than the healthy controls. Even if in euthyroid state, HT patients with levothroxine replacement show higher MPV and PDW levels than those with no levothroxine replacement. MPV and PDW parameters are also positively correlated with serum TSH levels.
Conclusions
Because of have a higher risk of thyroid malignancies in HT patients,higher MPV and PDW levels may be associated with inflammation and thyroid malignancies.

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EP969

Association between serum insulin-like growth factor-1 and thyroid nodules

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Background
Insulin-like growth factor-1 (IGF-1) is known to be closely related to the growth of thyroid cells and thyroid diseases. However, the association between IGF-1, thyroid nodule, and thyroid cancer has not been clearly established yet. Therefore, this study investigated the association between IGF-1 and thyroid nodule size.
Methods
A total of 346 patients with thyroid nodules confirmed by ultrasonography were included. For all participants, the levels of serum T3, free T4, TSH and IGF-1, were determined by radioimmunoassay. Among the participants, the risk group was defined as those with nodule size greater than 10mm or those with suspicious features on ultrasonography even for nodule size smaller than 10mm, and they underwent fine needle aspiration biopsy. The measurement data were expressed as the mean $\pm$ standard deviation (S.D.). The analysis of variance was performed by t-test, and the correlation analysis was performed by linear regression.
Results
The proportion of patients with large nodule size and suspicious sonographic features was significantly higher in risk group. In non-risk group, IGF-1 and nodule size did not show a significant association. Subgroup analysis for the risk groupfound IGF-1 to be significantly elevated in subjects whose cytology returned as thyroid cancer. (173.3 ng/ml vs 213.1ng/ml, P-value <0.05). In this group, IGF-1 and nodule size demonstrated a positive association ($r=0.195$, P-value <0.05), and multiple linear regressions found IGF-1 to be independently associated with nodule size.(ß$=5.579$, P-value <0.05)
Conclusions
A positive association between IGF-1 and nodule size was observed only in risk group, and IGF-1 was elevated in thyroid cancer group. Measuring serum IGF-1 in patients with large thyroid nodule on ultrasonography and with suspicious sonographic features may be clinically significant.

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EP970

The immune status peculiarities depending on the level of thyroid peroxidase antibodies in Graves' disease

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It is known that thyroid peroxidase is expressed on the apical surface of thyrocytes, where catalyze the iodination of thyroglobulin and may, also, be a surface-cell antigen, which involves in the complement-dependent cytotoxicity reactions. Objective: to study the immune status indicies depending on thyroid peroxidase (anti-TPO) antibodies in patients with Graves' disease (GD). Materials and methods. The study included 35 women aged from 18 to 55 years, mean age of 39.1 ± 7.2, with manifestations of GD, before antithyroid therapy. Concentrations of thyroid hormones were measured by RIA. Anti-TPO concentrations was assessed by ELISA. The analysis of lymphocytes subset pattern were performed by indirect immunofluorescence using the FITC-marked monoclonal antibodies to CD3, CD4, CD8, CD16, CD19, HLA-DR. The Ig A, M, G concentrations were determined by ELISA. The $CD4^+/CD8^+$T cell ratio and the relative synthesis of IgA (IgA /$CD19^+$), IgM (Ig M/$CD19^+$) and IgG (IgG/$CD19^+$) were also calculated. Results. The patients with more than 100 IU/L anti-TPO level were characterized by an increase in absolute lymphocytes, relative and absolute number of $CD19^+$ and HLA-DR^+cells, $CD3^+$ and $CD8^+$cells, compared to the control range and patients with anti-TPO less than 100 IU/L. In GD patients with at-TPO level more than 100 IU/l the leuko-T- and

leuko-B-cell ratios reduction, along with the IgA and IgM relative synthesis decreasing were observed. The only difference of patients with anti-TPO less than 100 IU/l was the increasing of absolute lymphocytes number ($P<0.05$). But in this group relationship anti-TPO with relative and absolute content of B-lymphocytes ($r=+0.50$, $P=0.026$ and $r=+0.47$, $P=0.39$, respectively), and leuko-T-cell ratio ($r=-0.58$, $P=0.007$) have been appeared. Conclusion. The most significant changes of immunological indices in GD were found in patients with more than 100 IU/L anti-TPO level. In the case of anti-TPO level less than 100 IU/l the immunopathogenesis of GD is characterized by the appearance of positive relationships anti-TPO with B-, and negative with T-cell immunity indicies.

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EP971

25-Hydroxy vitamin D levels and inflammatory markers in patients with graves disease activation

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Objective
By the definition of vitamin D receptors in many tissues, many functions of vitamin D other than calcium homeostasis and bone metabolism were shown. A role for vitamin D is suggested in the pathogenesis of Graves disease because of the effects of vitamin D on the immune system. In our study the role of vitamin D deficiency in the activation of Graves disease, development of autoimmune thyroid disease and the relationship between vitamin D and inflammatory markers were investigated.
Material and methods
Our study included 40 patients with active Graves disease, 20 patients with euthyroid autoimmune thyroid disease, 20 healthy individuals and total 80 people. Serum 25(OH)D levels, thyroid autoantibodies and fibrinogen, erithrocyte sedimentation rate and hsCRP as inflammation markers were studied in all subjects and waist and hip circumferences were measured and body mass indices were calculated. We seeked relationship of vitamin D levels between Graves disease activation and inflammatory markers in all groups.
Results
Vitamin D levels were found to be significantly lower in active Graves disease and autoimmune thyroid disease patients from the control group. Vitamin D showed a positive correlation with corrected calcium, serum phosphorus, urinary calcium excretion and was negatively correlated with alkaline phosphatase, parathyroid hormone, TRAb and anti TPO. Vitamin D levels of patients with ophthalmopathy were significantly lower than the patients without ophthalmopathy. In our study, we observed that vitamin D deficiency is also associated with obesity and inflammation.
Conclusion
Vitamin D deficiency can play a role in the pathogenesis of autoimmune thyroid disease and thyroid ophthalmopathy. Vitamin D deficiency can also predispose to inflammation in patients with active Graves disease.
KeyWords: Vitamin D; Graves disease; inflammatory markers; obesity; ophthalmopathy

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EP972

Inverse relationship between seasonal vitamin D variations and thyroid antibodies (TAb) and TSH

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Vitamin D has a role in the pathogenesis of thyroid autoimmunity.
There is evidence in humans that serum levels of 1,25(OH) D3 were found to be significantly lower in patients with autoimmune thyroid diseases.
We have evaluated all samples performed in the endocrine labs tested for vitamin D, AbTg, Ab-TPO and TSH from 2006 to 2015; 29216 samples for vitamin D and 41014 for TSH, AbTg and TPO were considered.
We studied if the seasonal variations of vitamin D, that peaks in summer and has a nadir in winter, could influence levels of TAb and TSH.
Vitamin D levels in summer were significantly higher than in other seasons. Vitamin D from a mean level of 19 ng/ml in winter raises significantly in spring reaching an average level of 26 ng/ml in summer and descending in autumn reaching nadir in winter.
About TSH and thyroid antibodies, in particular AbTg shows an opposite trend compared to Vitamin D. AbTg has a peak in winter around 7 ng/dl descending to 6 ng/dl in spring and remaining of similar value during the rest of the year. Interestingly TSH has a small but direct correlation with the AbTg variation ranging within normal values but following a similar trend of that of the antibodies (Pearson correlation $r=0.009$, $P=0.03$).
In conclusion our results seem to confirm an immunodepressive role of vitamin D on thyroid autoimmunity; in summer when the maximum level of vitamin D was reached, the concentration of TgAb was at minimum, while in winter at the lowest level of vitamin D the TgAb titer reached their peak.
Respectively TSH follows the trend of AbT, when AbT level decreases in summer at the maximum of vitamin D, thyroid function expressed by TSH ameliorates, while in winter at the maximum of AbT TSH is higher, corresponding to the lowest level of vitamin D.

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EP973

Autoimmune thyroiditis: association with two common polymorphisms of the RAGE gene and oxidative stress

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Introduction
Polymorphisms of the receptor for advanced glycation end products (AGEs), RAGE, have been associated with autoimmune disorders and their complications. There are no studies concerning Hashimoto's thyroiditis (HT); the aim of our study was to investigate the possible role of two *RAGE* polymorphisms (−429T>C, −374T>A) in combination with indices of oxidative status in women with HT.
Design
We examined 300 euthyroid women (44.8±13yrs); 205 had HT (positive thyroid antibodies (ThAb(+)) and were separated in two groups; 96 under T4 replacement, 109 without. 95 women without ThAb and negative family history for HT were also studied (control). To evaluate oxidative stress, we measured total lipid peroxide levels in serum (TOS). Thyroid function tests were also performed. Genomic DNA was analyzed for the *RAGE* polymorphisms −429T>C *Alu*I and −374T>A *Mfe*I.
Results
Women with HT on T4 had higher TOS levels compared to those without treatment and to controls (mean TOS: 520 μmol/l vs 421.04 μmol/l vs 447.6 μmol/l, respectively, $P=0.026$). The prevalence of −429T>C *RAGE* polymorphism was significantly higher in this group compared to HT without treatment and controls (18.8% vs 11.9% vs 6.3% respectively, $P=0.032$). In the entire cohort, increased TOS and carrying the -429T>C polymorphism were independent predictors of HT (OR1.64, OR1.60 respectively. The coexistence of these factors had an additive effect (OR 5.4). The prevalence of −429T>C polymorphism was higher in women with DM2 compared to those without (33.3% vs 10.9%, $P=0.009$). There was no difference in the prevalence of −374T>A polymorphism r between the studied groups.
Conclusions
Women with increased TOS levels who are also carriers of the -429T>C polymorphism of *RAGE* are at increased risk to have Hashimoto's thyroiditis and receive T4 replacement. These findings possibly suggest a role of this system in the elevated oxidative stress accompanying autoimmune thyroiditis.

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EP974

Surgery of benign thyroid disease – Analysis of vocal fold paralysis in 3019 patients

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Methods
To evaluate factors influencing the relative risk (RR) for vocal fold paralysis we analyzed 3019 patients (69.5% female) having surgery for benign thyroid diseases (58.7% nodular goiter, 17.5% inactive nodes, 16.3% thyroid autonomy, 6.5% Grave's disease). Operations were performed with intraoperative neuromonitoring by general surgeons (GS, $n=1637$) or physicians specially trained for ENT ($n=1382$). 19.2% of the procedures were carried out by residents in training.
Results
Vocal fold paralysis occurred in 198 subjects (6.6%), 6.3% in females and 7.0% in males. Prevalence was not influenced by gender, age, recurrent disease (RR 1.20), surgeries performed by physicians in training (6.2%, $n=581$) or if minimal invasive (6.5%, $n=769$) and conventional surgery (6.6%, $n=2250$) were compared. Risk was increased in nodular goiter (7.3%, RR 1.37), but not in Grave's disease (6.6%, RR 1.01). A higher rate was seen in total ($n=1576$, 6.9%) and nearly total ($n=507$, 8.1%) than in subtotal thyroidectomy ($n=866$, 5.2%). A lower rate (RR 0.54) was observed in operations performed by ENT (4.6%) than by GS (8.2%). Postoperative haemorrhage (4.6% vs. 1.6%, RR 2.94), hypocalcemia $<$ 2.0 mmol/l (28.8% vs. 19.9%, RR 1.63) and the need for calcium substitution (RR 1.65) or dihydrotachysterol treatment (RR 2.18) at discharge from the hospital was documented more frequently in patients with laryngeal nerve palsy.
Conclusion
In thyroid surgery a multinodular goiter, invasiveness of the operations and a physician not trained for head and neck surgery are risk factors for vocal fold paralysis. Postoperative haemorrhage and hypocalcemia are seen more frequently in patients with damage to the recurrent laryngeal nerve.

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EP975

Evaluation of incidental 18f-Fdg uptake of thyroid with ultrasonography and elastosonography

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Introduction
Thyroid incidentaloma detected by FDG-PET/CT (flourodeoxyglucose positron emition tomography/computed tomography) is important because of high rate of malignancy. Elastosonograpghy has proven valuable in discriminating malign and benign thyroid lesions. In this study, we aimed to evaluate PET incidentalomas by ultrasonography and elastosonography and to compare cytopathological results with imaging findings.
Methods
A total of 50 patients included into the study and maximum standardized uptake value (SUV max) values were recorded. All patients underwent laboratory evaluation (TSH, free T4, thyroglobulin antibody, thyroid peroxidase antibody and calcitonin) and underwent ultrasonography, elatosonography and fine needle aspiration cytology (FNAC). Cytopathological results were classified acoording to the Bethesda system. Elasticity of the suspicious nodule was scored as peviously described.
Results
Of the 50 patients, 16 patients (32%) were found diffuse uptake (group A) and 34 patients (68%) were found focal uptake (group B). In group A, at least 1 antibody was found as positively (100%) and thyroid nodule was detected in 9 patients (56%). FNAC was revealed malignant cytology consistent with papillary carcinoma in 1 patient. In group B, thyroid nodule was detected in 31 patients. FNAC was revealed non-diagnostic in 4 patients, benign in 14 patients, atypia of undetermined significance in 2 patients, follicular neoplasm in 1 patient, suspicious for malignancy in 7 patients and malignant in 3 patients. Surgical resection was performed only in 4 patients and follicular carcinoma was revealed in 1 patient and papillary carcinoma was revealed in 3 patients. There was no statistically significant difference in the SUV max between benign and malignant nodules in both group A and group B. There was a significant correlation between presence of malignancy and elasticity score ($r=0.756$, $P=0.000$).
Conclusions
Increased elasticity score correlate with high likelihood of malignancy. Performing an elastosonography with ultrasonography may provide additional information to evaluate PET incidentalomas.

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EP976

Serum immunoglobulin G4 is closely related to develop Graves' ophthalmopathy

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Abstract withdrawn.

EP977

Immunohistochemical expression of iNOS and eNOS in thyroid goiter

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Introduction
Oxidative stress has been implicated in the pathogenesis of many thyroid diseases, such as non-toxic nodular goiter and Hashimoto's thyroiditis. Nitric oxide synthases are responsible for the synthesis of nitric oxide from L-arginine. There are three isoforms of nitric oxide synthase (NOS): neuronal NOS (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS). They have important functions in inflammation and vasoregulation but their role in thyroid diseases is not well understood.
Methods
Thirty-one patients with thyroid goiter were included in the study: 18 cases with non-toxic nodular goiter (NTNG) and 13 patients with Hashimoto's thyroiditis (HT). Normal glands served as controls. Frozen sections were incubated with purified mouse monoclonal antihuman antibodies against iNOS and eNOS. The dilution of the primary antibodies was 1:100 and was verified in a series of pilot experiments. The immunohistological investigations were performed by the BrightVision method from ImmunoLogic. The number of positively stained cells were counted and expressed as a mean value of at least 10 high power fields (HPF, 400x).
Results
Hashimoto's thyroiditis demonstrated higher expression of both iNOS and eNOS in comparison with non-toxic nodular goiter and healthy thyroid gland. Positive staining for iNOS was observed in 96% of HT (4.6 cells/high power field - HPF), whereas only 42% of NTNG (2.1 cells/HPF) and 30% (1.9 cells/HPF) of healthy tissue showed immunoreactivity. eNOS was expressed in 89% of HT (4.1 cells/HPF), 40% of NTNG (2.0 cells/HPF) and 19% of healthy gland (1.9/HPF)

Conclusions
Oxidative stress markers could become indicators of disease activity and immunological phenotype. Alterations in the process of oxidative stress are implicated in the pathogenesis of autoimmune thyroid diseases, such as Hashimoto's thyroiditis. However, the role of oxidative stress in inflammation of thyroid is still not completely known and further studies in this matter should be continued.

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EP978

Factors associated with persistent atrial fibrillation after achievement of euthyroid state

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Introduction
Atrial fibrillation (AF) occurs in up to 15% of patients with hyperthyroidism. Although hyperthyroidism is usually regarded as a reversible cause of AF, spontaneous sinus conversion occurs in only 2/3 of patients upon the normalization of T4 levels. The aim of this study was to identify factors associated with persistent atrial fibrillation after restoration of euthyroid state.
Methods
We conducted a retrospective study of 13 years. Twenty patients hospitalized for hyperthyroidism with AF and who had normalized their FT4 level during follow-up were enrolled. Non parametric Mann Whitney test was used to compare medians.
Results
The median follow-up period was 58 months. At the end of the follow-up period, 6 patients were euthyroid, 13 hypothyroid and 1 patient had a subclinical hyperthyroidism. Eight of the 20 patients returned to sinus rhythm after a median of 15 months. We found no significant difference between subjects who returned to sinus rhythm and those with persistent AF in terms of age (55.3 ± 18.6 vs 55.9 ± 12.3 years, $P=1$), gender (58.3% vs 41.7% men, $P=0.65$), history of hypertension (25% vs 25%, $P=1$), history of diabetes (12.5% vs 16.7%, $P=1$), abnormal echocardiography (33.3% vs 10%, $P=0.51$), the value of the ejection fraction (55.1 ± 13.2% vs 59.0 ± 5.0, $P=0.71$), toxic nodular etiology of hyperthyroidism (16.7% vs 83.3%, $P=0.33$), the value of the initial FT4 level (3.5 ± 0.8 vs 5.1 ± 5.1 ng/dl, $P=0.77$) and the period between the diagnosis of hyperthyroidism and the normalization of FT4 level (29.1 ± 48.2 vs 31.9 ± 27.6 months, $P=0.17$).
Conclusion
Successful treatment of hyperthyroidism resulted in conversion from atrial fibrillation in up to one third of our patients. No factors were associated with persistent atrial fibrillation in our study.

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EP979

Effect of smoking on thyroid function during pregnancy

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Introduction
Smoking affects thyroid function, the magnitude and direction of the effect varies greatly with different studies. Less is known about the effect of smoking in thyroid function during pregnancy.
Materials and methods
Healthy pregnant women with not known thyroid dysfunction were questioned about smoking habit in the first trimester of pregnancy. Blood samples for TSH, free T4 (fT4) and free T3 (fT3) were obtained in each trimester and for thyroid antibodies (TPO- and Tg- antibodies) in the first trimester.
Results
A total of 445 pregnant women were included (357 non-smokers and 88 smokers). Median age 32.00 (IQR 6), median BMI 23.4 (IQR 4.75). Education level: 1 woman without education (0.22%), 15 women incomplete primary education (3.38%), 69 women complete primary education (15.54%), 210 women general certificate of education or vocational education and training (47.30%), 61 women bachelor's degree (13.74%) and 88 women university degree (19.82%). Iodized salt was consumed by 176 women (39.53%) and iodine supplement by 324 women (72.97%). There were no differences between smokers and non-smokers in age, BMI, and consumption of iodized salt or iodine supplement. There was a trend to higher consumption of tobacco among pregnant women with a lower educational level (r -0.219; $P<0.01$). Smokers had a lower fT4 in the first trimester (1.03 vs 1.08 ng/dl; $P<0.01$) and a higher fT3 in the first trimester (3.04 vs 2.95 pg/ml; $P<0.01$) and second trimester (2.97 vs 2.85 pg/ml; $P<0.01$) than non-smokers. No significant differences were found in TSH levels. Thyroid antibodies were positive in the first trimester in 8.4% of non-smokers and 4.5% of smokers ($P=0.269$).
Conclusion
Smoking during pregnancy is associated with a lower fT4 in the first trimester and a higher fT3 in the first and second trimester of gestation. The effect size is slight and its clinical implications are unknown.

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EP980

Evaluation of ambulatory arterial stiffness index in hyperthyroidism

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Hyperthyroidism whether endogenous or exogenous in origin causes hemodynamic changes which associated with adverse cardiovascular outcomes. Ambulatory arterial Stiffness index (AASI) is a non invasive way of measuring arterial stiffness. Short term BP variability is derived from 24-hour ambulatory blood pressure monitoring (ABPM) recordings. BP variability and AASI are associtaed with increased cardiovascular risk.
We aimed to investigate AASI and short term BP variability in both overt and subclinical hyperthyroidism and their relationship with thyroid hormones.
We enrolled 59 patients with hyperthyroidism and 25 healthy euthyroid controls in the study. The hyperthyroid group included 36 patients with subclinical hyperthyroidism and 23 patients with overt hyperthyroidism. There were no statistically significant differences among overt hyperthyroidism, subclinical hyperthyroidism and control groups in terms of AASI (0.43 ± 0.15, 0.38 ± 0.12, 0.42 ± 0.13, respectively; $P=0.315$). Variability of diastolic BP, as expressed by 24-hour diastolic CV, was significantly higher in patients with overt hyperthyroidism than patients with subclinical hyperthyroidism (14.8 ± 2.6 vs 12.8 ± 2.5%, $P=0.023$). There were significant positive correlations between AASI and fT3 ($r=0.246$, $P=0.02$) and fT4 ($r=0.219$, $P=0.04$) while TSH was not correlated with AASI ($r=0.023$, $P=0.838$). After adjusting for confounders, age, 24-hour systolic and diastolic BP, variability of systolic and diastolic BP (24-hour systolic and diastolic CV) and fT4 were independent predictors of AASI ($r^2=0.460$, $P<0.001$). Our study showed that AASI did not differ between overt and subclinical hyperthyroidism whereas short term BP variability was higher in overt hyperthyroidism than subclinical hyperthyroidism. Also, there was a positive relationship between AASI and free thyroid hormones.

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EP981

Herbal medicines used for thyroid disease in Turkey, and short-term effects of Anethum graveolens

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Aim
To investigate the herbal medicines (HM) used for thyroid disease, their effects and use rates in Turkey.
Materials and methods
A total of 547 patients (494 females and 53 males) had a thyroid disease were included in the study. The patients were questioned whether they used any alternative therapies or HM for their thyroid disease. The patients who used HM were asked about the kind of the HM, and duration of use. The data regarding the dose of the medicine used, levels of thyroid stimulating hormone (TSH), free triiodothyronine (sT3), free thyroxine (sT4), anti-thyroid peroxidase (anti-TPO), antithyroglobuline (anti-TG), and thyroid receptor antibody (TRAb), and the number and the volume of the nodules before and after use of HM were noted from the files of the patients.
Results
A total of 55 (10.1%) patients used at least one HM. Anethum graveolens (AG) was used by 9.1% (n:50) of the patients. There was a decrease in median sT3 level (4 pg/ml vs 3 pg/ml; $P=0.004$), and an increase in nodule volume (0.3 ml vs 0.8 ml; $P=0.005$) in patients that used dill alone. The analysis on the amount of dill consumed revealed that the median nodule volume increased in all groups in relation with the amount of dill used ($P<0.05$). There was a significant increase in median TSH levels, and significant decrease in median sT4 and sT3 levels in the patients that used one bunch of dill (100 g).
Conclusions
We determined that use of AG affected thyroid hormone levels and thyroid nodules. Use of 100 g AG was found to decrease thyroid hormone levels. Therefore, we suggest that AG should not be recommended to patients diagnosed with hypothyroidism.

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EP982

The impact of the TIRAD system on medical tactics in patients with thyroid nodules

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Widespread use of ultrasound has led an increase of patients with thyroid nodules. But individual scores of ultrasound images leads to different estimates of the results and the misunderstandings between specialists. A decision of problem is possible through standardization based on TIRADS.
Purpose
Evaluated the impact the application of TIRADS and TBSRTC on medical assistance to patients with thyroid nodules. The examination dates of 4415 people was estimated retrospectively. In group A (3370 people) the FNAB was done in all nodules more 10 mm. In group B (1045 people) selection of patients for FNAB was performed into account TIRADS. The results of FNAB was evaluated for TBSRTC.
Results
Conclusions in group A were received: TBSRTC1 in 32.9%, TBSRTC2 – 57.2%, TBSRTC3.4 – 4.2%, TBSRTC5 – 2.6%, TBSRTC6 – 3.1%. Conclusions in group B were different: TBSRTC1 – 3.4%, TBSRTC2 – 85.8%, TBSRTC3.4 – 4.5%, TBSRTC5 – 2.7%, TBSRTC6 – 3.6%. Results were connected with indications for FNAB and motivation of specialists who performed investigation. The number of not sufficiently informative results in group A was 32.9%, in group B – 3.4%. Widespread use of FNAB (account recommendations) has led to increase of benign conclusions (TBSRTC2): 57.2% (group A) & 85.8% (group B). Detection of thyroid cancer in both groups was similar: 3.1% (A) & 3.6% (B). In group B in categories TIRADS4-5 frequency of detection of tumors was 62.1%, including cancer – 54.1%. In categories TIRADS1-3 frequency of detection tumor was 8.1%, including cancer – 1.8%.
Conclusion
Most patients with TIRADS2 does not require FNAB. The patients with TIRADS2 needs for FNAB necessarily despite previous conclusions excluding cancer. The patients with TIRADS4-5 have high risk of thyroid cancer therefore they need of the periodical control (FNAB). TIRADS makes more specific evidence for FNAB, limits the number of people who needs of FNAB and sends cytologist at the probability of detecting thyroid tumors. TIRADS governs assistance to patients with thyroid nodules.

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EP983

Percutaneous laser ablation of benign thyroid nodules

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Objectives
To define sonographic and color Doppler peculiarities of thyroid nodules influencing the efficacy and follow-up principles of percutaneous laser ablation (PLA).
Methods
Three hundred forty-five thyroid nodules were treated with 1–3 PLA sessions and subsequently sonographically examined every three months within one year. Indication for PLA was increase sizes of nodules. All nodes were benign according to FNAB.
Results
The best results after PLA were achieved in solitary solid nodules 20 mm or smaller with low vascularity of peripheral or combined pattern. Effectiveness depended on the size of the nodules. Big nodules and hypervascular nodules needed more PLA sessions with increased laser power supply. The nodules with calcification, avascular regions of extremely high or low US-density and big fluid collections showed poor volume regression. Nodules having high density according to US elastography worse decreased. Homogenous surrounding tissue US-pattern allows faster nodule volume decrease comparatively to autoimmune thyroiditis. In 72% nodules reduced their volume more than to two times and 24% disappeared. Avascular and hypoechoic nodules in four week period after PLA show further volume regression; persisting vascularization suggests a second PLA session.
Conclusions
US- guided PLA is effective in benign thyroid nodules and may be alternative to conservative methods. Grey-scale and color Doppler sonography is the leading follow-up modality for patients after PLA. The best period of control for effectiveness of treatment was ninth month after PLA

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EP984

Incidence and prevalence of overt hypothyroidism and causative diseases in Korea as determined using claims data provided by the health insurance review and assessment service

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Background
The incidence and prevalence of overt hypothyroidism have been reported to be 2 to 4/1,000 population/year and 8 to 13/1,000 population, respectively, in foreign countries. As there has been no nationwide survey to obtain data in Korea, the present study investigated the incidence and prevalence of overt hypothyroidism in Korea using claims data provided by the Health Insurance Review and Assessment Service. The proportions of causative diseases for hypothyroidism were also analyzed.
Methods
This study was retrospectively performed with 541,969 Korean patients (92,832 men and 449,137 women), with overt hypothyroidism, treated with thyroid hormone between 2008 and 2012.
Results
The incidence of overt hypothyroidism in Korea was 2.26/1,000 population/year (0.78 in men and 3.72 in women), and the prevalence was 14.28/1,000 population (4.40 in men and 24.03 in women). When patients with thyroid cancer were excluded, the incidence was 1.56/1,000 population/year (0.54 in men and 2.57 in women). The incidence increased with age, with peaks in and after the late 60s in men and in the early 50s in women. The prevalence peaked in the early 70s in men and in the late 50s in women.

Conclusion
This is a report of the first nationwide investigation of the incidence and prevalence of overt hypothyroidism in Korea, although it is limited to patients treated with thyroid hormone.

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EP985

Clinical, imaging and cytological differences between palpable and non-palpable thyroid nodules

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Introduction
The prevalence of palpable nodules varies between 3–7% and nodules diagnosed by ultrasonography between 20–76%. According to the American Thyroid Association's guidelines it isn't recommended to perform routine thyroid ultrasound for thyroid nodules diagnosis, unless they are palpable or there are any risk factors.
Objective
Evaluation of sonographic and cytological differences between palpable and non-palpable thyroid nodules.
Methods
Evaluation of patients referred to perform of Fine Needle aspiration Cytology (FNAC) in an Endocrinology department. Clinical evaluation was performed by the same doctor without access to clinical or ultrasound information, characterizing if they had palpable nodules and where they were located. Ultrasound and FNAC were made after clinician evaluation.
Results
We analyzed 186 nodules of 139 patients (85.6% female) with a mean age of $57.3 \pm 14{,}8$y. 80 nodules were palpable (43%). 19 patients (19 nodules) did not perform cytology for failing criteria.
The palpable nodules compared to non-palpable were larger (± 23.36 vs. 16.94 ± 7.46 cm 8.21 cm; $P=0.032$) and located superiorly ($P=0.03$). There was no statistically significant difference between age, gender, location second anteroposterior axis and sonographic characteristics of the nodule. Cytological evaluation of this series we obtained 6.5% of non-diagnostic (11/167), 81.4% benign, 8.9% FLUS, 1.2% follicular tumor, 1.2% suspected malignancy and 0.6% malignant. There was no statistical difference comparing palpable nodules with non-palpable nodules.
Conclusions
The palpable nodules were only 43% of nodules observed by ultrasound, were larger and were located more superiorly. There was no statistically significant difference between cytological results. The assessment of palpable and non-palpable nodules should be similar.

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EP986

Selenium concentration in Korean patients with thyroid disease: a preliminary report

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Background
Selenium is an important trace element for thyroid hormone metabolism and its deficiency can cause hypothyroidism. Serum or plasma selenium concentration has been known as best biomarker which reflects selenium intake and reserve. We preliminarily assessed the serum or urine selenium concentrations in patients with thyroid disease compared to healthy normal population. We also investigated the correlation of serum selenium concentration with urine selenium concentration, thyroid hormone levels as well as urinary iodine concentration (UIC).
Methods
A total of 97 patients (32 men, 65 women, 52.4 ± 14.7 years) with benign thyroid nodule or thyroid dysfunction who visited the Thyroid Center at Samsung Medical Center between 2008 and 2013 were included. Data of 175 healthy subjects provided by Lee et al. were used as control. Serum T3, free T4, and TSH concentrations were measured using commercialized RIA or IRMA kits. Serum/urine selenium and UIC were measured by inductively coupled plasma-mass spectrometry (ICP-MS).
Results
Median serum selenium concentration was 110 μg/l (95% CI, 73–156) with a range from 67 to 169 μg/l. Median urine selenium concentration was 66.3 μg/gCr (95% CI, 28.7–283.5) with a range from 14.4 to 489.0 μg/gCr. When compared to 175 healthy subjects [serum 84 μg/l (95% CI, 30–144), urine 34.5 μg/gCr (95% CI, 0.8–107.2)], serum & urine selenium concentrations of the patients with thyroid disease were significantly higher than those of healthy subjects ($P<0.001$, respectively). Serum selenium concentration was significantly correlated with urine selenium concentration after log transformation ($r=0.88$, $P=0.022$) but not with UIC, T3, free T4 and TSH concentrations.
Conclusions
Selenium concentrations of the patients with thyroid disease were significantly higher than those of healthy subjects. Serum selenium concentration was significantly correlated with urine selenium concentration.

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EP987

Evaluation of TSH receptor antibodies and histopathological features in patients with toxic multinodular and toxic nodular goiter

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Introduction
Association between high thyrotrophin receptor antibodies (TRAb) and relapse of thyroid cancer in Graves' patients was reported previously. In this study, we aimed to investigate possible relation between TRAb and thyroid malignancies in patients with toxic multinodular (TMNG) and toxic nodular goiter (TNG).
Methods
Thyroidectomized patients with a preoperative diagnosis of TMNG, TNG and euthyroid multinodular or nodular goiter (MNG/NG) were retrospectively recruited for the study. Preoperative TRAb measurements were available in 221 patients with TMNG/TNG and 43 patients with euthyroid MNG/NG. Results were compared in these two groups.
Results
Histopathology was malignant in 71 (32.1%) and benign in 150 (67.9%) of TMNG/TNG patients. In euthyroid group, malignancy was observed in 18 (41.9%) and benign histopathology was observed in 25 (58.1%) patients. In TMNG/TNG group, TRAb was positive in 7 (9.9%) patients with malignant and 17 (11.3%) patients with benign histopathology ($P=0.742$). In euthyroid group, TRAb was positive in 1 (5.6%) patient with malignant and 2 (8.0%) patients with benign histopathology ($P=0.756$). TRAb positivity did not change between TMNG/TNG and euthyroid patients with malignant and benign histopathology ($P=0.569$ and $P=0.620$, respectively).
Conclusion
TRAb positivity seems to have no effect on malignant histopathology in patients with TMNG and TNG. Limited number of cases and lack of TRAb measurement in all TMNG/TNG patients undergoing thyroidectomy might contribute to this finding.

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EP988

Malignancy is associated with microcalcification and AP/T ratio in ultrasonography, but not with Hashimoto's thyroiditis in histopathology in patients with thyroid nodules evaluated as Bethesda Category III (AUS/FLUS) in cytology

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Introduction
The predictors of malignancy are important for decision of appropriate management in nodules with atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS). Our aim was to determine the ultrasonographical, clinical and biochemical predictors of malignancy in these patients.
Methods
A total of 427 patients with Bethesda Category III (AUS/FLUS) thyroid nodules were included in this retrospective study. We divided the nodules into two subgroups according to the histopathology as benign and malignant, and compared the preoperative ultrasonographical, clinical and biochemical findings.
Results
In overall, 427 patients with 449 AUS/FLUS nodules that went on surgery, the rate of malignancy was 23.4% (105/449). When evaluated seperately, the rate of malignancy was 25.8% in nodules with AUS (82/318) and 17.6% in nodules with FLUS (23/131) ($P=0.061$). The vast majority of malignant specimens in histopathology consisted of papillary thyroid carcinoma (PTC) ($n=91$, 86.7%). Preoperative ultrasonographic features of 105 malignant nodules in histopathology were compared with the 344 benign nodules. AP/T ratio was significantly higher in malignant group compared to benign group ($P=0.013$). In multiple logistic analyses, we found that AP/T ratio, and microcalcification were independently correlated with malignancy ($P<0.05$). Although, in univariate analysis, presence of thyroid autoantibodies and Hashimoto's thyroiditis in histopathology were higher in malignant group significantly, we did not find any correlation between malignancy and Hashimoto's thyroiditis in histopathology in multivariate analysis ($P>0.05$).
Conclusion
In Bethesda Category III nodules with higher AP/T ratio and microcalcification, surgery might be considered as the first theurapeutic option instead of repeat FNAB or observation.

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EP989

Increased Serum Levels of IL-28 and IL-29 and Protective Effect of IL28B rs8099917 Polymorphism in Patients with Hashimoto's Thyroiditis

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Hashimoto's thyroiditis is thought to result from the decreased of T helper type 2 (Th2) responses, leading to progressive destruction of thyrocytes. IFN-λ1, -λ2, and -λ3 (also known as IL-29, IL-28A, and IL-28B, respectively) is a recently described member of the IFN-λ family and has been shown to decrease production of Th2 cytokines in vitro. However, the role and mechanism of IFN-λ1 in *Hashimoto's thyroiditis* remain unknown. The purpose of our study is to elucidate whether the IL-29 and IL-28B gene polymorphisms are susceptibility genes for the development of HT. Also we aimed to investigate the effects of IL-29 and IL-28 serum levels on pathogenesis of HT. Using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method, the single-nucleotide polymorphisms (SNPs) of IL28B rs8099917 (IL28 G/T) and IL29 rs30461 (IL29 T/C) were studied in 99 patients with HT and 100 healthy controls. Considering the allelic distribution for IL28 G/T polymorphism a higher frequency of G allele was observed in the control group when compared to the HT group. So it was suggested that G allele may be a protective role for HT pathogenesis (OR=0.388 95%-CI 0.217-0.693; $P=0.001$). Also our findings demonstrate that there was statistically significant difference in serum IL-28 and IL-29 levels between case and control groups ($P<0.001$). The increased serum levels of IL-28 and IL-29 in patients with HT was determined. In conclusion, IL-28B gene polymorphism and serum IL-28 and IL-29 levels seemed to play a role in the pathogenesis of HT.

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EP990

The value of blood cell markers in patients with thyroid nodules including atypia of undetermined significance/follicular lesion of undetermined significance cytology

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Background
Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) is a heterogeneous that cannot be definitively diagnosed as benign, malignancy-suspect, or malignant. The estimated risk of AUS/FLUS malignancy is reported 5% to 15% according to the Bethesda System (BS). This study was conducted to evaluate the ability of mean platelet volume (MPV) and neutrophil-to-lymphocyte ratio (NLR) to predict the malignant potential of nodules diagnosed as AUS/FLUS.
Materials and Methods
We retrospectively analyzed 101 patients for whom thyroid fine needle aspiration biopsy (FNAB) analysis indicated AUS/FLUS and who underwent surgery between 2011 and 2015. Demographic, laboratory, and histopathological data were obtained from a database. The patients were categorized into two groups: malignant or benign and comparisons between groups were performed.
Results
The mean age was 49.01 ± 11.59 (20–80) years, the mean TSH level was 2.04 ± 2.09 μIU/ml. (0.01–11.87), the mean FT4 level was 0.98 ± 0.43 pg/ml (0.54–3.96), and the mean FT3 level was 3.71 ± 0.80 pg /ml, (2.15–7.46). Of the 101 patients, 26 (25.7%) had solitary nodules and 75 (74.3%) had multinodulary goiter. The malignancy rate (cytological atypia) was 33.7%, and there were no differences between the two groups in terms of age, gender, or TSH or FT4 levels. Median preoperative red cell distribution width (RDW) level was 13.4 inthe benign group, while it was 14.4 in patients with malignancy, demonstrating a significant correlation ($P=0.034$) Both MPV and NLR were elevated in malignant nodules.
Conclusions
The malignancy risk of AUS/FLUS evident upon thyroid FNAB was higher than anticipated by the BS. MPV, NLR and RDW are useful for estimating the malignancy risks of these diseases.

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EP991

Neck lesions located outside the thyroid bed with similar echogenity of thyroid tissue

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Introduction
We aimed to determine demographical, hormonal, ultrasonography(US) and cytological features of cases with neck lesions that are located outside the thyroid region and have similar echogenity with thyroid tissue.
Method
Neck US reports of patients who underwent fine needle aspiration(FNAB) under US guidance in our clinic in a period of one year were reviewed retrospectively. Lesions having similar echogenity with thyroid tissue and defined as ectopic or outside the thyroid bed were enrolled. Demographical, hormonal, US and cytological features were obtained from medical records.
Results
There were 76 patients(69 female, 7 male) with a mean age of 51.07 ± 12.81. 64(84.2%) of patients had a history of thyroid surgery and 12(15.8%) were not operated before. 85.5%of lesions were located at the level of hyoid bone, 9.2% inferior to thyroid lower pole and 5.3% in other sites. Localization of lesions did

not differ between patients with and without previous thyroidectomy ($P=0.083$). Median lesion volume was 0.57 ml (0.06–24.13). Ultrasonographically, 93.4% of lesions were isoechoic and 6.6% were hypoechoic. 89.5% of lesions were solid and 10.5% had mixed texture. Marginal irregularity was observed in 13.2% of lesions. US features were similar in patients with and without thyroidectomy. 62 (81.6%) lesions were positive with Tc99m pertechnetate scintigraphy and avidity rate was significantly higher in operated patients ($P=0.001$). Cytological diagnosis was benign in 73.7%, atypia of undetermined significance/follicular lesion of undetermined significance in 2.6%, nondiagnostic in 22.4% and acute supurative infection in 1.3%. There were no differences in cytopathological results between patients with and without thyroidectomy ($P=0.649$).

Conclusion

In patients with a history of thyroid surgery, US examination should be extended to outside the thyroid bed to detect possible ectopic tissue. We showed that such lesions might also occur in patients without surgery and US features and cytopathological findings were similar in thyroidectomized and nonthyroidectomized patients.

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EP992

Increased chemiluminescence activity of blood neutrophilic granulocytes from patients with Graves' disease

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The cellular structures lipid peroxidation related to immune system dysfunction seems to have a key role in autoimmune theory of Graves' disease (GD). Aim: to investigate chemiluminescent (CL) activity of blood neutrophilic granulocytes in patients with GD. Materials and methods: Twenty six women, mean age 40.7 ± 13.2, with manifestation of GD up to antithyroid therapy and 30 sex- and age-matched healthy subjects were examined. Serum thyroid hormone concentrations were measured by RIA. The median of TSH, fT4 anti-TPO concentration in GD patient were 0.17 (0.01; 0.72) mU/l, 17.9 (13.1; 30.3) pmol/l and 374.0 (223.0; 817.4) IU/ml respectively. The neutrophilic granulocytes were isolated from heparinized whole blood by double density gradient centrifugation in the ficoll-urografin: $\rho=1.077$ g/cm^3 for lymphocytes separation, $\rho=1.119$ g/cm^3 for the neutrophils isolation. The spontaneous and zymosan-induced (ZiCL) was studied for 90 minutes on 36-channel chemiluminescent analyzer "CL3606". The following characteristics have been identified: time to maximum (Tmax), maximum intensity value (Imax), reflecting the maximum reactive oxygen species (ROS) level synthesis and the area under the curve (S), describing total synthesis of ROS during 90 min. of the study. Results: Whole blood CL was significantly greater in GD patients than in controls. Increased Imax of luminol-dependent spontaneous- and Zi-CL ($P<0.05$) of neutrophils was observed. The lucigenin-dependent CL study revealed that patients with GD have reduced the Tmax of ZiCL. In healthy controls the concentration of TSH negatively correlated with Tmax of lucigenin-dependent spontaneous($r=-0.89$, $P=0.019$) and induced ($r=-0.94$; $P=0.005$) CL, the fT4 level is also negatively correlated with S ($r=-0.83$, $P=0.042$) of lucigenin-dependent spontaneous CL, Tmax ($r=-0.83$, $P=0.042$) and S ($r=-0.94$; $P=0.005$) of lucigenin-dependent induced CL of neutrophils. In GD patients interaction in pairs of anti-TPO/Tmax ($r=-0.70$, $P=0.036$) and anti-TPO/Imax($r=-0.72$, $P=0.030$) of luminol-dependent induced CL was observed. Conclusion. Hyperactivity and reactivity of peripheral blood neutrophils in GD certify by respiratory explosion in spontaneous and induced of secondary ROS level synthesis. Enhanced excitability to phagocytosis-related stimuli can mediate the autoimmune mechanism in GD.

2. The relationship between indicators of respiratory burst of neutrophils and thyroid hormone when BG is lost, but there is a moderate negative correlation between CL response and the level of at-TPO.

Keywords: graves disease, neutrophilic granulocyte, chemiluminescence, reactive oxygen species

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EP993

Effectiveness of radiofrequency ablation of the autonomously functioning benign thyroid nodules

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Introduction

The usual treatment for autonomously functioning benign thyroid nodules was surgery until the advent of new techniques such as radiofrequency ablation (RFA). This study aimed at estimating RFA efficacy of autonomously functioning benign thyroid nodules.

Material and Methods

The analysis included the results of treatment of 108 patients with autonomously functioning benign tumors of the thyroid gland, received in the Samara Oncology Center. All patients had high level of thyroid hormones and low level of thyreotropin. In all of them scintigraphy determined hot nodules. All the patients underwent fine needle biopsy twice. RF ablation was performed using an 18-gauge, internally cooled electrode, length 10 cm, working part 0.7 cm. During the follow-up nodule volume and thyroid function were evaluated.

Results

The mean follow-up was 15.3 ± 3.6 months. RFA was an effective method for treating hot nodules. The mean nodule max diameter was initially 6.5 ± 4.1 cm and significantly decreased after treatment at 1 month (3.1 ± 1.9 cm, $P<0.05$) and at 6 months (0.5 ± 2.9 cm, $P<0.05$). Levels of triiodothyronine, free thyroxine, and thyrotropin reach normal in 2–3 weeks after RFA.

No serious complications such as thyroiditis, voice change, and hematomas were observed.

Conclusion

RFA was effective and safe for treating autonomously functioning benign thyroid nodules and it might be recommended for treating hot benign thyroid nodules as the first-line treatment.

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EP994

Sorafenib-induced changes in thyroid hormone levels in patients with hepatocellular carcinoma

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Background

Recent studies suggest enhanced peripheral thyroid hormone metabolism as an explanation for the changes in thyroid hormone levels in patient treated with Sorafenib.

Methods

In this single centre, prospective, observational cohort study 60 patients with hepatocellular carcinoma were treated with Sorafenib. Thyroid stimulating hormone (TSH) and free thyroxine (FT4) were measured at baseline (time-0), at 6 weeks (time-1) and at the end of therapy (time-end).

In 36 patients extensive thyroid hormone profile including thyroxine (T4), triiodothyronine (T3) and reverse triiodothyronine (rT3) was determined.

Results

Four patients (7%) developed clinically significant thyroid disorder compatible with thyroiditis. Interestingly, nineteen patients (33%) showed mild thyroid disturbances with increasing FT4 or TSH. The mean FT4 increased significantly from time-0 to time-1 from 18.7 to 21.0 pmol/l, $P<0.001$. TSH levels increased from 1.78 to 2.54 mU/l, $P<0.001$.

T3 concentrations decreased significantly, whereas rT3 and T4 increased significantly. The serum T3/rT3 ratio significantly decreased from 3.91 to 3.85 ($P<0.001$) and the rT3/T4x100 ratio significantly increased from 0.41 to 0.48 ($P<0.001$).

From time-1 to time-end FT4 increased further from 21.0 to 22.4 pmol/l ($P<0.01$). TSH, T3/rT3 ratio and rT3/T4x100 ratio did not show significant changes from time-1 to time-end.

Conclusions

Thyroiditis occurred in 7% of the patients. The increase in FT4 in combination with an increased TSH suggests an altered setpoint of the hypothalamus pituitary thyroid-axis. The marked decrease in the T3/rT3 ratio and increase in the rT3/T4 ratio in patients during the treatment with Sorafenib, suggests increased type D3 deiodination and diminished D1 activity.

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EP995

Alterations of thyroid functions in obesity: is there any impact of co–existence of type 2 diabetes mellitus?

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Objective
The number of studies that investigate thyroid functions in obese patients is limited, and little known about the effect of co-existence of type 2 diabetes mellitus on thyroid functions. In our study, we aimed to evaluate the spectrum of thyroid function in the both diabetic and non-diabetic obese patients.
Materials-Methods
145 obese patients who were admitted to our department of endocrinology and metabolism, between June 2014 and December 2015, have been included in the study. The patients have been grouped according to their BMI values and co-existence of type 2 diabetes mellitus. Clinical and laboratory data of the patients were analyzed retrospectively and cross-sectionally. Statistical analyses were performed by using frequency analysis, T-test, Chi-square test and Pearson correlation tests.
Results
Primary hypothyroidism, subclinical hypothyroidism and subclinical hyperthyroidism were determined in 1.4, 0.7 and 2.8% of the patients respectively. Isolated elevation of free T3 and free T4 levels were determined in 26.6% and 1.4% of the patients respectively. No statistically significant difference was found between diabetic and non-diabetic groups for these parameters.
There were statistically significant positive correlations between BMI and free T4 levels, and also free T3 levels ($P=0.001$, $P=0.002$, respectively). There was no significant correlation between BMI and TSH ($P=0.717$). There was no significant correlation between age and BMI values ($P=0.237$).
There were no statistically significant difference for BMI, TSH (thyroid stimulating hormone) and anti-TPO (anti-thyroid peroxidase) values between diabetic ($n=69$) and non-diabetic obese patients ($n=76$) ($P=0.623$, $P=0.937$, $P=0.114$ respectively).
Conclusion
Our results suggest that obesity may be associated with elevated free T4 and free T3 levels. Co–existence of type 2 diabetes mellitus seems to have no effect on thyroid functions.

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EP996

Transforming growth factor β1 in postpartum thyroiditis

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Introduction and aims
TGF-β1 participates in the pathogenesis of autoimmune diseases e.g. diabetes, Hashimoto disease, autoimmune digestive system disorders. The aim of our study was to evaluate TGF-β1 levels during pregnancy and after childbirth in women who developed postpartum thyroiditis (PPT) in comparison to the healthy control group (CG) and women with positive anti-thyroid antibodies (ATA+) who did not develop PPT.
Material and method
96 women were examined in 1st and 3rd trimester of pregnancy (T1, T3) and 3.6 months postpartum (3MPP, 6MPP): 47 ATA+ without Hashimoto disease (28 with PPT, 19 ATA+ without PPT) and 49 controls. We measured TGF-β1 (ELISA), TSH, FT3, FT4, ATG, ATPO with the clinical chemistry analyzer Architect Chemistry System, TRAbs (RIA), fasting glucose, OGTT (enzymatic method with hexokinaze) and HbA1c (HPLC). All women underwent thyroid USG.
Results
28 ATA+ developed PPT. Median levels of TGF-β1 were highest in ATA+ who did not develop PPT but no significant differences were found between the levels in pregnancy and postpartum period. The lowest levels of TGF-β1 were observed in CG and also did not differ significantly between trimesters and postpartum period. Only in PPT group TGF-β1 levels increased significantly at 3MPP in comparison to T1 (T1 = 15.2 ± 6.6 ng/ml vs 3MPP = 18.4 ± 9.3 ng/ml; $P<0.01$ after Bonferroni correction). Significantly higher TGF-β1 levels were observed at 3MPP between PPT and CG ($P=0.02$), in T1 and T3 between ATA+ without PPT and CG ($P=0.049$; $P=0.017$, respectively). We found significantly higher TGF-β1 levels between all ATA+ and CG in T3, 3MPP and 6MPP ($P=0.012$; $P=0.015$; $P=0.034$, respectively).
Conclusions
Our results may suggest that TGF-β1 plays an important role in the pathogenesis of PPT. Significantly higher TGF-β1 levels between ATA+ women and CG suggest that this cytokine may play a crucial role in autoimmune thyroid disorders. This is the second study on the role of TGF-β1 in PPT and it confirms that TGF-β1 increases in postpartum period in women with PPT.

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EP997

Markers of apoptosis in thyroid goiter

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Introduction
Thyroid goiter may be present in different thyroid pathologies, such as non-toxic nodular goiter (NTNG) or Hashimoto's thyroiditis (HT), as a result of focal hyperplasia of thyrocytes (nodal goiter) or generalized enlargement of thyroid (diffuse goiter). Previous studies have demonstrated that programmed cell death, known as apoptosis, plays an important role in the pathogenesis of many thyroid diseases, especially inflammatory conditions.
Materials and methods
Pathological tissues of 49 patients with thyroid goiter: 38 cases with non-toxic nodular goiter and 11 patients with Hashimoto's thyroiditis were examined during the study. In a standard immunohistochemical procedure, monoclonal antibodies anti-CD95/Fas and anti-CD253/TRAIL were applied. The number of positively stained cells were counted and expressed as a mean value of at least 10 high power fields (HPF, 400x).
Results
Hashimoto's thyroiditis demonstrated higher expression of CD95/Fas and CD253/TRAIL in comparison with non-toxic nodular goiter and healthy thyroid gland. Positive staining for CD95/Fas was observed in 100% of HT (2.9 cells/HPF), whereas only 53% of NTNG showed immunoreactivity (1.6 cells/HPF). 91% of HT revealed expression of CD253/TRAIL (4.2 cells/HPF). Only 32% of NTNG demonstrated the presence of CD253/TRAIL (1.9 cells/HPF).
Conclusions
Apoptotic markers could become indicators of disease activity and immunological phenotype. Alterations in the process of apoptosis are implicated in the pathogenesis of autoimmune thyroid diseases, such as Hashimoto's thyroiditis.

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EP998

Hemithyroidectomy seems to be a reasonable initial surgical approach for patients with cytologically Bethesda Category III (AUS/FLUS) thyroid nodules

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Introduction
Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) termed as Bethesda Category III constitute 15–30% of thyroid cytology. However, the risk of malignancy in this heterogenous category is estimated as 5–15%. The recent studies has been reported the malignancy rate in the wide range of 6–48%. This causes surgical approach variability between different centers. We aimed to evaluate the initial malignancy rate, indication of

complementary thyroidectomy, and malignancy rate in contralateral thyroid lobe in patients with AUS/FLUS thyroid nodules who underwent hemithyroidectomy.
Methods
We reviewed the medical records of 47 (7 male, 40 female; mean aged 40.3 ± 13.3) patients with cytologically 48 AUS/FLUS nodules who underwent hemithyroidectomy operation at our institution. The patients with tumor size < 10 mm (microcarcinoma), papillary carcinoma with follicular, oncocytic, clear cell variants were accepted as low risk group. Patients with tumor size ≥ 10 mm, papillary carcinoma with columnar, tall cell, insular, solid, diffuse sclerosing variants, follicular carcinoma with widely invasive variant were accepted as high risk group.
Results
The preoperative cytology was evaluated as AUS in 32 (66.7%) nodules and FLUS in 16 (33.3%) nodules. Histopathology was reported as benign in 34 (72.3%) patients and as malignant in 13 (27.7%) patients. However, 9 (19.2%) patients was in high risk group, 4 (8.5%) patients was in low risk group. Of 13 patients, complementary thyroidectomy was performed in 11 (23.4%) patients. Of 11 patients who underwent contralateral lobectomy, 9 (81.8%) patients had benign histopathology and 2 (18.2%) patients had malignant histopathology.
Discussion
Malignancy rate in patients with AUS/FLUS nodules who underwent hemithyroidectomy was found as 27.7%. Moreover, malignancy rate in contralateral lobe was demonstrated as 18.2%. It seems that lobectomy is a reasonable initial surgical approach for these patients. Further studies with larger sample size are needed.

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EP999

Risk Factors for the development of hypothyroidism after thyroid lobectomy

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Bakground
Thyroid-lobectomy is a frequent procedure performed in patients with a variety of thyroid conditions.The aim of this study is to determine the prevalence of post-operative hypothyroidism and the risk factors of hypothyroidism in patients undergoing thyroid-lobectomy.
Patients and methods
We retrospectively reviewed patients who underwent a thyroid lobectomy for benign disease from january 2000 to 2014. Patients with known hypothyroidism before surgery or on thyroid hormone supressive therapy were excluded. We compared the age, the sex, the TSH level and the presence of thyroid antibodies between the patients who developped hypothyroidism after surgey and those without hypothyroidism.
Results
69 patients underwent a thyroid-lobectomy for benign disease.
The mean age of patients at the moment of the thyroidectomy was 41.67 ± 13.05 years, and the majority (95.7%) was female.
We identify a hypothyroidism in 28 patients (40.6%) with a mean duration of 35.1 ± 49.8 months (1–168 months) after lobectomy. Subclinical hypothyroidism was present in 42,8%.
Patient with hypothyroidism had a higher pre-operative TSH level compared to euthyroid patients (2.28 ± 1.08 vs. 1.15 ± 0.60 µUI/ml, $P = 0.001$). Preoperative TSH levels > 2.5 µUI/ml showed significant correlation with postoperative hypothyroidism ($P < 0.0001$). Nodules number was less in hypothyroidism group patient: 1.7 versus 2.5 ($P < .0027$). There was no significant relationship between age, sex and thyroid auto-antibodies and the subsequent risk of hypothyroidism.
Conclusions
The prevalence of post-hemithyroidectomy hypothyroidism was 40.6%.
A preoperative high-normal serum thyrotropin level as a risk factor of hypothyroidism was noted. Routine monitoring of serum thyrotropin level should be performed in all patients who undergo a hemithyroidectomy.

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EP1000

Autoimmune thyroid diseases (AITD) and mental illness: An evaluation of parietal cell antibodies, intrinsic factor antibodies, vitamin B12 and psychiatric symptoms in patients with AITD and Non-AITD controls

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Introduction
Associations of autoimmune thyroid disease (AITD) with autoimmune gastri-tis and mental disorders have been suggested, but evidence for a connection is lacking.
Methods
We compared the co-incidence of parietal cell antibodies (PCA > 20 RE/ml), intrinsic factor antibodies (IFA > 1.19 AU/ml), vitamin B12 plasma levels (< 200 pg/ml) and mental illness in patients with AITD ($n = 398$), e.g. active (TPO+), atrophic (TPO−) and solely thyroglobulin positive (TG+) Hashimoto's and Grave's disease (TRAB+), and Non-AITD controls ($n = 144$; no thyroid disorder or non-autoimmune hypothyroidism). Results show the overall prevalence of mental illness as well as anxiety disorders (A), depression (D) and somatization disorder (S) separately.
Results
A higher rate of PCA but not IFA was prevalent in AITS vs Non-AITD (22.1% vs 9.7%). Low vitamin B12 levels were found more frequently in TPO− (8.3%) and TG+ (8.7%) Hashimoto's and Grave's disease (10.8%, $P < 0.05$). Rates of mental illness were alike in all groups. No association of mental illness with PCA, IFA or vitamin B12 was found.
Conclusion
PCA, but not IFA are frequently observed in AITD, and no association of AITD and mental illness was evident in the preliminary results of the present study.

						Mental illness (%)			
	n	Anti-body	PCA↑ %	IFA↑ %	B12↓ %	all	A	D	S
AITD	398		**22.1**	3.8	4.8	31.4	5.6	11.1	13.8
Active Hashimoto	278	TPO+	21.6	2.5	2.9	31.7	6.8	11.9	14.4
Atrophic Hashimoto	60	TPO−	33.3	10.0	**8.3**	30.0	6.7	15.0	10.0
TG+ Hashimoto	23	TG+	8.7	8.7	**8.7**	43.5	17.4	0.0	30.4
Grave's disease	37	TRAB+	16.2	0.0	**10.8**	24.3	8.1	5.4	5.4
Non AITD	144		**9.7**	2.8	3.5	32.6	7.0	14.6	11.1
Hypothyr-eoidism	96	0	7.3	1.0	3.1	32.3	5.2	17.7	9.4
No thyroid disease	48	0	14.6	6.3	4.2	33.3	10.4	8.3	14.6

$n =$ patients; Bold numbers indicate a significant difference ($P < 0.05$).

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EP1001

Assessment of 25-Hydroxy vitamin D level in pre- and postmenopausal women with euthyroid Hashimoto's thyroiditis

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Objective
Hashimoto's thyroiditis is a common autoimmune disorder. A few studies have analyzed the association between serum vitamin D levels and Hashimoto's thyroiditis and available data remains inconclusive. The aim of this study was to evaluate the association between serum 25-Hydroxy vitamin D levels in pre- and postmenopausal woman with Hashimoto's thyroiditis.
Methods
We evaluated 120 premenopausal women with euthyroid Hashimoto's thyroiditis (Group 1), 51 postmenopausal women with Hashimoto's thyroiditis (Group 2), and the control groups consisted of 102 (74 premenauposal and 28

postmenauposal) age matched healthy subjects; who applied to our outpatient clinic of the internal medicine and endocrinology department. Anti-thyroid peroxidase (TPOAb) and anti- thyroglobuline (TGAb) antibody were positive in all patients. Serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), 25-Hydroxy vitamin D and parathyroid hormone (PTH) levels were measured.
Results
In the group 1 the mean vitamin D level was 12.46 μg/L (SD ± 12.34), compared to 19.467 μg/L (s.d. ± 8.19) in the control group for premenopausal women, $P=0.02$ (Table 1). In the group 2 the mean vitamin D level was 18.46 (s.d. ± 10.97) μg/L, compared to 23.12 μg/L (s.d. ± 8.60) in the control group for postmenopausal women (Table 2).

Table 1 Comparison of premenopausal women with euthyroid Hashimoto's thyroiditis and control group

	Group 1 ($n=120$)	**Control** ($n=74$)	***P***
Age	36.41 ± 7.8	36.59 ± 7.86	NS
TSH (μIU/ml)	2.86 ± 1.45	1.90 ± 0.92	<0.001
Free T4 (ng/dl)	1.15 ± 0.34	1.13 ± 0.13	NS
Free T3 (ng/dl)	2.96 ± 0.51	2.96 ± 0.42	NS
TPOAb (IU/ml)	288.32 ± 290.78	8.82 ± 5.56	<0.001
TGAb (IU/ml)	285.84 ± 604.72	16.01 ± 11.29	<0.001
Vitamin D (μg/l)	12.46 ± 12.34	19.47 ± 8.19	0.02
PTH (ng/l)	46.80 ± 17.30	49.15 ± 18.03	NS

(NS; Not Significant).

Table 2 Comparison of postmenopausal women with euthyroid Hashimoto's thyroiditis and control group

	Group 2 ($n=51$)	**Control** ($n=28$)	***P***
Age	54.2 ± 5.65	53.28 ± 5.31	NS
TSH (μIU/ml)	2.74 ± 2.05	2.47 ± 1.11	NS
Free T4 (ng/dl)	1.14 ± 0.25	1.13 ± 0.15	NS
Free T3 (ng/dl)	2.99 ± 0.46	3.01 ± 0.39	NS
TPOAb (IU/ml)	329.81 ± 326.51	7.89 ± 2.83	<0.001
TGAb (IU/ml)	381.32 ± 721.65	20.50 ± 17.11	<0.01
Vitamin D (μg/l)	18.46 ± 10.97	23.12 ± 8.60	NS
PTH (ng/l)	52.16 ± 23.25	51.18 ± 18.34	NS

(NS; Not Significant).

Keywords: Hashimoto's thyroiditis, 25-Hydroxy vitamin D, pre- and post-menopausal woman
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EP1002

Occurrence of ATD-induced agranulocytosis and its treatment

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Introduction
Agranulocytosis represents a serious complication of thyreostatic (ATD) treatment. The aim of our work was to determine how often did agranulocytosis occur in Graves' disease patients admitted to the thyroid treatment department of our clinic for RAI treatment between the years 1999 and 2014.
Patients and methods
We have retrospectively analysed 699 patients (572 women and 127 men at the average age of 51.5 ± 12.9 years). 327 (47%) of them took carbimazole (CBZ), 293 (42%) took methimazole (MMI) and 79 (11%) took propylthiouracyl.
Results
Agranulocytosis was the reason for RAI treatment in 10 out of 699 patients. There were 9 women and 1 man affected; at the average age of 51 ± 21.9 years. In 7 cases, the agranulocytosis occurred after MMI. In 3 cases it was after CBZ. After CBZ was recalculated to the corresponding dose of MMI, the average dose of ATD was 22.7 ± 12.9 mg MMI/day. The time span between the initiation of the ATD therapy and the development of agranulocytosis was 20–85 days. 8 patients experienced the symptoms, while in 2 cases the agranulocytosis was diagnosed by chance from a routine blood count check. The average duration of agranulocytosis was 7.6 ± 3.2 days. 5 patient were administered G-CSF (9.6 ± 3.4 days) and 5 patients were not (5.6 ± 1.5 days).
Conclusion
The occurrence of agranulocytosis in our population of patients was 1.43%, while the literary data indicate a prevalence of 0.2–0.5%. In all the patients the agranulocytosis developed early in first three months. One fifth of the patients was without any symptoms. Application of G-CSF did not reduce the duration of agranulocytosis

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EP1003

Does Immunosuppressive Therapy improve outcomes in Graves' disease: Results from a Systematic Review and Meta-analysis

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Objective
Whether additional immunosuppressive drugs to standard treatment with thyreostatic drugs reduce the risk for relapse in Graves' disease is not well understood. We performed a systematic review and meta-analysis to study the effects of immunosuppressive drugs on relapse rate and treatment effect of patients with hyperthyroidism due to Graves' disease.
Methods
We searched PubMed, EMBASE and Cochrane in July 2015 for randomized-controlled trials [RCT] comparing immunosuppressive drugs including corticosteroids, rituximab and azathioprine in patients with Graves' disease. We did not restrict the electronic searches for trials by date or language. The primary endpoint was relapse of disease until follow-up, secondary endpoints were reduction of thyroid volume and TSH-receptor-antibodies [TRAb].
Results
We included 7 RCTs with a total of 862 participants. Trials were mostly small with moderate to high risk for bias. There were 113 relapses in 481 patients receiving immunosuppressants compared to 225 relapses in 381 patients (RR for recurrence of 0.39, 95% confidence interval [CI] 0.21, 0.71). There was also a significant risk reduction found for patients in RCT (0.28 RR, 95% CI 0.18, 0.46), whereas the pooled data for controlled trials showed only a trend (0.54 RR, 95% CI 0.26, 1.13). There was a significant reduction of thyroid volume (−10.61ml, 95% CI −15.48, −5.75) and TRAb levels (−17.01 U/L, 95% CI −33.31, −0.72).
Conclusions
We found a significant reduction in relapse when immunosuppressive drugs were added to standard treatment, although the number of the trials was small with high heterogeneity in regard to type of drugs used.

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EP1004

Vitamin D levels in Graves' disease with and without exophthalmos: a case-control study

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There is evidence that vitamin D has a variety of effects on immune system function, which may enhance innate immunity and inhibit the development of autoimmunity. It suppresses T-cell proliferation, and inhibits secretion of pro-inflammatory Th1- and Th2-related Cytokines. In Graves' ophthalmopathy (GO), a diffuse infiltration of lymphocytes is seen in the orbital adipose tissues and extracellular muscles. Th1 and 2 appear to play a role GO.
Aim
To assess the relation between vitamin D deficiency and Graves' disease with or without exophthalmos.
Method
85 Egyptian individuals with Graves' disease attending Ain Shams University Hospital Endocrinology clinic participated in this study, they were 3 groups: Group 1: 30 subjects with Graves' disease with exophthalmos. Group 2: 30 subjects with Graves' disease without exophthalmos. Group 3: 25 healthy individuals. Patients with chronic kidney or liver disease, diabetes or those taking vitamin D or any drugs affecting its level were excluded. Thorough history taking and full clinical examination was done. Measurement of vitamin D level and FT3, FT4, TSH.
Results
There was a highly significant difference between group 1 and 2 as regard their disease duration and carbimazole dose and duration ($P=0.001$) and TSH, FT3 and FT4 levels ($P<0.05$). Those in group 1 had longer duration of the disease, higher dose of carbimazole, higher FT3 and FT4 and lower TSH. There was significant difference between the 3 groups as regard vitamin D ($P<0.01$). All subjects in group 1 were vitamin D deficient (100%). In group 2 (66.7%) were deficient, 23.3% were insufficient and 10% were normal. In the control 56% were deficient, 40% were insufficient and 4% were normal. There is a significant difference within groups (1, 2) and (1, 3) ($P<0.01$) as regard vitamin D. There was a significant inverse correlation between vitamin D & the degree of exophthalmos ($P<0.01$) in group 1. There was a significant positive correlation between vitamin D and TSH ($P<0.05$) in group 2. TSH levels were independent predictor of vitamin D Levels in the studied subjects ($P<0.01$).
Conclusion
Vitamin D was deficient in subjects with Graves' disease with exophthalmos than those without exophthalmos and control. The degree of exophthalmos is inversely correlated with the degree of vitamin D deficiency.

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EP1005

Amiodarone-induced thyrotoxicosis

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Background
Amiodarone is an antiarrhytmic drug used mainly in atrial fibrillation. Amiodarone-induced thyrotoxicosis (AIT) is less common than hypothyroidism, but it represents a true therapeutic challenge. AIT can be due iodine load (type 1) or a destructive thyroiditis (type 2).
Methods
Retrospective study of patients with AIT, diagnosed between 2010 and 2015, in a central hospital. We reviewed medical records regarding age, gender, amiodarone therapy, hospitalizations, cardiovascular events, thyroid function and therapy. We used descriptive statistics, *t*-test for continuous variables and chi-squared distribution for categorical variables.
Results
We identified 40 patients with AIT ($n=40$): 15% were type 1, 62.5% type 2 and 22.5% mixed or undefined forms. Mean age of presentation was 71.1 ± 9.7 years, with an equal distribution of gender. 47.5% were managed as inpatients, mainly due worsening of atrial fibrillation or cardiac insufficiency, with higher FT4 levels ($P=0.014$). All patients stopped Amiodarone after the diagnose, however 25% stopped this drug before the appearance of AIT, with a maximum of 11 months between them. Most patients had TSH suppressed, with a mean FT4 level of 46 pmol/l and FT3 of 10.6 pmol/l. Thyroid anticorps were more prevalent in type 1 TIA ($P<0.001$). Methimazole was used in 85% of the patients, 52.5% did Prednisolone and 15% of cases were transient without treatment. Treatment duration mean was 11.5 months (2 – 48), statistically significantly higher in type 1 vs type 2 ($P<0.001$). A total of 10 cardiovascular events after the beginning of AIT treatment, with another hospitalization needed. 3 patients died, 2 of them due to the thyroid disfunction.
Conclusion
AIT is a concern in elderly people, because treatment is challenging. Patients treated with Amiodarona and AIT need frequent hospitalizations. Type 2 AIT was the most frequent (62.5%), with higher FT4 ($P=0.014$), but treatment duration was smaller ($P<0.001$).

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EP1006

Relationship of insulin sensitivity with HOMA-IR and QUICKI index in euthyroid woman with Hashimoto's

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Objective
It is recognized that autoimmun thyroid dysfunction is associated with weight and metabolic changes, insulin resistance and type 1 diabetes. In this study, we aimed to investigate whether thyroid autoimmunity had an effect on insulin sensitivity in euthyroid woman with Hashimoto's thyroiditis.
Methods
Forty-seven newly diagnosed euthyroid woman with Hashimoto' thyroiditis with a mean age of 43 years were included in the study. The control group consisted of 39 age and BMI matched healthy subjects. Thyroid hormones and antibodies, thyroid peroxidase antibody (TPOAb) and thyroglobuline antibody (TGAb), insulin, glucose, c-peptid, HbA1c and uric acid levels, and Homeostasis Model Assessment İnsulin Resistance (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI) parameters were measured in all the subjects.
Results
No significant correlation was observed between thyroid autoimmunity and HOMA-IR and between thyroid autoimmunity and QUICKI in both groups (Table 1).

Table 1

	Patient	Control	*P*
Age	43.62±8.64	41.68±7.43	NS
TSH (μIU/ml)	2.1±1.61	2.0±1.01	<0.001
Free T4 (ng/dl)	1.15±0.32	1.13±0.13	NS
Free T3 (ng/dl)	2.97±0.49	3.0±0.39	NS
TPOAb (IU/ml)	288.43±291.17	8.81±5.20	<0.001
TGAb (IU/ml)	323.17±651.96	16.98±12.36	<0.001
Uric acid (mg/dl)	4.09±1.09	3.94±0.93	NS
Fasting glucose (mg/dl)	86.95±10.83	88.64±9.61	NS
Fasting insülin (μg/dl)	11.28±6.68	11.31±13.30	NS
C peptid (ng/ml)	2.38±1.05	2.44±1.36	NS
HbA1c (%)	5.5±0.37	5.42±0.50	NS
BMI	28.37±6.06	28.80±9.28	NS
HOMA-IR	2.41±1.66	2.44±2.90	NS
QUICKI index	0.34±0.03	0.35±0.03	NS

NS: Not significant.

Conclusion
Thyroid autoimmunity seem to not have a potential effect on insulin sensitivity in patients with newly diagnosed euthyroid Hashimoto's.

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EP1007

Thyroid dyshormonogenesis: therapeutic data of a group of seventeen patients

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Introduction
Thyroid dyshormonogenesis (TD) accounts for 15–20% of congenital hypothyroidism (CH). Levothyroxine is the treatment of choice with the immediate goal to

raise the serum T4 as rapidly as possible. Surgical treatment is indicated in case of compressive or suspected goiter.
Patients and methods
Seventeen patients with thyroid dyshormonogenesis belonging to 4 Tunisian families were included in a descriptive prospective study. They were followed up for a period of 12 years.
Results
We recruited 11 males and 6 females. The average age of our patients at diagnosis was 6.97 years (range: 1 month–30 years). Diagnosis of thyroid dyshormonogenesis was after developing clinical signs of hypothyroidism for 11 patients (64%), on occasion of family screening for 4 patients (32%) and after exploration of goiter for 2 patients (14%). 6 patients had goiter at diagnosis.
Treatment with levothyroxine has been decided for all our patients after confirmation of hypothyroidism. The average dose of L-thyroxine, evaluated in 13 patients, was 134.37 ug/day with extremes of 50 and 200 ug. Adherence was evaluated good for 6 patients (35%) and poor for 9 patients (52%). 2 patients were not evaluated. Normal thyroid function was obtained for 86% of patients.
Under treatment, 7 patients have had developped multinodular goiter. An increase of goiter volume was observed for 4 patients among 6 patients who initially presented goiter.
Total thyroidectomy was decided secondarily for 2 patients after 27 and 34 years of diagnosing thyroid dyshormonogenesis. This thyroidectomy has been indicated for a compressive goiter for one patient and for a suspected nodules for the second. The histopathologic findings were in favor of benignity.
Conclusion
The absence of neonatal screening of congenital hypothyroidism in Tunisia is responsible of diagnostic and therapeutic important delay.

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EP1008

Soluble (Pro)rennin receptor levels in patients with graves disease

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Background
(Pro)renin receptor[(P)RR] is a multi-functioning transmembrane protein which plays key roles in the regulation of tissue renin-angiotensin system (RAS). (P)RR is cleaved by furin to generate soluble (P)RR[s(P)RR], which is secreted into extracellular space. We previously reported that high blood concentration of s(P)RR indicates poor organ prognosis in several diseases. In this way, s(P)RR is expected as a candidate biomarker for reflecting the tissue RAS status, but its regulating factor remains unclear. We also reported the positive relationship between serum s(P)RR concentration and thyroid function in hypertensive patients, which suggests that the enhanced metabolism might regulate the synthesis of s(P)RR.
Methods
We measured serum s(P)RR concentration in untreated patients with Graves disease (GD, $n=52$), hashimoto disease ($n=23$), acromegary ($n=11$) and pheochromocytoma ($n=15$). We also assessed the relationship between background factor associated with endocrine disease and serum s(P)RR levels.
Results
In patients with GD, serum s(P)RR levels (27.51 ± 0.75 ng/ml) were significantly higher than the levels of normal subject (21.94 ± 0.29 ng/ml). There was no significant change of s(P)RR levels in other endocrine disease patients. The GD patients with low BMI (≤ 22 kg/m^2) showed higher levels of serum s(P)RR, while serum s(P)RR levels was positively correlated with BMI in normal subject. The GD patients with high level of s(P)RR (>27 ng/ml) showed treatment-resistant against medication (RR = 2.62).
Conclusion
Serum s(P)RR levels were significantly high in GD patients with low BMI and high levels of serum s(P)RR levels predict a resistance for medication. These results suggests that poor nutritional condition caused by the excess of thyroid hormone may stimulate the s(P)RR production, leading to the RAS-related organ damage.

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EP1009

Conjunctival impression cytology is worsened in Hashimoto's thyroiditis without thyroid associated ophthalmopathy

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Introduction
We aimed to investigate the conjunctival surface changes in Hashimoto's thyroiditis (HT) patients and controls comparatively, and search the correlation of these changes with thyroid functions and thyroid autoantibody level in patients without thyroid associated ophthalmopathy (TAO).
Methods
A total of 25 patients with HT and 33 healthy individuals were enrolled in the study. Serum TSH, fT_4 and fT_3 level, and anti-thyroid peroxidase (anti-TPO) levels were studied and then, they had thyroid ultrasonography. Following the routine eye examinations, Schirmer test was applied to determine the dry eye and specimen were taken from the temporal bulbar conjunctiva with a cellulose acetate membrane filter for the conjunctival impression cytology.
Results
We found; 1. Grade 2–3 conjunctival squamous metaplasia was more frequently seen in HT than controls (48% vs 6.1%, $P < 0.001$). 2. Patients who have Grade 3 changes had increased serum TSH and anti-TPO, decreased fT_4 levels. 3. Serum Anti-TPO level and BMI were detected as independent predictors of worsening at the conjunctival impression cytology.
Conclusions
In conclusion, we showed for the first time that conjunctiva was affected in HT distinct from TAO and anti-TPO levels and obesity were possible triggering factors on this process.

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EP1010

The effects of iodoprophylaxis on thyroid volume and nodular size during pregnancy in an iodine-sufficient area

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Introduction
During pregnancy, the thyroid volume (TV) increases by 20% to 35% in areas with iodine deficiency. In iodine-sufficient countries, while some studies showed an increase in TV by 10–15%, others did not observe any change in TV during pregnancy. Thyroid nodules may be present in up to 15–35% of pregnant women in areas with moderate iodine deficiency. However, in areas with iodine-sufficient, thyroid nodules were investigated in a few number of studies
Objective
We aimed to evaluate the TV and prevalence of thyroid nodules during pregnancy in an iodine-sufficient area.
Study design
We prospectively followed, in an iodine-sufficient area, 205 pregnant women (mean age 32.98 ± 5.01 years) in the first-trimester (1T) and 65 control group of non-pregnant healthy women matched by age and body mass index. Pregnant women were supplemented with 200 µg of iodine daily. We evaluated thyroid hormone levels, ultrasound examination of thyroid and urine iodine concentration (UIC) in the 1T, and thyroid nodules in the third-trimester (3T).
Results
The pregnant women group showed: median UIC 193 µg/l, mean serum TSH 3.44 ± 1.96 mUI/l and mean TV 9.17 ± 3.30 ml in the 1T. Twenty-two women had thyroid nodules on thyroid ultrasonography at the 1T. The number of nodules and the maximum diameter of dominant nodule did not change in the 3T (11.2 ± 4.2 ml against 10.2 ± 4.2 ml in the 1T). The control group of non-pregnant women showed: median UIC 143 µg/l, mean serum TSH 2.75 ± 2.02 mUI/l and mean TV 8.07 ± 2.20 ml. Ten women had thyroid nodules on thyroid ultrasonography (15.38%).

Conclusions
In an iodine-sufficient area as Spain, during pregnancy, the TV increase by 13.63% and is associated with urine iodine concentration. Thyroid nodules were present in 10.73% of pregnant women and did not increased in the 3T.

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EP1011

Changes in thyroid ultrasound during the first trimester of pregnancy are not related to levels of TSH

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Introduction
The changes observed in thyroid ultrasound during pregnancy are related to the nutritional status of iodine, but its association with TSH levels or the presence of thyroid peroxidase antibodies (TPOAb) is unclear.
Objective
To compare the relationship between the findings in thyroid ultrasound and thyroid function tests in the first trimester of pregnancy in an iodine sufficient area.
Subjects and methods
We conducted an observational cohort study and included 205 pregnant women (mean age 32.9 ± 5.0 years) in the 1(st) trimester, recruited from universal screening. We performed a nutritional survey and we measure urinary iodine, TSH, free T4, free T3 and TPOAb. Through a thyroid ultrasound we evaluate the thyroid volume, ultrasound textura and the number and size of thyroid nodules. We performed the comparison between the different variables according to their levels of TSH, and established three subgroups: TSH $\leq$ 2.5, 2.6–4 and $>$ 4 mU/l, with 65, 70 and 70 pregnant women in each group respectively.
Results
We found no statistically significant differences between pregnant women by levels of TSH in age, urinary iodine, percentage of positive TPOAb, thyroid volume, thyroid texture, and number of nodules. The pregnant woman with higher TSH levels had higher BMI, higher levels of free T4, higher titers of TPOAb and increased consumption of iodized salt. In the univariate analysis only the presence of positive TPOAb (and not the presence of elevated TSH levels) was associated with the presence of goiter ($r=0.26$; $P< 0.01$) and heterogeneous echotexture ($r=0.72$; $P< 0.001$).
Conclusions
We found no significant differences in the nutritional status of iodine, in the thyroid volume, in the prevalence of goiter or nodule prevalence in pregnant women according to their levels of TSH. Ultrasound abnormalities found in the first trimester of pregnancy appear to be linked with the presence of TPOAb.

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EP1012

Central/Peripheral vascularization and resistance index at Doppler ultrasound examination of thyroid nodules: are they useful to differentiate between benign and malignant pathology?

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Thyroid Doppler ultrasound (TDUS) is highly used in the evaluation of thyroid nodules (TN). Malignant thyroid pathology has been more frequently associated with central vascularization of such nodules. There is controversy regarding the usefulness of the Resistance Index (RI) in the assessment of TN.
Our aim was to analyze the utility of vascularization characteristics and RI at TDUS in the distinction of benign and malignant TN.
Materials and methods
Characteristics of vascularization (peripheral or central and peripheral) and RI (estimated by blood flow speed at the prominent artery at TDUS) were analyzed in all patients who underwent thyroid surgery and had an US-guided fine needle aspiration biopsy (FNAB) performed in our institution from June 2011 to November 2015.
Results
Sixty two patients were included, 60 women and 2 men. Mean age was 68.2 ± 6.8 years. Twenty two patients resulted in malignant (mostly papillary carcinoma) and 40 in benign pathology (mostly follicular adenomas and adenomatous nodules). Fifteen patients had 2 TN evaluated, leading to a total of 77 nodules (50 benign and 27 malignant).
We found no significant difference between RI of benign and malignant nodules: 0.59 ± 0.09 vs. 0.60 ± 0.10 respectively.
Thirty one TN showed peripheral vascularization (PV) exclusively: 20 were benign (64.5%) and 11 malignant (35.5%). Fourty six exhibited central and peripheral vascularization (C/PV): 30 were benign (65.2%) and 16 malignant (34.8%). There was not statistically significant difference between both. Sensitivity for C/PV for malignant pathology was 34.8% and specificity was 64.5%.
Conclusion
In our experience, characteristics of vascularization (peripheral or central and peripheral) and the RI of TN at TDUS alone were not useful to distinguish between benign and malignant pathology in our population.

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EP1013

Evaluation of thyroid function tests in patients with acute kidney injury

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Aim
Euthyroid sick syndrome can be described as abnormal findings on thyroid function tests that occur in the setting of a nonthyroidal illness (NTI) without preexisting hypothalamic-pituitary and thyroid gland dysfunction. In this study we tried to compare thyroid function tests between patients with acute kidney injury (AKI) and healthy controls.
Materials and Methods
This study consisted of 31 patients with AKI and 26 healthy controls. All patients' physical examination findings, laboratory data, comorbid illnesses were recorded and compared with healthy subjects.
Results
Of the patients group 69.2% patients were female and of the control group 64.5% patients were female. Also of the patients 25.8% had diabetes mellitus, 16.1% had hypertension, %16.1 had cancer, 12.9% had cardiovascular disease, 9.7% had acute gastroenteritis, 38.7% had urinary tract infection, 9.7% had pneumonia. Mean creatinine value in the patients group was 4.70 ± 2.17 and in the control group was 1.10 ± 0.28 mg/dl ($P=0.0001$). There were no significant differences in TSH and fT4 levels between patients and controls whereas fT3 levels were significantly lower in patients group ($P=0.0001$). No correlation was determined between creatinine and age, body mass index, fT_4, TSH but there was a positive correlation between creatinine and urea ($r=0.691$, $P=0.0001$) and there was a negative correlation between creatinine and fT_3 ($r=-0.691$, $P=0.0001$).
Discussion
The frequency of thyroid function abnormalities is related to the magnitude of the illness. The most common abnormality is a T3 reduction, occurring in about 40–100% of cases of NTI, which parallels the increase of rT3. As the disease severity increases, T4 levels also decrease. Most patients who are critically ill have reduced T4 levels. In patients who are hospitalized with an NTI, about 10% have abnormally low TSH values. As in chronic kidney disease, fT_3 levels could be a marker for euthyroid sick syndrome in patients with AKI.

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EP1014

Is there seasonality in the month of birth of patients with autoimmune thyroid diseases?

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Background
Graves' disease (GD) and Hashimoto's thyroiditis (HT) are common disorders with an autoimmune etiology, which are known as autoimmune thyroid diseases (AITD). A specific seasonal pattern of the month of birth has been suggested in several autoimmune disorders, supporting the hypothesis of a link between viral infections and the development of aberrant immune-regulatory mechanisms. However, there are few studies which specifically address this issue in AITD.
Materials and Methods
We reviewed the month of birth of a large cohort of patients with AITD at a single tertiary-care reference hospital. We compared this cohort with the total number of newborns in our city between 1996 and 2011. Chi-square and Hewitt tests were used to analyze seasonality.
Results
We included a total of 417 patients (270 GD and 147 HT), 357 (85.6%) women, with a mean age of 49.1 ± 14.3 years old. January, May and November were the months in which the majority of patients were born. The winter/summer ratio was 0.98. Hewitt test was not statistically significant (for k = 3, $T = 24$, $P = 0.992$; for k = 6, $T = 40$, $P > 0.880$). Taking the number of births in each month in Madrid as reference values, there were no significant differences between the number of births observed in patients with AITD and the number of births expected throughout the whole cohort. There were no differences in the percentage of births in each month between sexes or between the types of AITD (GD vs TH). Seasonality was neither observed for the month of diagnosis in patients with GD (for k = 3, $T = 24$, $P = 0.992$).
Conclusions
Our results suggest that there is no specific seasonal pattern in the month of birth in patients with AITD. This could favor the hypothesis of further mechanisms involved in the development of autoimmunity, different from those observed in other autoimmune diseases in which a seasonality was observed.

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EP1015

Cardiovascular risk assessment using serum hs-CRP and Framingham risk score in newly diagnosed Graves' disease patients

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Introduction
In hyperthyroid patients mortality is increased by 20%, the major causes of death being cardiovascular disorders. Recent data suggest that subclinical or treated thyroid disease is associated with increased long-term vascular risk despite restoration of euthyroidism.
Methods
We measured high-sensitivity C reactive protein (hs-CRP) in 116 newly diagnosed Graves' disease (GD) patients, without prior antithyroid treatment. Levels of hs-CRP < 1 mg/l are associated with a low cardiovascular risk, between 1–3 mg/l with medium risk and > 3 mg/l with high risk. We calculated Framingham risk score in 97 patients, using as risk factors: the presence of arterial hypertension, total cholesterol, HDL-cholesterol, age, sex and smoking status. Individuals with low risk have ≤10% CHD risk at 10 years, with intermediate risk 10–20%, and with high risk ≥20%. Patients < 20 years old, with diabetes mellitus, known cardiac diseases or symptoms were excluded.
Results
The mean value of serum hs-CRP was 4.13 ± 7.71 mg/l, mediane = 1.80, IQR = 4.59 mg/l. Serum hs-CRP mediane level of 1.80 mg/l is asociated with a medium cardiovascular risk. Framingham risk score had a mean value of 2.84 ± 3.58% S.D. and a mediane of 1, interval = 1–16, IQR = 2%. Framingham score placed the majority of patients (91.8%) in a low cardiovascular risk category and only 8.2% in an intermediate risk category, with no patients in the high risk category. Framingham risk score was higher in men compared to women (mediane = 4.50, IQR = 11 vs mediane = 1, IQR = 2%, $P < 0.001$). Intermediate risk patients were older than patients in the low risk group (64.13 ± 10.30 vs 43.89 ± 13.68 years, $P < 0.001$).
Conclusions
Serum hs-CRP values placed GD patients in a medium cardiovascular risk while Framingham risk score placed the majority of patients in low risk group, <10% within the next 10 years. Considering the increased morbidity and mortality associated with hyperthyroidism the development of a specific cardiovascular risk score for this specific category of patients could be useful.

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EP1016

Total thyroidectomy in refractory amiodarone induced thyrotoxicosis: a case series of 12 patients

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Introduction
Amiodarone induced thyrotoxicosis (AIT) occurs in 5–10% of patients and may occur at any time throughout the course of treatment including months after discontinuation. Two distinct forms of AIT are distinguished and treated differently. Iodine-induced hyperthyroidism, typically seen in patients with underlying thyroid disease, is referred to as typ1 AIT and treated with high doses of thionamide antithyroid drugs and perchlorate. Type 2 AIT is a destructive thyroiditis and most cases respond to high-dose glucocorticoids. However, mixed forms and refractory cases are occasionally observed and prolongued hyperthyroidism may lead to siginificant morbidity, especially in patients with significant cardiac comorbidities. Thyroidectomy rapidly restores normal thyroid function but must be performed in still overtly hyperthyroid often critically ill patients.
Methods
Retrospective analysis of the clinical records of all 12 patients with AIT, who underwent total thyroidectomy at the Department of Surgery, Kantonsspital St. Gallen, since 2006.
Results/cases
The age of the patients ranged from 50–81 years and 2 were female. All patients had an underlying structural cardiac disease and 8 had an ICD. All patients had been treated with thionamides, glucocorticoids or both for 3–10 weeks prior to surgery. Indications for total thyroidectomy included unresponsiveness to medical treatment and worsening of the underlying cardiac condition in several cases. Euthyroidism was restored quickly in all subjects. The length of the postoperative hospital stay ranged from 2–5 days and temporary intensive care was required in 3 patients. One patient died 3 weeks after surgery because of multiple preexisting complications. All other patients were euthyroid on levothyroxin replacement and in stable or improved cardiac condition for at least 1 year.
Conclusion
Total thyroidectomy is an effective and safe treatment in patients with AIT unresponsive to medical therapy and should be considered early to prevent subsequent cardiac morbidity due to prolongued overt hyperthyroidism.

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EP1017

Accuracy of repeated core biopsy (CB) after inadequate first CB in thyroid nodules

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In our centre, thyroid core-biopsy (CB) has replaced fine needle aspiration biopsy (FNAB) in the study of thyroid nodules because its better accuracy. International guidelines recommend repeating the FNA in cases of inadequate or insufficient first specimen, but nothing is published about the case in failed CB.
Objective
To study the differences between nodules with inadequate and diagnostic thyroid Core Biopsy and the accuracy of repeating a CB after a previous inadequate result.
Methods
Methods of 3.972 CB performed along ten years (2005–2015) in 3.384 patients, 139 (3.5%) were considered inadequate for diagnosis, due to insufficient tissue, intense fibrosis or bad processing. CB was performed using an 18G spring-loaded device. We standardized four diagnostic categories: insufficient, benign, microfollicular proliferation and malignant.
Results
Patients with inadequate CB were younger than the patients with diagnostic biopsies (53.7 vs 57 y-o; p: 0.012). Mean nodule diameter was smaller in insufficient CB (20.6 mm vs 25.9 mm), isthmic localization was more frequent (19.5% vs. 7%). and they were less frequently predominantly solid (50% vs. 70.5%). In 22 cases, simultaneous FNA were conducted in predominantly cystic nodules, eleven of them diagnostic in cytological study, all of them benign.

In 51 cases a second CB was performed being diagnostic in 48 cases (94.1%), 45 of them hyperplasic tissue, 2 follicular proliferations and 1 papillary thyroid cancer. Surgery was performed in 10 cases which confirmed the diagnosis in the last 3 cases, two follicular adenomas and one PTC, and in another 7 benign lesions.
Conclusion
Second CB has 94.1% of successful sampling. Most nodules with non-diagnostic initial CB are benign. Combination of 2 thyroid CB allows a diagnosis in nearly all thyroid nodules.

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EP1018

The prevalence of iodothyronine deiodinase genes and their association with neuropsychological status in Korean hypothyroid patients

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Background
Three deiodinase genes (DIO) play an important role in thyroid hormone metabolism. Among them, type 2 iodothyronine deiodinase (DIO2) converts T4 to T3 in brain and impaired psychological well-being was reported in minor variants of DIO2. However, the prevalence of three DIOs and their relation to neuropsychological status has not been evaluated in Asian hypothyroid subjects.
Methods
We prospectively enrolled 196 subjects who were taking levothyroxine between Nov. 2012 and May 2015 at Samsung Medical Center. We analyzed 19 single nucleotide polymorphisms (SNPs) in the three deiodinase genes using MassARRAY matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (Sequenom, San Diego, CA, USA). We assessed the neuropsychological status by the six questionnaires and identified the association between DIO variants and well-being scores.
Results
Thyroid cancer patients ($n=60$) who underwent total thyroidectomy and patients with chronic autoimmune thyroiditis ($n=136$) showed similar distributions of DIO variants and questionnaire scores. The prevalence of minor homozygote in four DIO2 SNPs tested was 2% (rs12885300), 4% (rs225011), 14% (rs225014) and 14% (rs225015). Questionnaire scores (HADS-Anxiety, HADS-Depression and Brief Fatigue Inventory) in minor homozygote of DIO2 SNPs were worse than common homozygote and heterozygote, but not significant.
Conclusion
Worse neuropsychological scores seemed to be related to minor variants of DIO2 SNPs in subjects with thyroid disease. This issue should be validated in further larger studies to clarify the relevance between psychological status and DIO variants as well as the improvement of well-being using T3/T4 combination or T4 monotherapy in subjects with minor variants.

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EP1019

Anti neutiphil cytoplasmic antibodies & hyperthyroidism in fayoum (Egypt)

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Background
It was noted in the last few years there was an increased incidence of vasculitis and vasculitic reactions in patients with thyrotoxicosis. Those vasculitic reactions ranged from simple purpuric skin lesion to sever intra-alveolar hemorrhage and even to Steven Johnson Syndrome, Most of those vasculitic reactions occurred in patients receiving propylthiouracil or methimazole. But many other cases were detected in thyrotoxic patients even before starting to receive those medications.
Aim
The aim of this work is to clarify whether the vasculatic lesions associated with hyperthyroidism were due to anti-thyroid medications or due to the hyperthyroid diseases itself or due to both of them.
Methods
This study included 125 subjects divided into 4 groups, group -1 included patients with newly diagnosed autoimmune hyperthyroidism, 2- newly diagnosed non immune hyperthyroidism, 3- patients receiving propylthyouracil and 4- patients receiving methemazol , all routine labs and *P*-ANCA were done for all the patients as well as the control group
Results
It was found that p ANCA level was higher in patients with autoimmune hyperthyroididism than the non immune hyperthyroidism ($P=0.002$) also p-ANCA level was higher in patients with protienurea than those with normal urine analysis (*P*-value 0.01). also p ANCA was significantly higher in patients with both arthralgia and or skin rash, than those without these findings. (*P*-value <0.01). There was statistically significant positive strong correlation between p-ANCA level and dose of propylthyouracil or methemazol given to treat hyperthyroidism (*P*-value <0.05) and statistically significant positive correlation between p-ANCA level and duration of treatment (*P*-value <0.05.) While correlation between p-ANCA and thyroid hormones profiles after controlling of dose and duration of treatment, revealed that There was no statistically significant correlation between p-ANCA level and level of T3, T4 and TSH.

Keywords: *P*-ANCA, thyrotoxicosis, propylthyouracil and methemazol
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EP1020

Recurrent sub acute thyroiditis lacking diagnostic imaging features: atypical scenario

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Introduction
Diagnosis of sub acute thyroiditis is readily considered in a patient presenting with classical history and characteristic clinical features. Confirmation of diagnosis is based on particular set of laboratory investigations and supported by characteristic imaging findingsof Tc-99 scan. However, prescence of sub acute thyroiditis with normal thyroid scintigraphy findings is exceedingly rare.
Case report
51 years old postmenopausal female with history of recurrent sub acute thyroiditis 10 years back presented with pain in neck initially over right side then later over the left for one and half month and fever for three days, heat intolerance, sleep disturbances, restlessness. Physical examination revealed enlargement and marked tenderness over the thyroid initially more marked on left side and after few days over the right side. Thyroid profile showed TSH 0.023 ulU/ml, FT4 2.31 ng/dl, FT3 2.74 ng/dl and TSH 0.008 ulU/ml, FT4 2.64 ng/dl, and FT3 2.5 ng/dl on two separate occasions. ESR was 94 mm/hr. Tc-99 m pertechnetate scintigraphy showed bilateral normal homogenous uptake. Clinical diagnosis of sub acute thyroiditis was made. Prednisolone started in tapering dose. Improvement in symptoms with normalization of ESR of 08 mm/hour and FT4 of 1.04 ng/dl occurred after taking prednisolone for six weeks at follow up.
Conclusion
This case presenting with typical clinical features of sub acute thyroiditis and elevated ESR but lack characteristic imaging emphasizes upon diagnosis of sub acute thyroiditis on the basis of history, physical examination and laboratory data even if thyroid scintigraphy findings are not in favor of disease.

Keywords: sub acute thyroidis, recurrent, normal thyroid scintigraphy
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EP1021

Evaluation of theurapeutic modalities of Graves' disease

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Objective
Radioiodine (RAI), surgical and anti-thyroid drug therapy are the main options to treat Graves' disease (GD). The aim of this study was to investigate theurapeutic options, their efficacy and adverse reactions of prophilthiouracil (PTU) and methimazole (MMI).

Design
A total of 650 patients with GD were evaluated retrospectively. Treatments, adverse reactions, clinical and laboratory results were recorded. After 18 months of primary medical treatment, recurrence rates of MMI and PTU were compared by the following one year.
Results
Mean age was 42.2±13.6. Of the patients, %55.4 ($n=360$) were treated with MMI and 44.6% ($n=290$) with PTU. RAI and surgery treatment were applied 9.4% vs 7.4% respectively because of adverse reactions or unable to achieve euthyroidism with maximum dose of drugs or malignity suspicion. %16.6 ($n=108$) of patients were still continuing to take anti-thyroid treatment. 66.6% ($n=433$) of the patients completed 18 month-period of the therapy and %61.2 ($n=256$) of them were in remission by the following 1 year. Recurrence were detected in 38.8% ($n=168$) of the patients and they were all treated with RAI (72%) and surgery (28%). %14.6 of patients (95/650) underwent surgery. Thyroid nodules were detected in 26.3% ($n=171$) of the patients. Papillary thyroid cancer were detected in 9.5% ($n=10$). Thyroid ophthalmopathy were seen in 8.6% ($n=56$). Adverse reactions of drugs were found in 6.9% ($n=45$) (with 2.5% of skin, 2.3% of hepatotoxicity, 1.8% of temporary neutropenia, 0.6% of agranulocytosis). there were not significance difference between MMI and PTU in terms of adverse effects.
Conclusion
Remission rates of medical treatment were high although minor and major adverse drug reactions were seen in the treatment of GD. We could not detect difference in terms of advers effects of MMI and PTU. They could be used safely.

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EP1022

Changes in irisin, titin and dystrophin concentrations in patients with overt thyroid dysfunction

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Introduction
Many original research studies describes significant impact of thyroid hormones on muscle tissue. Hypo- and hyperthyroidism cause both functional and structural damage of muscles presented by many signs and symptoms of thyroid myopathy. Thus, it is interesting to compare the impact of thyroid dysfunction on hormones secreted by muscles – myokines.
Aim
The main goal of the project is to assess serum concentration of three myokines – irisin, titin and dystrophin and creatine kinase (CK) in patients with thyroid function impairment (overt hypo- and hyperthyroidisim) and in healthy control subjects.
Methods
The study enrolled 97 patients, newly diagnosed with overt thyroid dysfunction (48 with hypothyroidism and 49 with hyperthyroidism) and 40 healthy control subjects. Additionally, patients diagnosed with hypothyroidism were divided into two subgroups – long-lasting and short-term dysfunction. All subjects underwent routine clinical examination, laboratory tests (irisin, titin, dystrophin, thyroid-stimulating hormone - TSH, free thyroid hormones, anti-thyroid autoantibodies and CK concentrations), and thyroid ultrasound examination.
Results
The mean serum irisin level was lower in patients with long-lasting hypothyroidism than in other three groups ($P<0.05$). There was generally statistical difference in dystrophin levels between groups ($P=0.035$), with the highest dystrophin level in healthy controls and lowest in hyperthyroid patients, however post hoc analysis revealed the values at the border of statistical significance ($P=0.076$) between these groups. Similarly, the highest titin levels were presented by healthy controls, and the lowest by hyperthyroid patients ($P=0.011$) and group with long-lasting hypothyroidism ($P=0.052$). CK levels were statistically higher in long-lasting and short-term hypothyroidism than in hyperthyroid and control subjects ($P<0.05$).
Conclusions
Obtained results suggest that impact of thyrometabolic state varies among described myokins. This might be explained with multiply impact of hypo- and hyperthyroidism on muscle tissue, both dysfunction and destruction - demonstrated with high CK level.

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EP1023

Thyroid function parameters in Polish pregnant women

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Thyroid function in pregnancy differs between populations. The aim of the study was to assess thyroid parameters in Polish pregnant women. It included 1095 pregnant volunteers aged 16–42 years (174, 501, 420 in the 1st, 2nd, and 3rd trimester, respectively), who gave their informed written consent. In each woman thyroid ultrasound was performed, 90.7% had TSH, fT4 and a-TPO measured, and 84.0% iodine urinary concentration (UIC) in urine spot sample estimated.
Results
Median UIC in study group was 92.3 µg/l. UIC above 150 µg/l was noted in 22.3% of women. Median, 2.5 and 97.5 percentile for TSH were 1.6, 0.13 and 4.97 mIU/l, respectively; for fT4 12.3, 8.72 and 17.92, respectively; for a-TPO 10.7, 8 and 16.4 IU/l, respectively. 88.6% of women were a-TPO. Median, 2.5 and 97.5 percentile for TSH in those subjects were 1.57, 0.10 and 4.76 mIU/l, respectively. Median, 2.5 and 97.5 percentile for TSH in the 1st trimester were 1.18, 0.029 and 6.08 mIU/l, respectively; in the 2nd trimester: 1.71, 0.22 and 4.87 mIU/l, respectively; in the 3rd trimester: 1.60, 0.35 and 4.97 mIU/l, respectively. TSH level $\geq$ 2.5 mIU/l was observed in 19.1% of women in the 1st trimester, and TSH $\geq$ 3 mIU/l – in 13.9% in the 2nd or 3rd trimester. Median, LQ and UQ for thyroid volume were 12.05, 9.44 and 15.07 ml, respectively. Thyroid nodules were noted in 21.1% of women, thyroid nodules $>$ 1 cm – in 6.6%.
Conclusions
The study indicated that in iodine deficient pregnant women TSH levels are higher than recommended by current guidelines. The adequate iodine supplementation should be provided, and the threshold for L-thyroxin treatment implementation in such population should be revised.

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EP1024

Skin autofluorescence and serum carboxymethyllysine levels in hypothyroid and hyperthyroid patients

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Levels of thyroid hormones may effect the levels of the glycation product and those of the oxidation products.
Objective
To evaluate the relationship between skin autofluorescence (SAF), and serum advanced glycation end products (AGEs) parameters in hypothyroid and hyperthyroid patients.
Method
Newlydiagnosed or untreated 100 overt and subclinical hypothyroid patients (42±13 yrs) and 50 overt-subclinical hyperthyroid patients (46±13 yrs) and 50 control subjects (47±10 yrs) were enrolled after excluding diabetes. Serum carboxymethyllysine (CML) and receptor for advanced glycation end products (sRAGE) levels were measured with ELİZA. TSH and fT4 measured Skin autofluorescence (SAF), a noninvasive measurement method, reflects tissue accumulation of AGEs. Skin AF was measured using the AGE-Reader (DiagnOptics B.V., Groningen, The Netherlands).
Results
SAF measurements were 1.82±0.04, 1.63±0.3, 1.80±0.4 arbitrary Units (AU) for hypothyroid, euthyroid and hyperthyroid groups respectively ($P=0.04$) Serum CML levels were 8.2±2.8 ng/ml, 8.0±3.3 ng/ml and 10.2 ng/ml for hypothyroid, euthyroid and hyperthyroid groups respectively ($P=0.01$). sRAGE levels were similar between the groups. TSH and SAF was positively correlated ($r=0.25$, $P=0.02$) in hypothyroid group while showed a negative correlation in hyperthyroid group ($r=-0.36$, $P=0.04$). There was no correaliton between CML and sRAGE levels and SAF.
Conclusion
Accumulation of skin AGEs is increased in hypothyroid and hyperthyroid patients compared to euthyroid subjects. Thyroid status may modulates glycoxidative and Modification of tissue proteins. Although longitudinal studies needed, SAF measurement, as a noninvasive method, may be useful for identification of clinical risk factors in hypo and hyperthyroid patients

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EP1025

Ectopic thyroid tissue in the midline of the neck coexisting with a normally located thyroid gland

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Introduction
Ectopic thyroid tissue (ETT) is a rare entity; it is more frequent in women (80%) and is usually located along the obliterated thyroglossal duct. ETT in the midline is even rarer (1.79%). Incidence of malignancy in this group is lower than in orthotopic thyroid nodules.
Case report
A 40 years old woman, resident in iodine sufficient area, but originating from an iodine deficient area, presented for a midline neck mass. TSH and FT4 were measured by electrochemiluminescence Ultrasound, 131I scintigraphy, computed tomography scan and cytological exam by fine needle aspiration biopsy were performed. There were no compressive symptoms. Clinical examination was normal, except a 3/2 cm supra sternal mass, homogeneous and painless. Thyroid function was normal (TSH = 0.71 mIU/l, FT4 = 14.2 pmol/l), TPO antibodies were positive (94 IU/ml) and calcitonin was normal (1 pg/ml). Neck ultrasound showed a hypoechoic solid nodule 31/16 mm (inhomogeneous with discreet vascularization) which was situated on the median line, below the lower poles of the thyroid gland, but without any contact with those. The thyroid scintigraphy revealed a normal located thyroid with inhomogeneous capture for 131I, and slight uptake in the mass described by ultrasound. Neck CT scan revealed a mass in the inferior cervical region and superior mediastinum. FNAB confirmed thyroid tissue (normal, well- differentiated thyroid follicles, with old and recent bleedings, associated post haemorrhagic resorption areas- old nodular goiter) and did not reveal any evidence of malignancy; surgical excision was scheduled.
Conclusions
Midline neck ectopic thyroid tissue is seen very rarely; it should be considered when we need to investigate a neck mass because it may coexist with a normally located and functioning thyroid gland.

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EP1026

Depression and anxiety in hashimoto thyroiditis after long-term levothyroxine replacement

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Introduction
Thyroid dysfunction may cause various psychiatric symptoms and disturbances. In addition, many factors affect the variable responses to hormone replacement. Many patients treated for Hashimoto thyroiditis(HT) report persistent impairments in general well-being despite long-term L-thyroxine (LT4) replacement and restoration of biochemical euthyroidism.
Aim
To investigate the prevalence of depression and anxiety in patients with HT on long-term LT4 replacement and potential associations with free T4 (FT4), TSH, and antithyroid peroxidase antibodies (anti-TPO) concentrations.
Subjects and methods
Cross-sectional, case-control study with 120 patients with HT on long-term LT4 replacement and 60 euthyroid control subjects, matched for age, gender, and educational level. Measurement of TSH, FT4 and anti-TPO was done. Evaluation of depression and anxiety using the Hospital Anxiety and Depression Scale (HADS) scores(self-reported symptom questionnaire). Patients and controls were further subdivided according to age: group A (20–49 yrs) and B (50–75 yrs). Fisher's ANOVA analysis was used to compare means between (sub)groups. Spearman's correlation coefficient(r) was used to assess the correlations between hormone levels, anti-TPO, and HADS scores.
Results
Patients had higher TSH levels vs. controls in both age groups (A:3.27 ± 1.94 vs. 1.98 ± 1.01, $P < 0.001$; B:3.38 ± 1.86 vs. 0.69 ± 0.90, $P < 0.001$), and higher anti-TPO (A:2585.5 ± 2813.9 vs 49.8 ± 137.9, $P < 0.001$ and B:2582.3 ± 2986.9 vs. 25.7 ± 43.0, $P < 0.001$). Patients reported more depression and anxiety than controls: HADSD (A:6.91 ± 4.32 vs. 3.42 ± 3.02, $P < 0.001$; and B:8.29 ± 4.18 vs. 5.74 ± 2.98, $P = 0.020$) and HADSA (A:9.15 ± 3.70 vs. 7.37 ± 3.22, $P > 0.05$, B: 10.56 ± 4.16 vs. 7.89 ± 3.21, $P = 0.009$). HADSD correlated positively with both disease duration ($r = 0.418$, $P < 0.001$) and therapy duration ($r = 0.221$, $P = 0.019$); while HADSA correlated positively only with disease duration ($r = 0.292$, $P < 0.001$). HADSD and HADSA correlated positively with TSH ($r = 0.246$, $P = 0.001$ and $r = 0.202$, $P = 0.005$ respectively), with anti-TPO ($r = 0.170$, $P = 0.021$ and $r = 0.169$, $P = 0.022$ respectively); while only HADSD inversely correlated with FT4 ($r = -0.156$, $P = 0.030$) and FT3 ($r = -0.166$, $P = 0.035$).
Conclusion
Patients with HT have more anxiety and depression despite long-term levothyroxine replacement. These symptoms were associated with the duration of treatment and with higher anti-TPO concentrations.

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EP1027

Follow-up of serum selenium concentrations in patients receiving selenium supplementation

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Selenium (Se) supplementation has been adopted as treatment for patients with elevated autoantibodies or in patients with mild Graves' orbitopathy. However, serum Se concentrations or other markers of Se status are usually not determined during treatment. The aim of our study was to measure serum Se concentrations at regular intervals during treatment and to register any side effects.
Twenty patients with mild orbitopathy and twenty patients with active autoimmune thyroiditis participated in the study. The following clinical parameters were determined: TSH, fT4, fT3, TSH receptor antibodies, anti-TPO and thyroglobulin antibody levels. In case of orbitopathy, the status of the orbit was registered at the beginning of the study and during treatment. The patients received 100 or 200 μg organic or inorganic Se daily. Se levels were measured before supplementation was started and at regular intervals during treatment. Altogether 168 serum Se concentrations were determined by hydride generation atomic absorption spectrometry.
In case of autoimmune thyroiditis, autoantibody levels decreased. Generally, thyroglobulin antibody levels decreased faster with concurrent Se supplementation than anti-TPO levels. In patients with orbitopathy, ATA and clinical activity scores improved in the majority of study participants and worsened only in patients whose serum Se levels did not increase. Mean Se concentrations were 83.2 ± 13.4 ng/ml (range: 59.1–92.0 ng/ml) before supplementation started and 136.7 ± 22.0 ng/ml (range: 118.18–220.84 ng/ml) up to two years later ($P < 0.001$). The effect of Se supplementation varied greatly between patients. Se levels surpassed the reference range much faster than previously reported. There were no side effects registered.
These are the first Hungarian data representing the effect of Se supplementation in patients with autoimmune thyroiditis and mild orbitopathy. Se concentrations increased significantly regardless whether organic or inorganic Se was administered. In summary, serum Se levels of patients receiving Se supplementation should be controlled regularly, at least every six months.

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EP1028

Is the high mean platelet volume associated with inflammation in subacute thyroiditis?

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Introduction and aims
Subacute thyroiditis (ST) is a spontaneous remitting inflammatory disease of thyroid gland. Although there is no clear evidence for its specific etiology, multiple factors may responsible for this inflammatory reaction. Mean platelet volume (MPV) is a new important inflammatory marker that indicates disease

activity. Aim of this study is to evaluate MPV value in patients with subacute thyroiditis.
Materials and methods
Thirty-one patients with subacute thyroiditis [mean age 42.55 ± 11.59 years; body mass index (BMI) 26.64 ± 1.33 kg/m^2] and 52 age- and BMI-matched control subjects (mean age 37.34 ± 17.81 years, BMI 25.45 ± 6.76 kg/m^2) were included our study. All blood samples in patients with ST were taken at diagnosis. The MPV was measured in a blood sample collected in Edta. The Beckman Coulter LH 750 (impedance method) analyzer was used for complete blood counts.
Results
At diagnosis, the mean FT3 levels were 4.34 ± 2.86 pg/ml; FT4 levels were 1.61 ± 1.01 pg/dl; TSH levels in ST were 0.31 ± 0.35 μIU/ml (median 0.16; minimum level 0.001-maximum level 1 μIU/Ml) whereas the mean FT3 levels were 4.47 ± 3.53 pg/ml; FT4 levels were 1.32 ± 0.65 pg/dl; TSH levels in control were 1.58 ± 0.99 (median 1.3; minimum 0.4-maximum 4.6) μIU/ml, $P < 0.001$. ESR in ST were higher than control (mean ESR 41.04 ± 36.19 in ST group vs. 13.24 ± 13.26 mm/hour in control, $P < 0.001$). However, CRP and white blood cell count in ST did not find statistically different from control. More importantly, the MPV was significantly higher in ST group than healthy control (8.79 ± 1.23 and 7.62 ± 0.75 fL, respectively; $P < 0.0001$). MPV had positive correlations between CRP ($r = 0.414$; $P = 0.013$) and ESR ($r = 0.74$; $P = 0.001$). There was a negative correlation between MPV and TSH ($r = -0.288$; $P = 0.017$).
Conclusions
According to our knowledge, we demonstrated first time that high MPV value was associated with subacute thyroiditis. MPV may be a new valuable marker of disease activity of ST as much as high ESR value.

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EP1029

Increased levels of bisphenol a in euthyroid autoimmun thyroiditis

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Introduction
Autoimmune thyroiditis (AIT), also called Hashimoto thyroiditis or chronic lymphocytic thyroiditis is characterized by destruction of the thyroid gland involving apoptosis of thyroid epithelial cells. It usually presents as euthyroidism or subclinically hypothyroidism, rarely as overt hypothyroidism. The cause of Hashimoto's thyroiditis is thought to be a combination of genetic susceptibility and environmental factors. Bisphenol A (BPA), an endocrine-disrupting chemical, is the main component of polycarbonate plastics and is one of the highest volume chemicals in production today. The human population is widely and continuously exposed to BPA through food, drinking water, dermal exposures, and inhalation of dusts. Aim of this study is to evaluate circulating levels of BPA in patients with euthyroid AIT.
Material and methods
Circulating levels of BPA were measured in 20 consecutive patients newly diagnosed with euthyroid AIT and 22 euthyroid controls. Patients were considered to have AIT if they were positive for at least one of either antibodies against thyroid peroxidase (AbTPO) and/or antibodies against thyroglobulin (AbTg), in addition to exhibiting morphological changes consistent with AIT, as diagnosed by thyroid ultrasound (hypoechogenicity, heterogeneity). Individuals were classified as euthyroid AIT at diagnosis if they had normal serum TSH (TSH < 4 mIU/mL) and normal free T4 concentrations. The correlation analysis of BPA with TSH, free T4, free T3, AbTg, AbTPO were also investigated.
Results
Circulating levels of BPA a was significantly higher in euthyroid AIT compared with controls ($P < 0.05$). In correlation analysis, bisphenol a was positively correlated with anti TPO ($r = -0.355$, $P < 0.05$).
Conclusion
The present study demonstrated for the first time that circulating bisphenol a levels are increased in euthyroid AIT. This result draws attention to the circulating levels of bisphenol a in euthyroid AIT and and may shed light on further researches at this topic.

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EP1030

Acute suppurative thyroiditis caused by burkholderia cepacia

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Introduction
The thyroid is generally resistant to infections due to its encapsulated location, high iodine concentration, hydrogen peroxide production, and high levels of blood and lymphoid circulation therefore acute suppurative thyroiditis is rarely seen. The most common agents are Staphilococcus and Streptococcus. In this case we present acute suppurative thyroiditis caused by Burkholdeira cepacia, that is a rare infectious agent in adults.
Case
34 year-old-male, admitted to our clinic with sudden on-set left- sided neck swelling with pain and redness. There was no history of chronic disease, recently upper respiratory tract infection or trauma. A painfull nodule was palpated on the left lob of his thyroid gland. There were monocytosis 1.011 × 103 μl (0.00–0.900 × 103), increased sedimentation rate; 52 mm/h (< 20 mm/h) and C- reactive protein (CRP) level; 14.2 mg/dl (0–0.5). Thyroid hormones were in normal limits. Neck ultrasonography revealed 6 × 5 mm high density cystic complex nodule, increased vascularity of left lobe and reactive lymph nodes localized at left jugular area. Based on the clinical and laboratory findings, acute suppurative thyroiditis was decided. Fine needle aspiration from the cystic nodule and blood culture was performed for the microbiological identification. Amoksicilin-clavulonic acid treatment was started. Ciprofloxacin and amikacin sensitive Burkholdeira Cepacia identified on the cystic nodule aspiration at the seventh day of the treatment. Antibiotic treatment switched to the ciprofloxacin. All the symptoms of the disease were regressed, sedimentation and CRP rates normalized at the twentieth day of the ciprofloksasin treatment. There was not any recurrence.
Conclusion
Acute suppurative thyroiditis is a rare infection disease. When the clinician encountered with acute suppurative thyroiditis, abscess aspiration culture and the blood culture for the microbiological identification and antibiogram should be performed. Because rare microorganism would be causative agent of existing acute suppurative thyroiditis.

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EP1031

Immunohistochemical expression of coagulation and fibrinolysis markers in thyroid goiter

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Introduction
Endocrine disorders can influence the hemostatic balance. Various abnormalities of coagulation-fibrinolytic system have been reported in patients with thyroid dysfunction. The aim of the study was to assess the immunohistochemical expression and distribution of coagulation and fibrinolysis markers in follicular cells of thyroid goiter.
Materials and methods
20 patients with thyroid goiter were included in the study: 11 cases with non-toxic nodular goiter (NTNG) and 9 patients with Hashimoto's thyroiditis (HT). Normal glands served as controls. In a standard immunohistochemical procedure, monoclonal antibodies anti- tissue factor (anti-TF), anti-tissue factor pathway inhibitor (anti-TFPI), anti-von Willebrand factor (anti-vWF), anti-thrombomodulin (anti-TM), anti-tissue plasminogen activator (anti-tPA), anti-plasminogen activator inhibitor-1 (anti-PAI-1) and anti-D-dimers (anti-DD) were applied. The percentage of positively stained cells were counted and expressed as a mean value of at least 10 high power fields (400×).
Results
80% of thyroid goiters demonstrated increased immunoreactivity for TM, 56% of cases showed up-regulated staining for vWF, 33% of thyroid tissues showed higher expression of TF, 25% of thyroids revealed enhanced immunopositivity for DD. In only 10% of goiters overexpression of both TFPI and tPA was found. PAI-1 level was unaltered in all of the examined thyroid glands. None of the healthy controls stained positively for these markers.

Conclusions
Abnormalities in the processes of coagulation and fibrinolysis are implicated in the pathogenesis of thyroid diseases, such as Hashimoto's thyroiditis.

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EP1032

Thyroid scintigraphy findings in patients without thyroid tissue in the ultrasonography

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Introduction
Patients that were suspected to have thyroid agenesis on imaging procedures were retrospectively evaluated.
Methods
Totally 4155 patients had scintigraphy imaging between years of 2010–2015 in our university. 4021 (96.77%) patients were adults (>18 years) and 134 patients (3.22%) were in the pediatric population. Among adult population, 3060 (76.1%) were female, and 1095 (27.2%) were male. In the pediatric population, 85 (63.4%) patients were girls and 49 (36.5%) were boys.
Results
Among 4155 patients, 15 (0.36%) of them had no thyroid tissue in the ultrasonography. In the adult population five patients (0.01%) were found to have thyroid agenesis in the ultrasonography whom four were women. Mean ages of the diagnosis was 22 years in the adult population. The oldest diagnosis was 50 years ago and the newest one was four years ago. In the patient with 50 years of history, USG appearence was atrophic thyroid tissue where as in the scintigraphy substernal ectopic thyroid tissue was detected. Three patients had thyroid tissue at the base of the tongue, and one patient had sublingual thyroid tissue in the scintigraphy.
In the pediatric group, 11 patients (8.95%) were diagnosed as thyroid agenesis in the ultrasonography. 3 (33.3%) of them were boys and 8 (66.6%) were girls. Scintigraphic examination showed thyroglossal ectopic tissue in one patient, and in 10 patients, uptake was in the base of the tongue. Four patients (36.6%) were newly diagnosed hypothyroid patients, Seven patients (63.3%) were on LT4 replacement therapy. TSH levels were evaluated in these patients (mean 96.3 mU/l).
Conclusion
Adult patients with hypothyroidism may have agenesis rarely but in the pediatric population it can be seen more frequently so it should be kept in mind especially in the newly diagnosed patients.

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EP1033

Immunohistochemical assessment of catalase in lesions of thyroid gland

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Introduction
Catalase is an enzyme, which functions in the detoxification of hydrogen peroxide, and is one of the most important antioxidant enzymes in humans. It is responsible for protecting the cell from oxidative damage by reactive oxygen species. Catalase promotes growth of cells including T-cells, B-cells, myeloid leukemia cells, melanoma cells, mastocytoma cells, and normal and transformed fibroblast cells. Nevertheless, the role of this enzyme in thyroid pathologies is still not completely known, therefore the aim of the study was to assess the immunohistochemical expression of catalase in lesions of thyroid gland.
Methods
22 patients with thyroid goiter were included in the study: 13 cases with non-toxic nodular goiter (NTNG) and 9 patients with Hashimoto's thyroiditis (HT). Normal glands served as controls. For immunohistochemistry, mouse monoclonal antibodies against catalase were applied. The investigations were performed by the BrightVision method from Immunologic. The sections were counterstained with Mayer's haematoxylin. The number of positively stained cells were counted and expressed as a mean value of at least 10 high power fields (400×).
Results
The expression of catalase in healthy thyroids was weak or focal. All cases of Hashimoto's thyroiditis demonstrated higher expression of catalase in comparison with non-toxic nodular goiter and healthy thyroid gland. Positively stained cells were also detected in infiltrating lymphocytes and macrophages. Only 16% of NTNG demonstrated the immunoreactivity for catalase.
Conclusions
Results may suggest that increased expression of catalase in Hashimoto's thyroiditis is implicated in the pathogenesis of this disorder. Nevertheless, the role of catalase in inflammation of thyroid is still not completely known and further studies in this matter should be continued.

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EP1034

Abnormal thyroid function tests following thyroidectomy

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Introduction
Permanent hypothyroidism is a common side effect of thyroidectomy. Thyroxine binding globulin (TBG) deficiency is characterized with low total thyroid hormones (TH) in the presence of normal free THs and thyroid stimulating hormone (TSH).
Case report
A previously healthy 37-year-old man underwent annual health check-up. Thyroid US revealed a 24×14×19 mm isoechoic solid nodule in the left lobe. TSH was 1.4 (0.27–4.2 μIU/ml). Fine needle aspiration (FNA) revealed Bethesda Category IV (follicular neoplasm or suspicious for follicular neoplasm) and thyroidectomy was recommended. He admitted to endocrinology outpatient clinic (EOC) for preoperative *assessment*. Thyroid antibodies, calcitonin, parathyroid hormone, calcium and phosphorus were normal. Left lobectomy was performed. Surgical pathology revealed a follicular adenoma. General surgery outpatient clinic referred patient to EOC 1.5 months later with low total TH levels (TSH: 2.12, total triiodothyronine (TT3): 0.41 (0.8–2 ng/ml), total thyroxine (TT4): 3.41 (5.1–14.10 μg/dl)). Laboratory tests were repeated: TSH: 1.9, free T4: 1.57 (0.93–1.7 ng/dl), free T3: 2.29 (1.8–4.6 pg/ml) were normal while TT3: 0.35 and TT4: 2.81 were low. Low total THs in the presence of normal TSH and free THs suggested TBG deficiency (TBGD). TBG was 3.54 (14–31 μg/ml). In the absence of secondary disorders (malnutrition, liver or renal disease, drugs) causing low TBG levels were, he was diagnosed as having inherited TBGD (iTBGD). He was informed about iTBGD but he declined any genetic analysis.
Conclusions
TBGD is a nonharmful condition that is either acquired (aTBGD) due to lack of protein supply or synthesis, loss of urinary protein or X linked inherited TBGD (iTBGD). Complications are those stemming from the primary disorders and erroneously administered L-thyroxine treatment. In complete iTBGD males have no detectable TBG while in partial iTBGD, males have some measurable TBG. Evaluation of thyroid function only with total THs may lead to a misdiagnosis of hypothyroidism and unnecessary treatment.

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EP1035

Propylthiouracil induced ANCA-associated vasculitis

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Introduction
Propylthiouracil is a drug used in the treatment of hyperthyroidism and autoimmunity phenomena have been described as a side effect of its use. Despite anti-neutrophil cytoplasmic *antibodies (anca) positivity is frequent in patients treated with propylthiouracil, the occurrence of clinically evident vasculitis is rare.*
Case report
A 65-year-old woman, diagnosed with hyperthyroidism 2 years ago and treated with propylthiouracil (50 + 50 mg) since then. She presented to the emergency department with dyspnoea, pleuritic chest pain and hemoptoic cough in the last 2 days. Physical examination showed a peripheral oxygen saturation of 82% and rales in the lower thirds of both lungs. Laboratorial study revealed hypoxia (po2 44.8 mmhg), falling haemoglobin levels (14.0 to 10.1 g/dl in one month), an elevated c-reactive protein (173.3 mg/dl; reference values [rv]: < 3 mg/dl) and *significant erythrocyturia (*6423.5/ul). The chest x-ray showed bilateral infiltrates on the lower pulmonary lobes. She was admitted to the medicine department with the diagnosis of pulmonary-renal vasculitic disorder. Facing the diagnosis of a probable pulmonary-renal vasculitic disorder, she was hospitalized. The patient performed a thoracic ct scan ("ground-glass pattern that suggested diffuse alveolar haemorrhage") and autoimmune (ancas-mpo > 200 u/ml) and thyroid (tsh 0.24 uui/ml; rv: 0.35–4.94; t4 1 0.7 ng/dl; rv: 0.7–1.48; negative trabs; positive anti-tpo antibodies) laboratory studies. A progressive raise of plasmatic creatinine motivated a kidney biopsy that revealed histopathological features of vasculitis. Propylthiouracil treatment was stopped and the patient received metilprednisolone and cyclophosphamide pulses with respiratory, renal and hematologic improvement. She was discharged from the hospital and now she is on remission under prednisolone and azathioprine and euthyroid without specific therapy.
Conclusions
Propylthiouracil induced anca-associated vasculitis is characterized by the positivity for anca of the mpo subtype and by a low recurrence rate when compared with primary vasculitis. This case report raises awareness about the possible systemic side effects of antithyroid agents.

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EP1036

An inverse relationship between weight and free thyroxine middle gestation

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Evaluation of the thyroid function in pregnant women is of extreme importance for maternal and neonatal health. The reference interval of thyroid function tests in pregnant women differs from that of the general population and among trimesters in the same patient. Trimester-specific thyrotropin (TSH) reference ranges for pregnant women are recommended in order to avoid misclassification of the thyroid dysfunction during pregnancy.
Less data about the free thyroxin (FT4) trimester-specific reference range is available.
In order to test the variability of free thyroxin we performed a prospective pilot study.
41 consecutive pregnant women with abnormal thyroid function tests were selected for this study. There were excluded the patients with known hypothyroidism before pregnancy (3), the patients diagnosed with Basedow disease (5) and the patients in the third trimester of pregnancy because of the low number of cases (4).
We stratified the women in two groups according to TSH values as having normal thyroid function or subclinical hypothyroidism (SCH). Non parametric tests revealed no significant differences for free thyroxine between the two groups when analyzed by trimester of pregnancy or as a whole. We found a negative correlation between free thyroxine and body weight in the 2nd trimester for the SCH.
Different reports about the variability of free thyroxine along the pregnancy should consider the body weight of the patient along with iodine supply and the laboratory methodology.

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EP1037

Cytological evaluation of thyroid nodules by fine-needle aspiration performed by endocrinologists. Our clinical experience in 2014.

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Introducción
Thyroid nodule is a very frequent pathology that affects 4-8% of population. Fine-needle aspiration (FNA) guided by ultrasound (US) is considered the gold standard test in diagnostic evaluation of thyroid nodules. This technique is being assumed more and more frequently by endocrinologists.
Description of Methods
We conducted a retrospective study that included all thyroid US-guided FNA performed in 2014. We considered the following variables: age, nodule size, cytological resul and histogical result after surgery.
Resultados
227 thyroid nodule FNA were performed in 185 patients (85% female, mean age 56.09 ± 14.44 years). Mean nodule size was 25.9 ± 8 mm (*n*:221, lost 6). We obtained the following cytological results: 48.9% benign; 11% Follicular neoplasm; 3.1% suspicious for malignancy; 0.9% malignant, 35.2% unsatisfactory and other 0.9%. We repeated FNA in 48.9% of cases: 41.4% benign; 54.1% unsatisfactory; 0.9% suspicious for malignancy, 0.9% folicular neoplasm and 0.9% other. (*n*:111, lost 2). 41 patients underwent total or partial thyroidectomy: 17% malignant (3 medullary carcinomas, 4 papillary carcinomas)
Conclusion
Thyroid nodule FNA is the technique of choice in evaluation of thyroid nodules and assumption of this technique by endocrinologists is a reality today. The incidence of malignance detected in our series is consistent with the literature, however the number of unsatisfactory results is above the international recommendations.

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EP1038

At least 15 mCi radioactive iodine dose should be considered in Graves' disease with larger goiter: A sonographic volumetric study

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Background
Fixed-dose radioactive iodine therapy (RAI) is one of the standard therapy for Graves' disease (GD). However, optimal RAI dose to achieve hypothyroidism in GD has been controversial.
Methods
The clinical outcome of 124 patients with GD treated with a RAI between Apr. 2004 and Dec. 2014 was analyzed retrospectively. Responder group was defined as patients who were rendered hypothyroid by the RAI. Thyroid volume (TV) was assessed with sonography using the ellipsoid formula.
Results
The median duration of GD was 3 years (0.1–18 y) and the mean TV was 40.7 ± 25.8 g. Seventy five patients (60.5%) had single RAI. Fifty-four patients (43.5%) became hypothyroid after first RAI, and additional 31 patients needed 2 to 4 times of RAI to achieve hypothyroidism. In 54 patients who became hypothyroid after first RAI, the TV was significantly lower, compared with non-responder group (25.1 ± 8.8 vs. 52.8 ± 28.2, $P < 0.001$). When divided into low dose responder

group (<15 mCi, $n=46$) and high dose responder group (≥15 mCi, $n=39$) based on total accumulated RAI doses, there were no differences in age, sex, disease duration and levels of TBII, but TV was significantly lower in patients treated with low dose RAI. The cut-off of thyroid volume for low dose responder group was 32.7 g (sensitivity 80.9% and specificity 76.7%).
Conclusions
Thyroid volume had a significant effect on the outcome of RAI in GD patients. The optimal fixed RAI dose for GD patients with larger goiter (≥33 g) should be at least 15 mCi to simplify the therapy and achieve the best outcome in iodine-replete Korea.

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EP1039

Comparison of thyroid nodule prevalence in two population-based studies in Bulgaria: 2006 and 2012

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The nodular goiter is the most prevalent thyroid disorder. Its prevalence increases with age and reaches over 70%. The aim of the study was to compare the nodule prevalence in two population-based studies, carried in Bulgaria in 2006 and 2012.
Material and methods
Two thousand four hundred and two subjects (1347 female and 1053 male, age range 20–94 years) were included in 2006 and 2022 (1073 female and 949 male, 20–88 years) in 2012. All subjects filled an interview and underwent thyroid ultrasound. Body weight, height and TSH and TPO Ab were measured. Nodules 5 mm or more were registered and their number – single or multiple and the echo structure – solid, cystic or mixed were recorded.
Results
Nodules were found in 23.4% of the subjects, in 30.1% of the females and 15.0% of the males, $P<0.001$ in 2006 and in 24.4%, 32.1% of the females and 15.7% of the males ($P<0.001$) in 2012. No significant difference was found between the two studies. In both studies the nodule prevalence increased with age (females: from 16% in the age group 20–29 to 45% in the over 70, 2006 and from 8% to 52%, 2012; males: from 6% to 29%, 2006 and from 6% to 27%, 2012). In both studies hyperthyroidism was significantly higher in the subjects with nodules, than in those without.
Conclusion
In both studies the thyroid nodule prevalence was similar to the figures cited for other European countries. No differences were observed between the two studies. It might be inferred that the interval between them is too small to demonstrate a change in the population nodule prevalence.

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EP1040

Prevalence of autoimmune thyroid disorders in kin/relatives with those diseases

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Abstract
Aim and objectives
To investigate the prevalence of relationships between kin/relatives with a known thyroid immune disorder related to Hashimoto thyroiditis.
Material and method
1. Thyroid disease diagnosis: a. ATPO > 34 u/ml = Hashimoto thyroiditis (HT); b. ATPO = normal but with high antithyroglobuline (ATG) = thyroiditis with only hyper-ATG (T-ATG); c. hypothyroidism without high ATPO/ATG = idiopathic mixedema (IM).
2. Searching for a relationships between kins (including anamnesis).
Results
There were registered 1401 pt with HT, 129 T-ATG, and 108 Idiopathic myxedema. A specific kin/relationship could be identified in 189 patients. The distribution was tabulated.
1. Mother-Daughter: Pairs: 74, 6, 5; Total: 86.
2. Mother-Son: Pairs: 12, 1, 0; Total = 16;
3. Father-Daughter: Pairs: 8, 0, 0; Total = 8
4. Father-Son: Pairs: 3, 0, 0. Total = 3.
5. Grandmother-Grandson/daughter: Pairs = 1, 0, 0; Total = 1.
6. Uncle/Aunt-Nephew: Pairs: 4, 1, 0; Total = 5.
7. Wife-Husband: Pairs: 4, 0, 1. Total = 5.
8. Sister-Sister: Pairs: 19, 2, 3. Total = 24.
9. Sister-Brother: Pairs: 5, 0, 0. Total = 5
10. Total pairs: 130, 10, 9.
11. Multiple members: 5, 0, 0.
12. Patients: 197, 16, 17. Percent: 11.28, for HT; 12.4, for TATG; 15.74 for Idiopathic Myxedema.
The presence of a relationship between kin could be registered in 11.28% from patients with Hashimoto thyroiditis, in 12.4% from those with only T-ATG and 15.74% from those with idiopathic myxedema.
Conclusion
Therefore, the penetration of a relationship between two kin with Hashimoto thyroiditis and related disorders could be registered in over 13% patients (more exactly, 13.17%).

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EP1041

Drug-induced hepatitis in a patient with Graves' disease

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A 52 year old lady presented with a history of weight loss, tachycardia and tremor. She was diagnosed with primary hyperthyroidism; TFTs were TSH <0.02 mU/l and FT4 >100 pmol/l, LFTs were mildly deranged (ALT 79 u/l, ALP 101 u/l). TSH receptor antibodies were positive, suggestive of Graves' disease.
The patient was started on carbimazole, initially at 10 mg TDS which was titrated down to 5 mg TDS. Repeat LFT showed ALP at 219 u/l and a fluctuating ALT between 58 u/l and 141 u/l over the first 5 months on carbimazole.
Repeat LFT during a routine clinic appointment showed grossly deranged LFTs, with ALT of 1001 u/l and ALP of 306 u/l. Carbimazole was stopped immediately. Full hepatic screen was unrewarding a part from positive smooth muscle autoantibodies. This could suggest a diagnosis of autoimmune hepatitis, which is associated with Graves' disease, but given that ALT was >30× normal, whilst ALP was only 2× normal, this picture is more in keeping with acute hepatitis secondary to carbimazole.
Only one week after stopping carbimazole the patient rapidly became thyrotoxic, with FT4 of 60.7 pmol/l and FT3 of 30.5 pmol/l. She was started on lithium and lugol's iodine in order to normalize TFTs prior to thyroidectomy. LFTs normalized over a period of 4 weeks after stopping carbimazole.
The patient underwent total thyroidectomy; histology showed diffuse hyperplasia. Post-operatively she had right vocal cord paralysis but this has resolved spontaneously. The patient is now on replacement thyroxine.
Conclusion
Hepatotoxicity is rare but serious side-effect of carbimazole. It is important to consider all causes of hepatitis. Where there is concern about the cause of hepatitis, surgery may be preferable when compared to changing to another anti-thyroid drug.

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EP1042

A case of concurrent Riedel's disease and Hashimoto's thyroiditis

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Introduction
Riedel thyroiditis is a rare form of infiltrative and fibrotic disease of the thyroid which may involve neighbouring tissues. The main differential diagnosis of Riedel thyroiditis includes malignant tumors and fibrosing Hashimoto's thyroiditis.
Herein, we report a case of concurrent Riedel's disease and Hashimoto's thyroiditis.

Observation
A 45-year-old woman was diagnosed with goiter and hypothyroidism. She was treated with Levothyroxine. Two months later, the patient presented with a rapidly growing goiter associated with dysphagia for solids and dyspnoea.
Physical examination revealed a hypothyroid state, a large and hard goiter.
Thyroid functions tests showed a TSH of 59.07 μIU/ml and a FT4 of 0.83 ng/dl. The antibody tests were performed, revealing positive thyroperoxidase antibodies of 386.8 IU/ml (NR: $<$35 ui/ml) and thyroglobulin antibodies $>$5000 IU/ml (NR: $<$225 IU/ml).
Cervical ultrasonography revealed an enlarged heterogeneous thyroid gland (right lobe: 66 $\times$ 37.5 $\times$ 32.5 mm, left lobe: 61 $\times$ 42 $\times$ 38 mm) with no evidence of nodular lesions. Ct-scan revealed a hypodense thyroid gland hypertrophy extending to adjacent tissues.
The Levothyroxine dose was increased and the patient was referred for total thyroidectomy.
However, thyroidectomy couldn't be performed due to hard adhesion to neighboring structures. Analysis of surgical biopsy section revealed fragments of fibrous tissue with diffuse inflammatory infiltrate composed of lymphocytes, plasma cells and eosinophils. Fibrosis and inflammation infiltrated muscle and adipose tissues around the thyroid gland. There were no evidences of malignancy.
Considering the clinical course and histopathological findings, the diagnosis of Riedel's goiter with coexistent Hashimoto's thyroiditis was established.
High dose of corticosteroids was successfully used in our patient.
Conclusion
It's difficult to differentiate between Riedel's thyroiditis and fibrosing Hashimoto's thyroiditis. However the coexisting of both diseases has been reported in few cases and seems to be coincidental.

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EP1043

Ophthalmopathy occurrence after two years of thyroidectomy on account of papillary thyroid microcarcinoma

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Introduction
Thyroid ophthalmopathy occurs generally due to Graves' disease. Only a few cases were reported about ophthalmopathy in the years following a thyroidectomy and RAI therapy or metastatic papillary thyroid cancer.
Case
A forty-six-year-old female patient was operated on for the fine needle aspiration biopsy (FNAB) result of a suspicious follicular neoplasia. A pathology examination showed a papillary microcarcinoma and Hashimoto thyroiditis. Her serum thyroglobulin level was $<$ 0.2 ng/ml with the 175 mcg/day l-thyroxin replacement. At 24 months postoperatively, she had noticed prominence of her eyes, especially the left. The patient was given an eye examination which revealed bilateral exophthalmus, the patient had a bilateral eyelid retraction. Measurements by Hertel exophthalmometry were 20 mm in the right eye and 22 mm in the left. Her Clinical Activity Score was 2. Orbital CT scans showed a bilateral enlargement of the inferior, medial and superior rectus at the upper limit of normal and did not exceed 5 mm in thickness. Both of the central parts of the bulbus oculi muscles were located in the anterior of the interzygomatic line (exophthalmus). Her TSH receptor antibody was 9.46 U/l (in the normal range (0-14 U/l)), anti-TPO and anti-Tg antibodies were high as in the preoperative period (304.5/ml and 134.4 U/ml, respectively). Low levels of focal uptake by the two foci of residual thyroid tissue was detected at the thyroid scintigraphy. Levothyroxine dosage was adjusted according to the TSH values which should be near 0.5 mIU/l. The patient's eye symptoms resolved completely approximately 6 months after.
Discussion
It should be kept in mind that, during follow-up of thyroidectomised patients with papillary thyroid cancer, ophthalmopathy may be developed, even if not given radioiodine or negative for usual autoantibodies.

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EP1044

Technique of story-telling in patients undergoing thyroid surgery

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Introduction
In the modern day busy clinical practice the communication between patient and care giver is at minimal level. The patients feel apprehensive when advised about the surgical intervention. In such situation they feel the need of detail information from the care givers.Story telling is a tool which can be used for this problem. We intended to study the efficacy of storytelling technique on patients undergoing Hemithyroidectomy for benign cytology.
Materials & methods
A story of a lady (cartoon version) aged 25 years with a benign thyroid nodule who underwent uneventful Hemithyroidectomy is depicted in this movie including the history, clinical examination, investigations, counselling and the operative procedure and the running time of the animation movie is four minutes. For developing this movie, high end graphic computer work station and various multimedia authoring tools were used. The story was shown to patients with clinically solitary thyroid nodules who were provisional candidates for surgery in the outpatient department.The patients filled in the evaluation of Multimedia animation questionnaire at the time of discharge.
Results
20 patients filled the questionnaire. 19 found the movie useful and their remaining questionnaire was analyzed. Mean age was 35.45 $\pm$ 12.8 years. 15 (75%) were females. All patients were euthyroid. The mean weight was 40.80 $\pm$ 20.79 gms. The final histopathology was colloid in majority. In the questionnaire, the mean score for improved understanding of the disease was 73.9 $\pm$ 14.7 (P = 0.003), better organization of treatment was 78.6 $\pm$ 13.1 (P = 0.000), stimulated interest in the relatives was 70.8 $\pm$ 15.8 and saved unnecessary discussion with the consultant was 55.5 $\pm$ 7.8.
Conclusion
Story telling is a useful tool in health communication. With widespread availability of high speed internet and affordable mobile computing devices such kind of information can be of use to the patients in decision making.

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EP1045

Hypothyroidism: a reversible cause of heart failure

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Introduction
Hypothyroidism is characterized by a decrease in oxygen and substrate utilization by major organ systems of the body. Hence patients with angina have fewer symptoms if they become hypothyroid. Hypothyroidism also results in bradycardia and weakening of myocardial contraction. Cardiac preload is decreased, afterload is increased, and chronotropic and inotropic functions are reduced. The impairment of these measures leads to a reduction in cardiac output.
Case Report
A 69-year-old male presents after a syncope. The patient reported no history of angina, syncope or seizure disorder except recent onset fatigue and dyspnea on exertion. He also complained of recent hair loss, hoarse voice and scrotal swelling. The patient had no thyromegaly but had non-pitting pedal edema. Initial results showed, TSH of 122.1 mcU/ml, free T4 of $<$0.02 ng/dl, total T3 of 22 ng/dl. Thyroglobulin and thyroid microsomal antibodies were positive. His mental status was intact and showed no features of myxedema coma. He was started on a lower dose of levothyroxine (LT4) to prevent an arrhythmia. Patient had a transthoracic ECHO that showed severe left ventricular systolic dysfunction with an ejection fraction (EF) of 25% and global hypokinesis. Left heart catheterization showed triple vessel disease without complete occlusion. However, from the left ventriculogram, the EF improved to 60% after 3 days of LT4. The free T4 increased to 0.2 ng/dl. Eventually the patient had a coronary artery bypass grafting (CABG) where intraoperatively, the EF remained stable at 50%.
Conclusion
Our case describes a patient who was profoundly hypothyroid, yet had no features of myxedema coma and showed dramatic improvement after initiating LT4. The improvement in cardiac contractility prior to the CABG demonstrates the relationship between hypothyroidism and left ventricular dysfunction, and its reversible nature with restoration of thyroid function. Simultaneously, appropriate LT4 dose initiation is important to prevent arrhythmias.

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EP1046

Exophthalmos as the first manifestation of mantle cell lymphoma of the patient with Hashimoto thyroiditis

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Introduction
The diagnosis of thyroid orbitopathy is based on clinical symptoms and typical changes in laboratory tests confirming thyroid disease. In approximately 5% it is Hashimoto's thyroiditis. Typical treatment is primarily steroids administered intravenously. But one disease does not exempts the other, and the drugs can not read. Therefore, we would like to present the history of our patient.
Case report
55 year-old man was admitted to the Endocrinology Ward due to a suspected thyroid orbitopathy, with the intention of steroid pulse therapy. The patient for a few weeks remained swollen eyelids, watery eyes, protrusion of eyeballs.
On physical examination, otherwise no significant deviations from the norm.
They showed normal levels of TSH, FT3 and FT4, and TR AB, and AB TPO exceed the norm of 25.3 (N 0–9 IU/ml), with of other tests drew our attention to a small lymphocytosis (5, G/l).
MRI of the orbits revealed on both sides surrounded eyeballs confluent, well demarcated areas undergoing moderate hypo-intensive strengthening mainly in the area of mine-medial orbital segments. The muscles of the correct size. The eyeballs symmetrical correct size and shape, moved slightly forward. That are likely infiltration of the type of lymphoma, inflammatory changes less likely. The ultrasound said enlarged lymph nodes in the neck bilaterally largest 20×10 mm on the right side, left side 19×8 mm, near the axillary node on the right size 25×14 mm, on the left the size of 26×12 mm.
The patient was taken right axillary node for pathology, which was a mantle cell lymphoma classical type. The patient was referred for further treatment to the Clinic of Hematology.
Comment
If in our patient's treatment was based on clinical features of orbitopathy, then most likely it would lead to a initial clinical improvement because lymphoma respond to treatment with corticosteroids. However, this delay proper diagnosis and treatment, and probably was detrimental to the patient.
Despite some similarities in histology this is the first case known to us coexistence of mantle cell lymphoma and Hashimoto thyroiditis.

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EP1047

Rhabdomyolysis case based on hypothyroidism

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Muscle involvement in hypothyroidism is a rare complication. These patients are often present with decreased muscle mass, cramps and myalgia. With these clinical symptoms increasing muscle enzyme suggests the rhabdomyolysis table. Rhabdomyolysis based on hypothyroidism is not a common condition. In this report, a case which detected rhabdomyolysis based on deep hypothyroidism will be discussed.
Seventy-two years old male patient applied to our clinic with the complaints of increasingly widespread muscle pain, muscle weakness and leg cramps. The patient who had total thyroidectomy based on multinodular goiter did not proceed using levothyroxine after surgery. There was no known drug, alcohol or smoking history. The patient's vital signs during the application; body temperature 37.3 °C, pulse 55/min, blood pressure 130/95 mm Hg, respiratory rate 13/min. On physical examination, cardiac and respiratory were normal, dry skin, decreased turgor tone, bilateral lower ekstremitre trace edama and palpation tenderness in the legs were available. In examined laboratory findings; urea:50 mg/dl (17–43), creatinine:1.8 mg/dl (0.5 to 1.2), calcium:6.6 mg/dl, phosphorus:5.2 mg/dl, uric acid:6.9 mg/dl, AST:94 IU/l (10–50), LDH:796 U/l (240–480), CK total:4370 U/l (<190), troponin I:0.021 ng/ml (0 to 0.15), CK-MB:8 U/l (7–25). TSH $>$ 100 μIU/ml (0.34 to 5.6), free thyroxine <0.15 ng/dl (0.61 to 1.12), free triiodothyronine:1.04 pg/ml. 0.6 mcg/kg of levothyroxine treatment was started considiring that the patient has rhabdomyolysis based on deep hypothyroidism. Creatinine and CK returned completely back to normal range at the end of three weeks levothyroxine treatment. Rhabdomyolysis myoglobin is characterized by muscle cells element escaping into the circulation which include electrolyte and sarcoplasmic proteins. Rhabdomyolysis also known as injuries, crush syndrome, may also present rare with hypothyroidism while it is a situation usually seen after major trauma. Rhabdomyolysis based on deep hypothyroidism, developed in this patient who did not proceed using levothyroxine after total thyroidectomy in this case report.

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EP1048

The relationship between thyroid function and type 1 diabetes Mellitus duration

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Thyroid disease is common among the population, and the prevalence increases with age. In patients with type 1 diabetes mellitus (T1DM) the risk of thyroid dysfunction and thyroid autoimmunity is increased. The aim of this study was to investigate the relationship between thyroid function and T1DM duration. There were evaluated 110 patients (71 women and 39 men) with T1DM between 2013 and 2015 and were appreciated antibodies against thyroid peroxidase (ATPO) (*normal values range* <34 UI/ml) and *thyroid-stimulating hormone* (*TSH*) (*normal values range* 0.17 – 4.05 mIU/l). From 110 patients, 15 (13.6%) patients were excluded because of treated clinical hypothyroidism, the other 95 patients were divided into 3 groups depending on the T1DM duration: 1st group (<5 years); 2nd group (5–10 years); 3rd group (>10 years).
Results
The 1st group included 18 (18.9%) patients with average TSH 1.438 ± 0.79 (0.6 – 2.9 mIU/l) and ATPO 20.2 ± 8.8 (9.8 – 36 UI/ml). The 2nd group was made by 32 (33.7%) patients with TSH 1.2 ± 0.2 (0.4 – 3.4 mIU/l) and ATPO 19.1 ± 4.6 (5–47 UI/ml). In the 3rd group were 45 (47.4%) patients with TSH 2.1 ± 0.3 (0.5–5.9 mIU/l) and ATPO 85.1 ± 34.7 (5 – 600 UI/ml). In this group 10 (22.2%) patients had subclinical hypothyroidism without any clinical signs. Statistically significant correlation was found between TSH level and T1DM duration ($r=0.404$; $P<0.01$).
Conclusions
Thyroid pathology in T1DM is often overlooked due to lack of clinical manifestations, which underscores screening importance. In the study were observed a correlation between TSH level and T1DM duration. So, with the increase T1DM duration the number of patients with autoimmune thyroid pathology is increasing especially subclinical hypothyroidism.

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EP1049

Surgical treatment Graves disease: long term results and their predictions

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The incidence of Graves disease in different regions of Russia ranges from 20 to 50 cases per 100000 population.
Purpose
To improve the results of surgical treatment of patients with Graves disease by identifying the optimum amount of remaining thyroid tissue and prediction of thyroidal status in the long term.
Methods and design
The 138 patients with Graves disease operated over the past 10 years: 131 women (94.9%) and 7 men (5.1%). The operations performed on classic method - subtotal subfascial resection thyroid by O.V.Nikolaev (1951).
Results
Euthyroid status was detected in 68 (49.2%) patients. The signs of subclinical hypothyroidism found at 30 (21.7%) patients. The 25 patients (18.2%) have postoperative hypothyroidism; 15 patients (10.9%) have recurrence of hyperthyroidism. The main cause of relapse of hyperthyroidism was saving on operation the part of thyroid more than 8–19 g.
Conclusion
The study allowed to select prognostic criteria, bearing in mind that it is possible to achieve euthyroid condition.

1. Volume of leaving thyroid tissue for patients older than 40 years must be 6 g, but for the patients younger 40 years – no more 4 g.
2. The duration of conservative antithyroidal therapy should not exceed 1 year. Recurrence of the Graves disease after abolition of antithyroid drugs is the indication for surgical treatment
3. The high level of thyroid antibody (Thyroid Peroxidase Antibody $\geq$ 600 IU/ml and/or Antithyroglobulin Antibody $\geq$ 300 IU/ml) is the main if thyroid tissue is smaller that 4 g.
4. Thyroid tissue with volume less than 2 gramm no able to meet the physiological needs of man in thyroid hormones

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EP1050

Relation between Serum 25-hydroxy-vitamin D Levels and TSH receptor antibody seropositivity

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Objective
Vitamin D is an immune-modulator that may play a role in thyroid related autoimmunity. But the relation between Vitamin D and Graves' disease (GD) is not well defined yet. The aim of this study was to investigate the association of 25-hydroxy-vitamin D (25[OH]D) levels and TSH receptor antibody (TRab) levels in GD.
Design
A total of 429 GD patients were analyzed retrospectively. 122 of 429 patients had vitamin D levels were enrolled in this study. The levels of 25(OH)D and TRAb were examined. Vitamin D deficiency was defined as a 25(OH)D below 20 ng/ml and insufficiency as a 25(OH) D of 20–29 ng/ml. Normal range was accepted as 30 ng/ml and above. TRAb negativity was defined as 0–13 U/l and positivity was defined as 14 U/l and above.
Results
Among 122 patients mean age was 42.9 $\pm$ 14 years. TRAb seropositivy was found in 69.7% (n = 85). TRAb titres' median was 16 U/l (minimum: 0- maximum: 295 U/l). Vitamin D deficiency was detected in 83.6% (102/122) of the patients. Vitamin D insufficiency was found in 11.5% (14/122) of the patients. Normal vitamin D levels were found in 4.9% (6/122) of the patients. Vitamin D deficiency was higher in TRAb-positive GD patients than TRAb-negative patients (respectively 75.5% (77/102) vs 24.5% (25/102) beside according to vitamin D insuffiency there was no difference between TRAb-positive and negative GD patients. There was also found a significant negative correlation between TRAb titres and vitamin D levels.
Conclusion
Low vitamin D status is associated with increased TRAb seropositivity in GD. Further research is necessary to fully elucidate the importance of vitamin D in the case of GD.

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EP1051

Long-term follow-up results of benign nodular goiter in a rural district of east Japan

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Introduction
Surgery for benign nodular goiter (NOD) is currently limited to cancer or cosmetic deformities. Most patients are, in principle, followed up for years or decades. The long-term outcome, however, is not always clear.
Patients and methods
NOD was diagnosed as benign in 1,825 patients (1990–2015). 102 patients (5%) were treated by surgery. 95% returned to home doctors (69%) or continued to visit our clinic (518 patients, 31%). Follow-up examination (median 656 days; longest 22 years) was performed by ultrasonography (US), measurement of serum thyroglobulin (Tg), or, if necessary, fine needle aspiration cytology (FNA).
Results
Cytological diagnosis: Follow-up FNA was performed once (61%), twice (22%), thrice (8%). Most patients (69%) received the second FNA within 3 years. Morphological changes in solitary nodules: 1) VOL of solitary nodules (n = 531) increased over 120% of initial VOL in 32% of patients, whereas it decreased to less than 80% in 32% of patients. 2) Cystic changes were later observed in 10% of solid nodules (n = 89) and formed cysts in 74 patients (7%). Tg levels: Tg levels remained stable during 5 years (n = 100). The level, however, tended to increase after 10 years of follow-up period (n = 35). Clinical outcome: 4 patients (0.7%) underwent surgery within 6 years due to cosmetic reasons (2 cases) or rapid enlargement (2 cases). Papillary carcinoma in a cyst was diagnosed in one patient after 3 times of FNA. Anaplastic carcinoma developed immediately after surgery in one patient (5 years of follow-up).
Conclusions
Benign NOD was safe for life. A third of nodules shrank and a tenth formed cysts. Late surgery, although rare, may have a risk to induce an anaplastic transformation.

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EP1052

Long-term universal salt iodization has resulted now in more than adequate iodine intake and consequent chronic autoimmune thyroiditis in school-age children living in some localities from Mures and Harghita Counties, Romania

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Introduction
In Romania universal salt iodization was implemented into practice since 2002, and iodine content of salt was gradually increased afterward. The efficiency and sustainability of this nationwide program were evaluated among school children from endemic regions of Mures and Harghita Counties. During these studies thyroid ultrasound characteristic for chronic autoimmune thyroiditis was observed in a considerable number of cases.
Objective
To estimate the iodine status in schoolchildren living in some localities of the two counties, and to detect cases with chronic autoimmune thyroiditis.
Material and methods
In 374 schoolchildren with age between 6 to 14 years physical exam, anthropometric evaluation, thyroid ultrasound, morning urinary iodine concentration (UIC), and in case of suggestive ultrasound appearance for thyroid autoimmunity the level of serum thyroid stimulating hormone (TSH), free-thyroxine (fT4) and anti-thyroid peroxidase antibodies (TPO-Ab) were assessed.
Results
Mean and median UIC were 342 $\pm$ 197 μg/l and 298 μg/l, respectively, in Mures County during 2013–2014, as well as 248 $\pm$ 127 μg/l and 215 μg/l in Harghita County during 2014–2015. Moreover 41.4% of children from Mures County and 38.4% from Harghita County had high UIC. The frequency of goiter was 4.7% in the whole cohort. We observed hypoechoic and/or inhomogeneous thyroid on ultrasound in 17.7%, from which in 9 children chronic autoimmune thyroiditis, and subsequent subclinical or overt hypothyroidism was demonstrated.
Conclusion
The universal salt iodization program has eliminated iodine deficiency in the investigated endemic regions from Mures and Harghita Counties, but it seems that the iodine intake is more than adequate, even excessive by now. Harmful consequences, such as chronic autoimmune thyroiditis might appear, as was seen in our cohort. Consequent follow-up is needed to clarify the clinical course and importance of cases with hypoechoic, inhomogeneous ultrasound picture of thyroid, without TPO-Ab-positivity in schoolchildren with normal/high iodine intake, living in former iodine-deficient regions.

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EP1053

Can routine steroid cover during radioiodine therapy of patients with Graves' disease (GD) prevent the onset of de novo Graves' orbitopathy (GO)?

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Introduction
Radioiodine therapy is considered as a risk factor for the development of Graves' orbitopathy (GO) de novo or worsening of pre-existing orbitopathy. This risk is estimated in the available literature as up to 15–20%. Steroid cover is considered to eliminated this risk.
Objective
The aim of our study was to established the relationship between the occurrence of GO and treatment with radioiodine. And the analysis of the time of appearance (onset) of OG after radioiodine treatment.
Material and methods
Between the years 2010-2015 in one centre, there were 152 patients treated with moderate or severe GO. Either the coexistence of radioiodine therapy with the onset of GO was analyzed, or the time (in months) of the onset of GO after I-131 therapy. The radioiodine therapy in all the patients (with or without prior GO) was carried out under steroid cover with a fixed dose of 30 mg prednisone for a month, with gradual weekly reduction's of 5 mg every week for 10 weeks after treatment with I-131.
Results
Fifty-two patients (representing 34%) with moderate or severe GO were previously treated with radioiodine. De novo GO occurred in 49 patients, and 3 patients experienced a worsening of pre-existing OG. The mean time from administration of 131 to onset of GO was 45.5 months (min 2 max 336 months), and a median of 16.5 months.
Conclusions
1. The routine use of steroid cover does not prevent the development of GO.
2. This risk should be considered when planning treatment with radioiodine for patients with Graves' disease and the patient should be informed about this risk.
3. OG can occur even several years after treatment with I-131.

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EP1054

Prevalence of anti-thyroid antibodies (TAb) in relationship with high TSH levels at different ages

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Some authors observed lower thyroid antibodies titers (AbT) in children than in the adult population. The aim of this work was to consider the prevalence of positive results in AbT and elevated TSH levels. We have considered AbT and TSH measurements in a large population. We divided samples in 7 age groups 0–18, 18–20, 20–40, 40–50, 50–60, 60–70 and >70 years old. Cut-off positivity for AbTg and AbTPO was 50 and for TSH was 10 mUI/ml.
The concordance of altered AbT and TSH was calculated and expressed as prevalence in the population. For both the tested antibodies and elevated TSH (AbTg and AbTPO) a prevalence remarkably lower (0.4%) was observed in the pediatric population (0–18 years old) compared to all the other age groups.
A linear increasing prevalence trend could be seen from pediatric population to the older age group, altered TSH and positive AbTg reached prevalence of 1,0% in the adulthood (40–50 years old) and a peak of 1.5% in the elderly (>70 years old).
Autoimmunity is correlated to different players, in particular in two orders of factors belonged to humoral immunity on one hand and cellular-mediated immunity on the other, strictly related. The first one is expressed as antibodies production, the second is mainly related to immune-competent cells. The damage is perhaps correlated to the second process rather than to the antibodies production, often epiphenomena of autoimmunity. Finally the elevation of TSH represents the actual damage consequent to thyroid autoimmunity.
Our results demonstrated that in the pediatric population there is a lower AbT positivity in conjunction with altered TSH. Probably because cell-mediated immunity more than humoral immunity plays the more relevant role and humoral autoimmunity remain ad epiphenomenon.
It could be assumed that in the natural history of thyroid autoimmunity the cell-mediated anticipates the expression of humoral immunity.

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EP1055

Thyroid dysfunction and insulin resistance

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Background Insulin resistance (IR) is a state in which a given concentration of insulin produces biological effect less than expected and IR actually make up a broad clinical spectrum, including obesity, glucose intolerance, DM, and the metabolic syndrome that are associated with various endocrine, metabolic, & genetic conditions. There is an association of IR with thyroid abnormalities. Evidence for a relationship between T4 and T3 and glucose metabolism appeared over 100 years ago when the influence of hyperthyroidism in the deterioration of glucose metabolism was first noticed. More, hypothyroidism has been linked to decreased IR. Thyroid hormones exert both insulin agonistic and antagonistic actions in different organs. However, this occurs in a fine balance necessary for normal glucose metabolism. Deficit or excess of thyroid hormones can break this equilibrium leading to alterations of carbohydrate metabolism. The aim of this study was to determine the association between thyroid function and IR. Methodology this study included 90 non diabetic patients recruited from Fayoum university hospital 30 patients had hypothyroidism, 30 had hyperthyroidism & 30 were euthyroid. HOMA IR were calculated. Our results revealed, 50% of hypothyroid patients, 36% of hyperthyroid patients & only 16.5% of the euthyroid patients had IR ($P=0.024$). The mean body weight of the hyperthyroid group was (73.3 ± 8.7) was significantly lower than that of the euthyroid group (84.8 ± 9.2) and the hypothyroid group (86.7 ± 11.3) ($P<0.001$). The mean BMI of the Hypothyroid patients was higher (32.1 ± 4.4) than the euthyroid group (30.1 ± 3.9) & the hyperthyroid group (26.0 ± 3.3) ($P<0.0001$). Hypothyroid patients were found to have a mean waist circumference that is greater (93.2 ± 8.9) than the euthyroid (88.00 ± 8.3) or hyperthyroid (81.7 ± 5.1) group ($P<0.0001$). Conclusion insulin resistance is common in patients with abnormal thyroid function compared to the euthyoid subjects.

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EP1056

ThyPROgr: translation and validation in Greek of the thyroid-specific quality of life questionnaire ThyPRO

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Introduction
Assessing the quality of life of patients with thyroid disease does represent a challenge. ThypRO questionnaire has been developed recently and comprises a reliable and valid scale structure of a patient-reported outcome measuring thyroid-specific quality of life.
Material and methods
The standard methodology for translation of patient-reported outcomes was followed. Two independent translators, Greek native speakers, fluent in english, were asked to translate THyPRO questionnaire from English to Greek, in order to form a consensus version of the questionnaire, after comparing the two versions. A third translator was asked to back-translate this consensus version to English. An in-country consultant and the developer of ThyPRO questionnaire then reviewed the backwards translation and additional revisions were made. After formation, ThyPROgr was tested among five patients with thyroid disorders with cognitive interview techniques and additional changes in wording were made, when necessary.
Results
ThyPRO was translated and validated in Greek according to standard methodology for translation of patient-reported outcomes.
Conclusion
ThyPROgr provides the possibility to measure patient-reported outcomes regarding thyroid-specific quality of life in the Greek population.

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EP1057

Antithyroid arthritis syndrome

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The most frequent side effects of antithyroid drugs are skin reactions (6%), gastrointestinal effects (5%) and arthralgia (5%). Other complications such as antithyroid arthritis syndrome (1%), agranulocytosis (0.5%) and hepatitis (0.2%) occur rarely.
We describe the case of a 20-year-old woman with Graves' disease. Two weeks after the beginning of carbimazole therapy, she developed an urticarial reaction that led to discontinuation of treatment. Nevertheless, diffuse aching limbs appeared abruptly later on. Due to the lack of clinical improvement, our patient was admitted to the hospital. She had skin reaction with itching, skin rash, dermatographic urticaria, and arthralgia involving her left knee and right shoulder. Treatment with antihistamin drugs and analgesics has been started but arthralgia progressed to migratory oligoarthritis and body temperature increased to 38 °C. Blood tests only showed inflammatory syndrome. Creatine kinase level, joint X rays, left knee joint viral serologies, ANCA antibodies, rheumatoid factor, anti-nuclear antibodies, anti CCP antibodies and anti SSA/RO antibodies were normal. The patient was treated with anti-histamin and non-steroidal anti-inflammatory drugs as well as corticosteroids and clinical improvement occurred a few weeks later with no recurrence of skin rash or arthralgia. Hyperthyroidism was treated with 131 iodine.
Polyarthritis is a rare major side effect of antithyroid drugs. It is important to distinguish anti thyroid arthritis syndrome from minor arthralgia. Contrary to minor arthralgia, anti thyroid arthritis syndrome requires treatment discontinuation, due to cross reactions between the different medications. The majority of polyarthritis cases due to antithyroid treatment described in the literature appear in an autoimmune context. Here we described a rare case of antithyroid arthritis syndrome without evidence of autoimmunity.

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EP1058

Relapse subacute thyroiditis: atypical symptoms

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Introduction
Subacute thyroiditis (ST) is a self limited condition; relapse is rarely seen. Anterior cervical complains and inflammatory syndrome is highly suggestive.
Aim
We report a series of female cases associating arelapse of ST which was confirmed after the admission for atypical distant symptoms as diffuse headache or ear pain.
Material and Methods
The endocrine profile is presented.
Results
A 48-year patient was diagnosed with ST one year ago and treated with daily prednisone for 3 months. On admission, she complains of asthenia, palpitations, but mostly of persistent headache (not correlated with arterial hypertension). Thyroid exam revealed a mild pain. Inflammatory tests showed: erythrocyte sedimentation rate (ESR) of 63 mm/1-h, fibrinogen of 659.932 mg/dl (N:200–500), C reactive protein (CRP) of 3.5 mg/dl (N:0-1 mg/dl). Thyroid ultrasound showed: intense inhomogeneous aspects, a few nodules of <1 cm. TSH was suppressed (of 0.016 μUI/ml, N:0.5–4.5 μUI/ml), high freeT4 (of 47.4 pmol/l, N:10.3–24.4 pmol/l), and negative autoimmunity: TPO (anti-thyreoperoxidase antibodies) of 10 UI/ml (N:0–35 UI/ml), TRAB (TSH-Receptor antibodies) of 0.3 UI/ml (N:$<$1UI/ml). ^{131}I radioiodine uptake was low: of 2% (at 2-h; N:12$\pm$5%), respective of 3% (at 24-h, N:35$\pm$5%). Oral cortico-therapy (daily prednisone up to 20 mg/day) was further recommended for 8 more weeks (when ESR decreased to 4mm/1-h, and TSH normalized to 2.27 μUI/ml).
A 37-year subject has an episode of ST 6 months ago and she was treated with non-steroidal anti-inflammatory drugs. She was admitted for persistent intense bilateral ear pain, weight loss (5 kilos/last month), and mild anterior cervical sensibility only at palpation. Intense inhomogeneous pattern at ultrasound was correlated with inhibited ^{131}I radioiodine uptake: of 0.8% (2-h), respective of 0.2% (24-h). ESR of 109.6 mm/1-h, and CRP of 25 mg/dl, TSH$<$0.03 μUI/ml were consistent for relapse of ST. After 2 months of prednisone ESR became 5.9 mm/1-h, and TSH$=$1.7 μUI/ml.
Conclusion
Headache or otalgia represents atypical symptoms as clue for a relapse ST.

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EP1059

Hoffmann syndrome: a case report

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Background
Hoffmann syndrome is a rare form of hypothyroid myopathy in adults characterized by presence of muscle weakness, stiffness and pseudo-hypertrophy. Here, we report a case of Hoffman syndrome aggravated by statin therapy.
Case report
We describe the case of a 60 year old woman with primary hypothyroidism who presented with fatigue, cold intolerance, constipation, exertional breathlessness, progressive proximal muscle weakness and swelling of the legs for 3 months. She had a history of coronary heart disease treated by statin therapy. Examination revealed pseudo-hypertrophy of calf muscles with marked symmetrical proximal upper and lower limb weakness. The electrocardigram revealed an atrial fibrillation.
Her TSH and Creatine phosphokinase (CPK) levels were significantly elevated. Following institution of replacement therapy with thyroxine, the patient showed marked clinical and biochemical improvements after six months, but insignificant decrease in muscle mass.
Conclusion
Hoffman syndrome is a very rare form of hypothyroid myopathy seen in adults with longstanding untreated hypothyroidism. seen in adults with long standing untreated hypothyroidism.
The diagnosis should be suspected when a patient with calf muscle hypertrophy is also treated by statin therapy.

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EP1060

Thyrolipoma: a rare entity of the thyroid gland

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Introduction
Thyrolipoma (focal adenolipoma of thyroid gland) and thyrolipomatosis (diffuse lipomatosis in the gland) are rarely encountered pathologies in daily practice. We reported a case of small thyrolipoma incidentally diagnosed in a multinodular goiter patient.
Case report
A 56 year-old man was admitted to our out-patient clinics with the complaint of a lump in his cervical region. His thyroid function tests were normal. In physical examination, a mobile soft nodule of about 4 cm in the left lobe was realized. In thyroid ultrasonography, multiple nodules with a maximum dimension of 45$\times$30 mm were reported. No pathological lymph nodes were detected. In fine needle aspiration biopsy of the biggest nodule, benign thyrocytes with the presumption of cystic colloidal nodule were reported. Because of the hugeness of the nodule and multiple nodular nature, total thyroidectomy was performed. In thyroidectomy pathology, bilateral multinodular hyperplasia and a thyrolipoma (coexistence of mature adipocytes and thyroid follicular cells in a nodule) in 9$\times$6 mm right lobe nodule were detected. No adipose tissue infiltration other than this lesion was detected in the whole thyroid gland. The patient recovered well after surgery and levothyroxine replacement therapy was initiated.
Conclusions
Thyrolipomas are rare, benign, biologically inactive tumoral lesions of the thyroid gland. Because of their relatively outer localization in the thyroid gland and its

fatty nature mimicking parathyroid glands, they might be confused with parathyroid glands intraoperatively.

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EP1061

A retrospective analysis of the relationship between obesity and thyroid nodule size

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Objective
The prevalence of overweight and obesity has been increasing for several decades. Few studies have recently showed functional and morphological changes of the thyroid gland in relation to obesity. The aim of this study was to correlate thyroid nodule size with body mass index (BMI), waist-hip ratio (WHR) and thyroid stimulating hormone (TSH) levels.
Methods
A total of 119 patients diagnosed with euthyroidic nodular goiter were included in this retrospective study. The clinical presentations, anthropometric measurements, thyroid function tests and ultrasonographic characteristics of patients were analyzed.
Results
The majority of the patients were female (79.8%) with a mean age of 56.3 ± 15.4 years at the time of diagnosis. The patients were divided into two groups according to a cut-off BMI value of 25 kg/m^2. No statistically significant difference was found between the groups in respect of gender, place of birth, place of residence, smoking and family history. Thyroid US patterns were similar between groups. Thyroid nodule size did not correlate with serum TSH, BMI and WHR in both of groups.
Conclusion
Our data showed that thyroid nodule size was not associated with weight, height, BMI and WHR. Further studies are needed to confirm and to understand our observation.

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EP1062

A nonspecific complaint such as diarrhea in elderly with hyperthyroidism: evaluation with a case

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Introduction
Hyperthyroidism in the elderly can present with subtle nonspecific complaints. Patients with long-standing goiter can develop autonomous nodules resulting in toxic nodular goiter.
Case report
An 86 year old women was referred from gastroenterologist for thyroid disease because of low TSH. She had diarrhea with five to eight bowel movements a day for six months. She denied palpitations, heat intolerance or muscle weakness. She had been noted to have goiter at about age 45 years. Some times, she was treated with propyiltiouracil. There was a family history in her coisen. And also, she had hypertensive and statin treatments such as valsartan and simvastatin, respectively. After she had suffered from diarrhea, drugs related hypertension and hyperlipidemia were stopped. However, no change of characteristics of diarrhea were found. Physical examination revealed markedly enlarged to at least to times the normal size thyroid gland such as multinodular. The heart showed regular rhythm. Pulse was 76 and blood pressure was 130/60 mmHg. There were no thyroid eye sign. Laboratory data that accomanied the patient included TSH of less than 0.01 mikroIU/ml (0.35–5.5), FT4 of 2.1 ng/dl (0.89–1.76), FT3 of 5.9 pg/ml (2.3–4.2). Thyroid nuclear scan showed irregular uptake with multiple hot nodules bilaterally. Ultrasound of thyroid showed a left sided hypoechoic nodules measuring 2×3 cm and 1.1×1 cm with minimal peripheral vascularity. And also, 1×1.5 cm solid and 1.3×2 cm cystic nodules were shown at the right lobe.
The diagnosis was toxic multinoduler goiter with subclinical hyperthyroidism. However, she was clinically hyperthyroidism and was treated with RAI. After 1 moths, she was euthyroide and had no diarrhea and any complaint.

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EP1063

Autoimmune thyroid disease among type 2 diabetic Egyptian female patients

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Background
High prevalence of thyroid disorders is more common in T1 compared to T2 Diabetes Mellitus due to the associated autoimmunity, with hypothyroidism being the most common disorder.
Objectives
The aim of this study is to assess the prevalence of autoimmune thyroid dysfunction among T2 diabetic Egyptian females and to find the correlation between the metabolic syndrome components and autoimmune thyroid dysfunction.
Methods
The study included 62 T2 diabetic Egyptian female subjects and 27 sex and aged matched controls. All patients in the study were subjected to anthropometric measures, HbA1c, lipid profile, serum uric acid, TSH, FT3, FT4, Anti TPO, Anti TG and thyroid ultrasound.
Results
Hypothyroidism was found in 45.2% of patients (5.49 ± 3.37 μIU/ml) vs 11.1% of controls (1.79 ± 1.21 μIU/ml) ($P < 0.001$). Anti TPO was found in 75.8% (347.15 ± 244.87 IU/ml) of patients vs 7.4% (32.89 ± 33.26 IU/ml) of control ($P < 0.001$). Anti TG was found in 61.3% (508.03 ± 369.16 IU/ml) of patients versus 0% (51.26 ± 35.53 IU/ml) of control ($P < 0.001$). A significant positive correlation was found between TSH and antithyroid antibodies (ATG, ATPO) (P: 0.002, 0.043 respectively) and between TSH and thyroid gland volume (P: 0.002) in diabetic patients. No correlation was found between all components of metabolic syndrome and thyroid antibodies in diabetic patients.
Conclusion
Autoimmune thyroid disease is more common in Egyptian women with T2 diabetes than non diabetic women and therefore raising a role of autoimmunity in the pathogenesis of T2DM.
Keywords: autoimmune thyroid disease, TSH, Anti TPO, Anti TG, T2 Diabetes, Metabolic syndrome

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EP1064

Autoimmunity as a cause of goiter, obesity and miscarriage in north of Iran, an iodine sufficient area

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Introduction
The thyroid gland plays an important role in metabolism of human body. Abnormal growth of this gland is called Goiter. Iodine deficiency was thought to be the main cause of goiter. However, despite years of salt iodization, goiter continues to be a major public health, worldwide. As the thyroid gland is the most common organ affected by autoimmune diseases, it is suggested that autoimmunity can disturb thyroid function and develop to goiter. This study tries to investigate the relationship between goiter and Anti-TPO as a marker of autoimmunity.
Method
In this cross-sectional study 150 goiter patients who were referred to endocrinology clinic of Gorgan, Iran were observed. Thyroid function tests (T3, T4, and TSH) and Anti TPO were investigated in all patients. BMI was also calculated by measurement of height and weight.
Results
In general, 132 women and 18 men were studied. There were 50 simple goiters, 50 hypothyroid and 50 hyperthyroid patients. Overall, 110 patients had positive and 40 Patients had Negative Anti-TPO. Anti-TPO positive patients were significantly higher in Hypothyroid and Hyperthyroid groups in comparison with simple goiter patients (P Value < 0.05), while there was no significant difference between Hypothyroid and Hyperthyroid groups. The average of BMI in Anti-TPO positive patients was significantly higher. Women with positive Anti-TPO had also a higher rate of miscarriage.

Conclusion
In iodine sufficient areas, autoimmunity can affect thyroid function and can be a major cause of goiter. Autoimmunity can also be an important cause of obesity and miscarriage.

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EP1065

Large thyroid cysts

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Introduction
Thyroid fluid-filled cavities are mostly resulted from degenerating thyroid adenomas but blood vessel anomalies are also described. Despite the typical benign behavior the local anatomical effects may require fine needle aspiration or directly surgery.
Materials and methods
This is series of cases presenting intermittent breathing problems leading to the diagnosis of thyroid cysts. Thyroid evaluation included ultrasound, computed tomography (CT), TSH assay (Thyroid Stimulating Hormone), TPO antibodies (anti-thyreoperoxidase), circulating calcitonin.
Results
A 28-year female was evaluated for irregular menses, weight gain, and occasional dyspnea. The personal medical history is irrelevant. The investigations confirmed polycystic ovaries syndrome but also a hemorrhagic thyroid cyst of 4.3 by 2.9 by 2.88 cm (with several hyper-echoic areas insight, and a left deviation of the trachea) was detected by ultrasound (a right thyroid lobe of 3.15 by 3.3 by 5.35 cm, left lobe of 1.92 by 1.53 by 4.82 cm) with homogenous structure. Thyroid profile was normal: TSH = 0.78 μUI/ml (N:0.5–4.5 μUI/ml), TPO = 10 UI/ml (N:0–35 UI/ml), FreeT4 = 14.3 pmol/l (N:10.3–24.4 pmol/l), calcitonin = 3.38 pg/ml (N:5.17–9.82 pg/ml). Total thyroidectomy is recommended.
A 47-year female, known with Raynaud's syndrome and euthyroid Hasmimoto's thyroiditis presents from the last two weeks mild breathing troubles. 15 years ago she has an episode of nephritic syndrome and corticotherapy was offered for a few months. On admission, thyroid profiles reveled: TSH = 1.19 μUI/ml, TPO = 143 UI/ml, calcitonin = 1 pg/ml with a hypo-echoic ultrasound pattern and a large cyst of 3 by 2.32 by 2.93 cm with negative 131 iodine uptake at scintigram. CT pointed a well shaped, encapsulated cyst emerging to the anterior superior mediastinum of 17–33 Hounsfield Units. The mass removal was done and benign features were found.
Conclusion
Regarding the first case, the polycystic ovaries syndrome is most probably incidental with the thyroid cystic lesion. Whether autoimmune background and previous prednisone administration may contribute to a thyroid cyst formation is difficult to establish.

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EP1066

Hypertrophic Hashimoto's thyroiditis mimicking thyroid lymphoma

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Introduction
Hashimoto's thyroiditis (HT) is a well known risk factor for thyroid lymphoma. A rapidly enlarging goiter accompanied by lymph nodes pressure on surrounding structures usually suggest the development of thyroid lymphoma.
Case report
An 85 years old hypertensive women presented for a massive goiter extending from the lower jaw to clavicle which increased in size for the last 5 months. She also complained of dysphagia, hoarseness and shortness of breath. Two previous computed tomographies (CT) showed a huge diffuse goiter progressively narrowing the cervical trachea and cervical and mediastinal grossly enlarged lymph nodes. A suspicious cervical lymph node was removed and the pathology report suggested a small B-cell non-Hodgkin lymphoma. However, the immunohistochemistry was in favour of a nonspecific lymphadenitis. In our clinic the cervical CT confirmed the massive diffuse goiter, at least 32 by 53 by 89 mm per lobe. The goiter was intensely hypoechoic on ultrasound suggesting HT or thyroid lymphoma. Thyroperoxidase and thyroglobulin antibodies were strongly positive (over 1000 UI/ml and 3000 UI/ml respectively) but the thyroid function was almost normal (thyroid stimulating hormone was 4.9 mU/l). Serum calcitonin was 2.2 pg/ml. An open thyroid biopsy was performed and the pathology indicated HT. No treatment was started and after 2 months the goiter was still increasing in size but with widening of the trachea and relieve of symptoms. The autoimmunity was similar and the thyroid function continued to be normal.
Conclusions
Hypertrophic HT can clinically and imagistically mimic thyroid lymphoma. An open biopsy of the thyroid may be required in these cases.

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EP1067

The level of awareness on thyroid disorders

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Objective
To evaluate the level of awareness among patients with thyroid disorders presenting to our hospital and determine patient profiles.
Design
The present study was conducted using a survey technique on patients aged between 18 and 75 years, who were admitted to our hospital for follow-up between December 1, 2014 and December 31, 2014. The pregnant women and those with a thyroid malignancy and patients who did not consent for the study were excluded. Demographic data such as age, gender, educational level, disease duration, control frequency as well as drug usage pattern, dose, duration and whether or not the patient received fixed dose drug regimen and food/drugs that are not to be taken with the drug were recorded. Type of salt used by the patients was also recorded.
Results
An interview was conducted with a total of 107 patients (4 males [3.7%] and 103 females [96.3%]) with a mean age of 46 years. Of these patients, 85 (79.4%) attended follow-up visits for more than a one-year period and most patients ($n = 56$) were seen at least three times in the last one year (52.4%). Of these patients, 69 (64.5%) had hypothyroidism, 11 (10.3%) had hyperthyroidism, and the remaining 27 patients (25.2%) had euthyroid nodular goitre. It was found that 78 patients (72.9%) were inaccurately or incompletely informed about their disease. Of the patients, 54 (50.4%) were aware that they needed to use iodized salt and 41 patients (38.4%) were not aware of how to use the salt. When the patients in the study were asked whether they were aware of food and drugs interacting with levothyroxine, 55 patients (86%) were not aware of these food and drugs. Approximately 30% of patients used iron supplements and proton pump inhibitors together with levothyroxine.
Conclusions
The patients with thyroid disorders had a low level of awareness and low level of knowledge about their disease, follow-up data and their treatments. The physicians must make an endeavor to increase the level of awareness among the patients.
Keywords: thyroid disease, awareness, iodine deficiency, drug interaction

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EP1068

Glomerular filtration rate in euthyroid Hashimoto's patients

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Thyroid hormones influence renal development, kidney structure, renal hemodynamics, glomerular filtration rate, the function of many transport systems along the nephron and sodium and water homeostasis. Patients with hypothryoidism can have clinically important reductions in glomerular filtration rate (GFR). 41 patients (mean age 31.5±11 years) newly diagnosed as Hashimoto thyroiditis with presence of high thyroid autoantibodies with gland heterogenity in ultrasound and age-matched 30 healthy subjects attending to Erzurum Research and Training Hospital Endocrine outpatient clinic were included to the study. GFR of the patients and control groups were calculated using 4 variable MDRD Formula. GFR > 125 ml/dk considered as hyperfiltration. Pearson correlation test was made to determine the correlation between FT3, FT4, TSH, anti TPO, anti TG and GFR. There was no significant correlation between FT3, FT4 and GFR. ($r=0.12$, $P=0.33$). There was positive correlation between anti TPO ($r=0.32$, $P=0.02$), anti TG ($r=0.29$, $P=0.03$) and GFR. GFR decreases with age and BMI. In our study GFR was found decreased independent from age, gender and BMI. Although our study is one of the first studies to examine the association between GFR and thyroid autoimmunity was insufficient in explaining the mechanism.

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EP1069

The efficacy of Radioiodine Therapy in Patients with Graves' Disease

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Introduction
Radioiodine (RAI) has been used for the treatment of Graves' hyperthyroidism since 1940s. It is relatively safe and considered as one of the definitive therapies. Achievement of hypothyroidism or euthyroidism is defined as a successful therapy.
Methods
The study was conducted in 366 patients (80.60% of women) with Graves' disease (GD), aged 46.76±13.52 years. We analyzed retrospectively hormonal and imaging findings (scintigraphy, ultrasonography), including isotopic results in subjects treated at Department of Nuclear Medicine and Endocrinology Department during the eight-year period. The efficacy of RAI therapy has been assessed based on free thyroid hormones levels, measured 12 months after radioiodine administration.
Results
Mean concentrations of thyroid hormones before therapy were: FT4-38.40±22.17 (12.0–22.0 pmol/l) and FT3-21.9±17.11 (3.0–7.0 pmol/l). The thyroid mass was estimated to be 69.67±38.87 g. Mean RAI 24-h uptake was 63.93±16.15% and therapeutic activity of RAI, calculated using Marinelli's formula, was 544.28±176.35 MBq. The used thyroid-absorbed doses of RAI (Gy) were: ≤120, >120 and ≤150, >150 (49.18% vs 46.99% vs 3.83% of subjects with GD, respectively). After RAI therapy, hypothyroidism was found in 39.34% GD participants (39.34% of F; 39.44% of M), euthyreosis - in 24.32% (25.42% of F; 19.72% of M) and hyperthyroidism – in 36.34% (35.26% of F; 40.84% of M). The efficacy of RAI therapy was achieved in 63.66% of patients (F–64.75%; M-59.15%). An effective cure of hyperthyroidism was significantly correlated with lower: thyroid mass (59.35±33.26g vs 87.75±41.43g; $P=0.000$), RAI 24-h uptake (62.64±16.54% vs 66.20±15.21%; $P=0.042$) and, surprisingly, administered dose (519.25±180.16MBq vs 588.12±175.63MBq; $P=0.000$). No significant associations between successful therapy and patients' age, levels of free thyroid hormones before therapy and thyroid absorbed dose were found.
Conclusions
RAI therapy was effective in 63.66% of patients with GD. Females responded better to treatment than males. The cure correlated with thyroid mass, RAI 24-h uptake and dose of radioiodine.

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EP1070

The course of chronic autoimmune thyroiditis in pregnant women during iodine and selenium therapy

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Introduction
In iodine deficient regions maternal iodine supply is indispensable for the normal development of the fetus, but it might aggravate autoimmune thyroid diseases in the mother during pregnancy and postpartum. Selenium might be beneficent in these thyroid diseases by defending against the harmful effect of iodine on maternal thyroiditis.
Objective
To study the course of Hashimoto's thyroiditis in pregnant women, under combined therapy with l-thyroxin, selenium and iodine.
Material and method
In 13 pregnant women with chronic autoimmune thyroiditis we measured TSH, free-T4, anti-thyroid peroxidase-antibody (TPO-Ab), anti-thyroglobulin-antibody (Tg-Ab), serum selenium and urinary iodine concentration in the I-II trimester. Then l-thyroxin, selenium and iodine treatment was initiated, and thyroid function and the level of mentioned antibodies were followed in the IIIrd trimester and in the postpartum period.
Results
Urinary iodine excretion was low, or at the lower normal limit in eight pregnant women, from them 3 women associated reduced selenium level, too. TPO-Ab was increased in 12 women, only Tg-Ab in one. All women received l-thyroxine, and we combined to this iodine (100–200 microg/day) and selenium (50–200 microg/day). In all cases the level of thyroid antibodies decreased gradually during pregnancy, moreover in two cases it became normal, but after delivery all began to increase. Postpartum overt thyrotoxicosis developed in three cases (25%), which improved spontaneously within 2 months (meanwhile iodine was reduced or stopped, and selenium continued).
Conclusion
Despite universal salt iodization implemented since 2002, iodine deficiency was detected in considerable part (8/13) of pregnant women with chronic autoimmune thyroiditis, requiring iodine supply. Combined therapy with l-thyroxine, selenium and iodine did not increase the level of thyroid autoantibodies during pregnancy, moreover it was decreased. Conversely, their level increased gradually in the postpartum period, when the maternal immunity return to pre-pregnant state, and in 25% of the cases overt thyrotoxicosis developed.

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EP1071

Ectopic Thyroid Tissue: Imagery Findings versus Pathological Report

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Introduction
Accessory thyroid tissue is a part of thyroid dysgenesis and sometime represents an incidental adult finding displaying a normal function.
Material and Methods
This is a case presentation of an adult admitted for an atypical anterior cervical aspect which could not be recognized as accessory thyroid tissue only after surgery. Thyroid evaluation used imagery like ultrasound, computed tomography (CT), assays as TSH (Thyroid Stimulating Hormone), calcitonin, TPO antibodies (anti-thyreoperoxidase).
Results
A 62-year male is diagnosed with prostate cancer at age of 58 and treated with radiotherapy and hormone blocking therapy with consecutive normalization of

specific prostate antigen. His father was diagnosed and treated for bone cancer. While evaluation for his previous oncologic condition, CT scan with contrast revealed asymmetrical thyroid with a mass of unknown origin at the cervical lateral level, left to the esophagus, of oval shape with regular margins. The 2 centimeter –sized mass causes a small deviation of the esophagus, and it has a hypo-dense spontaneous structure. Thyroid function was normal (TSH of 0.9 μUI/ml, N:0.5–4.5 μUI/ml), negative TPO and normal calcitonin and parathormone of 24.48 pg/ml (N:15–65 pg/ml). A paraganglioma was suspected based on high circulating serotonin of 423 ng/ml (N:40–400 ng/mll) but otherwise normal profile 24-h urinary metanephrines of 72 μg (N:50–450 μg/24-h), and normetaneprines of 274 μg (N:100–600 μg/24-h), plasma metanephrines of 29.6 pg/ml (N:10–90 pg/ml), plasma normetanephrines of 82.2 pg/ml (N:15–180 pg/ml), chromogranin A of 102 ng/ml (N:20–125), neuron specific enolase of 9.13 ng/ml (N:0–12 ng/ml). The surgical removal was performed and thyroid tissue of adenomatous type was found. No malignancy, neither surrounding tissues were presented so a late diagnosis of thyroid dysgenesis was established.

Conclusion

Accessory thyroid tissue might not be highly suggestive at CT or ultrasound especially if the late diagnosis is done during adult years. The presence of a prior malignancy may require several imagery tests and consecutive discovery of the thyroid dysgenesia.

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EP1072

Iodine status and thyroid volume in pregnant women

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Introduction

Adequate iodine intake is important in pregnant women.

Objective

To determinate iodine status and thyroid volumen (TV) in healthy pregnant women from Navarra (Spain), and to evaluate possible influence of diet.

Methods

A cross-sectional study of 144 women in the first trimester of pregnancy (single pregnancies) was carried during 2014. We measured thyroid-stimulating hormone (TSH), free thyroxine (fT4) and antithyroid antibodies in serum at 9 week of gestational age, and urinary iodine (UI) in a spot-urine sample. A thyroid ultrasonography was performed, and a questionnaire to estimate iodine intakes from diet, iodized salt and supplements was cumplimented at 10 week of gestational age.

Results

Studied women were 90.3% caucasic, mean age was 33.6 ± 4.1 years old and mean BMI 24.3 ± 4.4. A total of 100 subjects (69.4%) consumed iodized salt, 75 of them before pregnancy. All women were taking iodinated supplements (200 μg/day), 40% pregestational. Serum TSH was 1.57 ± 1 mIU/l and fT4 1.04 ± 0.1 ng/dl. Thyroid antibodies were positive in 23 women (16%). Median UI at 10 gestational week was 242 μg/l, considered adequate by WHO criteria. 31.9% of women ($n = 46$) had UI < 150 μg/l, and only 4.9% < 50 μg/l. Mean TV was 8.1 ± 2.5 ml. Serum TSH, fT4 and thyroid autoinmunity were similar in iodine-sufficient and iodine-insufficient women (UI ≥ 150 and < 150 μg/l respectively). TV in iodine-insufficient women was greater than in iodine-sufficient group (8.9 ± 2.6 vs 7.7 ± 2.4 ml; $P = 0.008$). There were no differences in age, BMI, smoking status, use of iodized salt, pregestational use of iodine supplements or estimates of iodine intake from diet between UI < 150 and UI ≥ 150 μg/l women.

Conclusions

Pregnant women of our population are iodine sufficient, probably due to sistematic use of iodine supplements and high consume of iodized salt. Thyroid volume was larger in iodine-insufficient women. We failed to identify other diet factors associated with iodine status.

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EP1073

Efficacy and safety of radioiodine therapy for mild Graves' ophthalmopathy in dependence on nicotine consumption

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Introduction

Graves 'Orbitopathy (GO), is an autoimmune disease associated with Graves' thyrotoxicosis (GT). The therapy is largely dependent on the severity and activity of ocular changes. Additionally, the severity of GO is influenced by exogenous factors, such as thyroid dysfunction, cigarette smoking or radioiodine therapy (RIT). The aim of the study was to indicate how radioiodine therapy (RIT) influences on GO in smoking and non-smoking patients.

Materials and methods

Patients with GO treated in the Departments of Endocrinology in Poznan between March 2014 and October 2014 were included. Ophthalmological signs were evaluated by visual acuity, cover test, tonometry, fundus examination, lid fissure measurement, visual test, Hertel's exopthalmometer and Hess-Landcaster screen measure. Presence and activity of GO was assessed using standardized scales such as the Clinical Activity Scale (CAS). The study protocol included also measurement of the serum levels of TSH, thyroid hormone, TPO-Abs, Tg-Abs, TSHR-Abs, and urine cotinine. All patients received an identical therapeutic high dose of 800 MBq ^{131}I. Analyses were conducted at baseline, 2 and 6 months after therapy. Data from anamnesis on the tobacco smoking where confirmed by measurement of cotinine in urine.

Results

Statistically significant differences in serum level of TSHR-Abs were found between non-smokers and smokers at 2 ($P < 0.001$) and 6 months after RIT ($P < 0.0001$). In smokers, statistically significant differences in the assessment of the severity of ophthalmopathy were observed. The ophthalmological signs assessed by the CAS scale occurred more intensely in smokers before ($P = 0.003$) and after RIT ($P = 0.0001$). 46.2% of smokers and 4.3% of non-smokers were subsequently upstaged from mild to moderate GO (CAS scale) after 6 months.

Conclusions

Ocular changes occur with higher intensity in the group of smokers. High dose of RAI does not induce exacerbation of ophthalmopathy in non-smokers.

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EP1074

What is the cut-off level for commercial kits for antithyroperoxydase antibody

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Aim

The biological diagnostic of Hashimoto thyroiditis (HT) is based on higher than normal levels of antithyroperoxydase antibodies (ATPO). Our goal was to establish the cut-off limit of normality (the upper limit) for ATPO in our thyroid normal patients. This limit and not that of the laboratory, should be used as diagnosis of Hashimoto thyroiditis.

Material and method

1. ATPO was investigated in patients with normal level of thyroid hormones (euthyroidism) and normal ultrasound of thyroid (linear probe at 7.5 MHz).
2. ATPO was analyzed in several Bucharest laboratories, accredited for this investigation. The laboratory cut-off limit for normality was 34 Ul/ml.
3. Conventionally, the normality is considered as the average (mean) plus/minus standard deviation multiply by 2.

Results
A. Patients: 268; women, 227, men, 41, age, average, 45, 87, median, 44; average TSH, 1.8 mUI/ml, FT4, 15.6 nmol/l.
B. ATPO level was: average: 8.65 UI/ml, standard deviation: 7.22. Therefore, the upper limit should be 23.08 UI/ml.
Discussion
Based on 34 UI/ml cut-off limit, we registered 1510 patients with HT (higher ATPO), 129 patients with only high antithyroglobuline thyroiditis (ATG-T) (lower ATPO), and 108 patients with idiopathic myxedema (hypothyroidism, lower ATPO/ATG, and inflammatory ultrasound signs). Considering ATPO cut-off 23 UI/ml, 15 (11.9%) ATG-T and 6 (4.6%) myxedema were in fact HT patients.
Conclusions
1. Using the date from our patients, the cut-off limit for ATPO should be 23 UI/ml and not 34 UI/ml. 2. Based on 23 UI/ml cut-off limit, the number of patients with Hashimoto thyroiditis increased by 9l.5%.

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EP1075

Toxic adenoma as a cause of dementia

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Background
Psychiatric symptoms have been reported quite frequently in thyroid disease. Dementia associated with hyperthyroidism is less well documented.
The case
We present the case of a 62 years old woman, who initially presented for a neurological consultation about her symptoms suggested Alzheimer's disease. The patient had been under treatment for more than seven years for type 2 diabetes and developed frequently episodes of hypoglycemia. She was treated the treatment by neurologist as dementia, but the symptoms did not improve, so she was admitted to our hospital. The thyroid function problem had never been suspected at the patient.
During the consultation, we found a big nodule in the left side of the thyroid, with tachycardia and high blood glucose values. Clinically, hyperthyroidism was suspected.
Lab Data: TSH 0.01 mUI/ml (Normal range 0.35–4.78); FT3 9.63 pg/ml (Normal range 2.3–4.2); FT4 3.48 ng/dl (Normal range 0.89–1.76); Glucose 182 mg/dl; HbA1c 5.5%; FBC - Normal
Thyroid ultrasound: A nodule in the left side of thyroid, its dimensions 5.0 × 3.5 cm, with heterogenic structure and microcalcifications. Right lobe of thyroid normal.
Thyroid scan with Tc99: Hot nodule in the left side of thyroid. Uptake 11%.
Head MR: Normal
A treatment with methimazole and β-blockers was started and the diabetes pills was stopped, since a secondary diabetes related to hyperthyroidism developed. Four weeks after the start of the treatment the patients improved, without any symptoms of dementia. The thyroidectomy was recommended.
Conclusions
Since thyroid disease can be associated with various psychiatric symptoms, we recommend checking thyroid function at the patient with psychiatric diseases even in a patient with "possible" Alzheimer's disease.
hyperthyroidism, psychosis, dementia.
Keywords: hyperthyroidism, psychosis, dementia.

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EP1076

Secondary hypothyroidism and the tarsal tunnel syndrome

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Clinical Case
We referred one case with primary hypothyroidism and tarsal tunnel syndrome. The boy 11 6/12 years old was presents in our clinic with fatigue, obesity, difficulty during walking, low performance in school, hyposthenia and dementia. His weight was 48 kg +3.8 DS; height 153 cm +2 DS; the patient has bilateral symptoms of the tarsal tunnel syndrome and his foot symptom was aggravated by walking. The hormonal values were: TSH 2.3 mUI/ml (0.35–4.04); FT4 0.54 ng/dl (0.93–1.7); FT3 1.97 ng/dl (2.3–4.2); Ac anti TPO 12.2 UI/ml; Ac anti Thyroglobulin 24 UI/ml, Thyroid ultrasound: Isoecogenic structure in both lobes of thyroid. MRI of head: Normal; The electro diagnostic study show evidence of bilateral tarsal tunnel syndrome (examination show chronic diffuse suffering of neurologic type of central origin with normal distal motor latencies bilaterally. Compression of tibial nerve in the tarsal tunnel. The patient begin the treatment with levothyroxine and after 6 months of treatment the FT3 and FT4 was normal; FT4 1.17 ng/dl; FT3 3.4 ng/dl; but the tarsal syndrome is not improved and he was underwent surgical treatment for tarsal tunnel release.
Conclusion
Prolonged untreated hypothyroidism may have neurological complication including tarsal tunnel syndrome

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EP1077

Assessment of thyroid function during the three trimesters of pregnancy in alexandria region (Egypt)

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Introduction
Pregnancy is associated with significant reversible changes in thyroid functions due to certain hormonal changes e.g. HCG and estrogen.
Objective
To study thyroid functions in different trimesters of pregnancy compared to control age matched non pregnant women.
Design and Methods
Cross sectional study of 90 pregnant women divided into three groups in the three trimesters of pregnancy compared to 30 ages matched non-pregnant women. Study of FT3, FT4, TSH and TPO using COBAS analyser.
Results
In general, our study showed significant differences between pregnant and non-pregnant women regarding FT4 and TSH but not FT3 and antiTPO. Thyroid function abnormalities were increased with advance in pregnancy.
Conclusion
The discrepancy between FT4 and TSH in pregnancy is mostly due to presence of many stimulatory and inhibitory factors. Screening of FT4, TSH, HCG and TPO is important during pregnancy.

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EP1078

Relationship to TSH, and interleukin levels patients with Hashimoto's Thyroiditis

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Background
Hashimoto's Thyroiditis (HT) is the most common clinical expression of thyroid dysfunction and result from organ-specific autoimmune reaction. Cytokines are play an important role in autoimmunity, by stimulating B and T cells.
The aim of this study is to examine the relationship between cytokines and thyroid function tests in patient with Hashimoto's Thyroiditis
Methods
139 cases with HT included this study. Subjects were recruited from Endocrinology Clinic of Pamukkale University in Turkey. Serum levels of sT3 (pg/ml) sT4(ng/dl) TSH (μIU/ml) were measured and IL-4, IL-5, TNF-α, IFN-γ analysis were performed with Elisa kits.
Results
IL-4, and IFN-γ levels were significantly correlated with TSH levels. ($P < 0.01$) TNF-α level was correlated with TSH levels, but was not statistically significant. IL-2 and IL-5 were not correlated with TSH levels.

Conclusion
Studies shows that there is a relationship between thyroid function tests with cytokines.In thyroidal and nonthyroidal diseases that occur during thyroid dysfunction, it is considered that can be realized through cytokines. In our study we observed a correlation between thyroid function and cytokines, and we believe that supports this view.
Keywords: TSH, IL-2, IL-4, IL-5, IFN-γ, TNF-α Levels, Hashimoto's Thyroiditis.
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EP1079

Evaluation of ovarian reserve in terms of ovarian volume, antral follicule count and hormonal tests in Hashimoto's thyroiditis

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Introduction
Our aim is to investigate whether ovarian reserve is decreased in patients with euthyroid Hashimoto's thyroiditis (HT).
Method
Our study included 110 euthyroid HT patients and 72 age matched healthy women (controls; C). In all patients FSH, LH E2, and P levels were measured from blood samples, and ovarian volumes (OV) and antral follicule count (AFC) were measured using ultrasonography at 3rd day of menstruation.
Results
No statistically significant difference was detected in FSH, LH, E2 and P levels between groups (P value respectively; 0.117, 0.420, 0.941, 0.644). Total ovarian volumes were not statistically different between groups ($P=0.165$). Total AFC were significantly lower in the HT group than the controls ($P<0.001$). Total AFC were strongly and negatively correlated with AntiTPO ($r=-0.215$, $P=0.004$) and AntiTg ($r=-0.251$, $P=0.001$).
Conclusion
Our study shows decreased ovarian reserve in HT patients than healthy controls even in euthyroid state.
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EP1080

Thyroid screening in pregnancy –preliminary data from our outpatient clinic

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Introduction
The adverse impact of overt hypothyroidism that complicates pregnancy outcomes is well-established. In order to eliminate these complications has long been discussion about the need for early detection of the disease of the thyroid gland in the population of women planning pregnancy, respectively in early pregnancy. In Slovakia, this effort resulted in the approval of screening for thyroid diseases in pregnancy and has been enshrined in a legislative in 2009. Obligatory in screening is examination TSH, in case of pathological range, the patient is forwarded to endocrinologist.
Methods
we examined 60 pregnant patients in pilot study, with no history of thyroid disease, with a mean age of 32.7 years. They sent by gynecologists for pathological results of screening laboratory examinations (TSH, aTPO).
Results
We reported that patients were examined on average, in the 13th gestational week, 34 patients were diagnosed during the first trimester, 25 patients in the 2nd trimester of pregnancy and one patient in the third trimester. A time from blood collection by gynecologist to the endocrinology examination ranged from 1–9 weeks. Thirty-five patients were first time pregnant. TSH was in normal range only in 18 patients, 8 patients had suppressed TSH physiologically (suppressed by effect of HCG), the remaining 34 patients had hypothyroidism. Antibody positivity had 31 patients. FT4 values ranged from 11 to 24 pmol/l (normal range) in 47 patients. Only 2 patients had fT4 below 11 pmol/l.
Conclusion
The results show that despite the implementation of screening for thyroid diseases in pregnant, these patients were sent to endocrinologist relatively late. That is a reason of late diagnosis of hypothyroidism, although it is well known that only early treatment can prevent symptoms and complications in pregnant women and ensure the healthy development of the child.
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EP1081

The efficacy of radioiodine therapy in patients with hyperfunctioning thyroid nodules

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Introduction
Radioiodine (RAI) is used as a definitive therapy of hyperthyroidism due to toxic adenoma (TA) as well as toxic multinodular goiter (TMG). Achievement of hypothyroidism or euthyroidism is defined as a successful therapy.
Methods
The study was conducted in 666 patients – 484 with TA and 182 with TMG (85.58% of women), aged 56.19 ± 13.88 years. We analyzed retrospectively hormonal and imaging findings (scintigraphy, ultrasonography), including isotopic results in subjects treated at Department of Nuclear Medicine and Endocrinology Department during the eight-year period. The efficacy of RAI therapy has been assessed based on free thyroid hormones levels, measured 12 months after radioiodine administration.
Results
Mean concentrations of FT4 and FT3 and age did not differ significantly both groups. Patients with TA had lower thyroid mass and RAI 24-h uptake than subjects with TMG ($P=0.0000$). Administered therapeutic activities of RAI (MBq), calculated using Marinelli's formula, were smaller in subjects with TA (537.03 ± 181.39 vs 614.13 ± 147.22; $P=0.0000$) and the thyroid-absorbed doses of RAI (Gy) in such patients were greater ($P=0.0000$). After RAI therapy, hypothyroidism was found in 3.30% TA and 8.79% TMG participants, euthyreosis - in 80.79% TA and 69.23% TMG and hyperthyroidism – in 15.91% TA and 21.98% TMG. The efficacy of RAI therapy was achieved in 84.10% of TA patients (F–84.99%; M-78.87%) and in 78.02% of TMG subjects (F–75.80%; M-92.00%). The cure of hyperthyroidism was significantly correlated in both groups with lower: thyroid mass, RAI 24-h uptake and concentrations of FT4 and FT3 before therapy. No significant associations between successful therapy and patients' age, thyroid absorbed dose and used therapeutic activity of RAI were found.
Conclusions
RAI therapy was more effective in TA patients. Males responded better to treatment than females in case of TMG. The cure correlated with thyroid mass, RAI 24-h uptake and free thyroid hormones levels before therapy.
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EP1082

Clinical and epidemiological profile of patients with hyperthyroidism and hypothyroidism that receive endocrinological services from a medical institution in Medellín (Colombia) between 2013 and 2015

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Introduction
Endocrine Illnesses have high prevalence on a global level due to multiple etiologies that can lead alterations to this system.
Objective
Determine the epidemiological profile of hyperthyroid and hypothyroid patients that receive endocrinological services from a medical institution in Medellin (Colombia) between 2013 and 2015.
Methodology
A descriptive, retrospective study was conducted and included the clinical records of patients diagnosed with hyperthyroidism or hypothyroidism. A univariate analysis was applied using descriptive statistics by means of absolute frequencies and proportions in the SPSS software, version 19.0.
Results
A sample was obtained with 131 patients with hypothyroidism and 18 with hyperthyroidism, the average age was 56.7±17.8 years and 55.6±15.1 years, respectively. The frequency of female sex with hypothyroidism was greater than those patients with hyperthyroidism (86.3% versus 66.7%). Post-surgery hypothyroidism had a high prevalence (11.5%) followed by the Hashimoto disease (5.3%). The principal etiologies in hyperthyroidism were Graves disease (33.3%) and thyrotoxicosis (22.2%). With relation to the signs and frequent symptoms in the studied patients, the goiter was common in 14.5% of the patients with hypothyroidism versus 38.9% of those patients with hyperthyroidism. The most frequent diseases on past medical history in both groups of patients were high blood pressure and Diabetes Mellitus.
Conclusion
The results align with what is described in the literature of both pathologies, being more common in women with primary gland disfunction. In relation to classic symptoms of the disease such as fatigue and adynamia, neither were the most relevant in this study.
Keywords: Thyroid Diseases, Hypothyroidism, Hyperthyroidism, Goiter
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EP1083

The beneficial effect of L-thyroxine on lipid parameters in mild form of subclinical hypothyroidism

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Introduction
Overt hypothyroidism and severe subclinical hypothyroidism (ScH) are associated with dyslipidaemia, and its condition is reversible after thyroid replacement therapy. We investigated the effect of levothyroxine therapy on lipid parameters in patients with mild form of subclinical hypothyroidism (ScH).
Material and methods
Fifty-seven patients with newly diagnosed ScH with TSH levels below 10 mU/l and 30 age and sex-matched healthy subjects were included in the study. Lipid parameters were evaluated at the first visit in both groups, and after 6 months euthyroid stage in patients with ScH.
Results
Average value of TSH in patients with ScH was 8.1 mU/l. At the baseline, ScH patients has a significantly higher total cholesterol and LDL-C levels, and lower HDL-C, than the control group (5.6±0.9 vs. 4.8±1.1, 3.4±1.0 vs. 2.9±0.8, and 1.5±0.5 vs. 1.7±0.9, mmol/L, $P<0.05$, respectively). Thyroid substitution therapy in ScH group, significantly decreased total cholesterol and LDL-C, and increased HDL-C (5.6±0.9 vs. 5.3±1.1, 3.4±1.0 vs. 3.2±1.1, 1.5±0.5 vs. 1.6±0.5, mmol/L, $P<0.05$ respectively). Also, TSH positively correlated with total cholesterol ($r=0.147$, $P<0.05$).
Conclusion
Mild form of ScH is associated with hipercholesterolemia, which is reversible after levothyroxine treatment.
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EP1084

Princess and the Pea

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Introduction
Subacute (de Quervainś) thyroiditis is an uncommon altough not a rare condition. Pain in the thyroid and ill-defined hypoechogenic thyroid lesions in ultrasonography are typicall findings, occasionaly are increased thyroid hormones levels. Often preceded by upper respiratory tract infection. The disease is self-limited and often resolves spontaneously, usually without subsequent thyroid function abnormalities, or it may improve with anti-inflammatory drugs and corticosteroids. Fine needly biopsy can confirm the diagnosis in case of doubt, but is not performed frequently.
Case report
A 32-year-old woman complained of pain in a very small area on the anterior side of her neck. Sonographical examination revealed small hypoechogenic lesion 9×7×8 mm[0.3 ml] in an otherwise almost normal thyroid gland corresponding with the pain point. Within one month the pain worsened and the area sonographically enlarged to 27×13×12 mm [2.1 ml] with features typical of subacute thyroiditis. After rapid relief following treatment with prednisone the same problems appeared in the opposite lobe when prednisone therapy was interrupted. In this case the whole lobe was affected. Prednisone therapy again brought immediate improvement. Currently the patient has no problems and sonographical findings are completely normal.
Conclusion
This case report demonstartes an unusually small painful enough lesion caused by subacute thyroiditis.The diagnosis was clear only in the course of further development of the disease.
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EP1085

Delayed diagnosis of small bowel adenocarcinoma due to thyroiditis induced thyrotoxicosis in a healthy young adult

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Objectives
Various systemic symptoms may occur in patients with thyrotoxicosis. Gastrointestinal manifestations such as hyperphagia or frequent defecation, often coexist with other thyrotoxic symptoms. Vomiting also has been mentioned. In this setting, systemic symptoms of underlying malignancy may be confused with those of thyrotoxicosis leading to a delay in diagnosis.
Methods
We report a case with delayed diagnosis of small bowel adenocarcinoma due to thyroiditis induced thyrotoxicosis in a healthy young adult.
Results
A 22-year-old man presented with palpitation, vomiting and 10 kg weight loss over the past 1 month. About 3 months before visiting our hospital, the patient reduced the weight about 10 kg through diet and exercise. The patient had no proptosis, eyelid lag, the thyroid gland was not palpable, and no tenderness or rebound tenderness was found in the epigastrium. Laboratory examinations revealed low level of TSH, elevated free T4 level, hyponatremia and hypokalemia. Serum antibodies to TSH-receptor and thyroid peroxidase were negative. Tc-99m thyroid scan was performed and uptake was decreased in both thyroid lobe. The patient was diagnosed with thyroiditis induced thyrotoxicosis. At the initial approach, the symptoms of patient including nausea and vomiting were considered uncommon thyrotoxic manifestations. However, vomiting was not improved despite symptomatic treatment. Upper gastrointestinal series and computed tomography of abdomen revealed slow passage of contrast media and narrowing of small bowel with upstream dilatation due to small bowel mass. He underwent small bowel segmental resection. The pathology reported adenocarcinoma of proximal jejunum.
Conclusion
In conclusion, this case highlights the importance of a comprehensive clinical history and examination for all patients presenting with thyrotoxicosis.
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Thyroid cancer

EP1086

External beam radiation therapy: a promising tool to enhance mesenchymal stem cell migration towards tumors

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The tumor-homing property of mesenchymal stem cells (MSC) has led to their use as delivery vehicles for therapeutic genes such as the sodium iodide symporter (NIS), which has convincingly been demonstrated by our recent studies of systemic NIS gene delivery using MSCs as delivery vehicles in both subcutaneous and orthotopic xenograft mouse models. External beam radiation therapy (EBRT) represents a promising tool in the application of engineered MSC (eMSCs)-based gene therapy as tumor irradiation may enhance MSC recruitment into irradiated tumor microenvironments. This effect is presumably mediated through a radiation-induced stimulation of secretion of certain cytokines.
Effects of EBRT on the cytokine secretion profile of human liver cancer cells (HuH7) were investigated by ELISA on supernatants of HuH7 cells, which were irradiated with different doses (1-10 Gy) and removed at intervals from 0–48 h after radiation. Beside an increase in VEGF (up to 1.6-fold) and TSP-1 (up to 2-fold) secretion, a high increase in CXCL12 expression (up to 3-fold) was observed at 48 h post radiation. 48 h supernatants were further tested in a live cell tracking migration assay (IBIDI μ-slides Chemotaxis) monitored by time-lapse microscopy for 24 h. The analysis revealed a profound increase of mean forward migration index (yFMI), mean center of mass (yCoM) and mean directionality of MSCs towards supernatants from irradiated compared to non-irradiated tumor cells implying enhanced MSC migration.
Our data demonstrate that tumor cells secrete higher levels of cytokines and growth factors that are involved in MSC tumor homing after irradiation resulting in stimulation of chemotaxis of MSCs towards tumor cells. This clearly shows the promising potential of EBRT pretreatment to enhance the migratory capacity of MSCs and thus tumor selectivity and therapeutic effectiveness of MSC-mediated gene therapy approaches.

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EP1087

Comparisons of Endothelial Dysfunction, Inflammation and Insulin Resistance in Differentiated Thyroid Cancer Patients According to Their Radioactive Iodine Treatment Status

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Objective
Radioactive iodine (RAI) treatment has been reported to be associated to increased cardiovascular events and death compared to the general population, but the mechanism is not fully understood. Endothelial dysfunction, inflammation, and insulin resistance play important roles in the pathogenesis of atherosclerotic events. We aimed to compare papillary thyroid carcinoma patients receiving levothyroxine suppression therapy after bilateral total thyroidectomy with or without RAI treatment in terms of endothelial dysfunction, inflammation and insulin resistance.
Materials and Methods
A total of 30 patients were included in the study (F = 23 (76.6%); age = 38.83 ± 8.15 (min = 24, max = 54)). 17 of these patients (F/M = 14/3) received RAI ablation. In all cases, blood samples were taken before the operation. Blood samples were taken at 3 and 6 months after RAI or thyroid surgery. All patients with TSH <0.1 μIU/ml received levothyroxine suppression therapy. Serum asymmetric dimethyl arginine (ADMA), hs-CRP and HOMA-IR measurements were performed to demonstrate endothelial dysfunction, endothelial inflammation and insulin resistance, respectively.
Results
RAI receiving and not-receiving groups were similar in terms of age and gender. TSH levels were significantly lower than before treatment ($P<0.001$). Preoperative ADMA, HOMA-IR and hs-CRP levels were similar to 3rd and 6th month measurements. These parameters were similar between groups receiving and not-receiving RAI treatment. Changes in ADMA, hs-CRP and HOMA-IR levels were not associated with the amount of applied RAI.
Discussion
In this study, there was no significant effect of RAI ablation treatment on endothelial dysfunction, inflammation and insulin resistance in differentiated thyroid cancer patients. However, in order to better clarify the effects of RAI applications on these parameters, larger scale long-term follow-up studies are needed.

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EP1088

Benefits of anti-thyroid peroxidase antibody and anti- thyroglobulin antibody for the prediction of differentiated thyroid cancer in Hashimoto thyroiditis

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Purpose
The association between differentiated thyroid cancers and autoimmune thyroid diseases is well known. Therefore, we aimed to investigate the importance of thyroid peroxidase antibody (anti-TPO) and thyroglobulin antibody (Anti-Tg) in patients followed with the diagnosis of Hashimoto's thyroiditis regarding the development of differentiated thyroid cancer.
Methods
A total of 56 patients including 22 Hashimoto's thyroiditis patients operated on for nodules and with a histopathologic diagnosis of malignant differentiated thyroid cancer (17 papillary cancer, 5 follicular cancer) and 34 individuals with benign nodular goiter, and 35 healthy controls were included in the study. There were no statistically significant differences among the groups in terms of age and body mass index. Anti-thyroglobulin and anti-thyroid peroxidase antibody values within one month before surgery were taken. Association between postoperative histopathology and antibody levels was analyzed.
Results
In patients with Hashimoto's thyroiditis, anti-TPO and anti-Tg were significantly different between benign and malignant groups (9.4 ± 1.3 and 78.6 ± 142.7) ve anti-Tg (19.0 ± 5.3 and 421.9 ± 1061.4) ($P=0.026$, $P=0.013$, respectively). There was a positive correlation between anti-TPO and anti-TG in the malignant group ($P=0.01$ $r=0.386$, $P=0.03$ $r=0.259$, respectively). In ROC analysis, TPO ≥ 15 had 62.5% sensitivity and 100% specificity, anti TG ≥ 21 had 50% sensitivity and 100% specificity in predicting differentiated thyroid cancer in Hashimoto's thyroiditis.
Conclusion
It appears that preoperative high anti-TPO and anti-Tg levels are a useful indicator to predict differentiated thyroid cancers.

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EP1089

Malignancy in AUS/FLUS: can we create a predictive score?

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Background
Thyroid AUS/FLUS lesions continue to be a grey area regarding the surgery to be carried out. Our aim was to create a predictive malignancy score to help in surgical decision.
Methods
Retrospective study of 2981 patients and 3557 thyroid Fine-needle aspirations (FNAs) between January 2012 to December 2014. Ultrasound and cytological findings considered suspicious by the ATA guidelines were analyzed. Malignant group was compared with a control group of benign histology using SPSS analysis.
Results
AUS/FLUS rate was 15.9% (564). 180 patients underwent surgery. 54 revealed carcinoma on final histology.
From Q-square test we found: 1) Hypoechoic nodules (HN) and ecographic microcalcifications (MC) are individually associated with malignancy. 2) Taller than wide shape nodules and vascularity findings are significant but not statistic associated. 3) Microfolicular (MF), Hürthle cells (HC) and nuclear changes (NC) are always present in malignant cases but without individual association.
Multivariable analyses showed: 1) presence of 3 cytological findings was associated with higher probability of carcinoma. 2) HN and MC are strongly associated with malignancy.
By logistic regression associating the 5 criteria increased probability of carcinoma. Probabilities were as follows: HN-2.6; MC-18.69; MF-2.48; HC-2.02; NC-1.99. ROC curve was 72.9% above. Sensibility and specificity were 66.2%/72.7% with a cut-off point of 0.50.
Conclusion
A moderate sensibility and a high specificity for malignancy were observed in the association between hypoechoic nodule, ecographic microcalcifications, microfollicular lesions, Hürthle cells and nuclear changes. These criteria can be useful in surgical decision contributing for a possible decrease in the reintervention rate.

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EP1090

Differential expression of mRNA of the vitamin D receptor, 1α-hydroxylase 25-hydroxy vitamin D and estrogen receptors in human explants and cell cultures of thyroid cancer and normal tissues

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Several studies indicated that estrogen receptors (ERs) and vitamin D receptor (VDR), as well 1α-hydroxylase 25-hydroxy vitamin D (1OHase) are expressed in various normal and cancerous cell types. To date, there are no reported studies on the different expressions of VDR, 1OHase and ERs, in human thyroid normal and cancer cells. This study addresses these questions. Tissues harvested from papillary thyroid cancer (PTC) and normal glands explants were used throughout either as intact explants or as cell cultures. The relative VDR, 1OHase and ERα, ERβ, in these samples were determined by real time PCR. Both normal thyroid and PTC explants and cultured cells expressed VDR and 1OHase mRNA as well as ERα and ERβ. Cancer thyroid explants had higher abundance than normal ones of VDR, ERβ and ERβ but lower 1OHase. Cancer thyroid cultured cells had higher abundance than normal ones of VDR, ERα and ERβ but lower 1OHase. When cultured normal and cancer cells where treated with 0.1 nM of $1,25(OH)_2D_3$ (1,25D) or 1nM the less calcemic vitamin D analog (JKF) or the non calcemic analog (CB) there is increased mRNA expression in cancer cells of ERα, ERβ, VDR and 1OHase, whereas in normal cells the stimulations were to lower extent. In conclusion thyroid cancer and normal explants as well as cultured cells from these tissues, express mRNA for VDR and 1OHase as well as different ERs, to different extent and are modulated by 1,25D or the vitamin D analogs. These results are similar to those obtained with human thyroid cancer cell lines. This might form the basis for the use of hormonal modulation of different mRNAs for therapy and affinity drug targeting via VDR, 1OHase and/or ERs by controlling their levels. These results are consistent with the hypothesis that endogenous vitamin D and estrogens may affect thyroid cancer cell growth via opposing pathways: cell growth acceleration via induction of ER expression, in association with the induction of VDR and 1OHase to promote the synthesis of 1,25D which is known to inhibit cell proliferation via binding to VDR. This is the first report describing direct regulation of VDR and 1OHase expression by vitamin D compounds in primary cultured human thyroid cancer cells. A functional role for vitamin D system in human thyroid cancer is suggested by the finding that the vitamin D compounds can affect ERs expression which is in turn involved in estrogen-induced cell growth in an ER-type specific manner.

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EP1091

Bethesda classification is highly predictive especially for the diagnoses of aggressive variants of papillary thyroid carcinoma

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Background
Fine needle aspiration biopsy (FNAB) has proven to be the most valuable diagnostic procedure for preoperative discrimination of benign and malignant nodules. Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) has standardized reporting and cytomorphological criteria in aspiration smears. In this study, we aimed to determine malignancy rates in nodules with different cytology results and diagnostic value of TBSRTC for variants of papillary thyroid carcinoma (PTC).
Materials and Methods
A retrospective analysis of 2534 cases with 5784 thyroid nodules, who had undergone FNAB followed by surgery, were included in this study. FNA was performed with ultrasound guidance. Cytological diagnosis were classified as; nondiagnostic (ND), benign, atypia of undetermined significance/follicular lesions of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), suspicious for malignancy (SUS) and malignant. Histopathological diagnoses were classified into four groups; benign, papillary thyroid cancer (PTC), follicular thyroid cancer and other types of thyroid cancer (including medullary thyroid cancer, undifferentiated thyroid cancer and thyroid tumors of uncertain malignant potential). Cases with PTC were further divided in to four categories; conventional variant, follicular variant, aggressive variants (tall cell, diffuse sclerosing and columnar variant) and other variants (oncocytic, solid/trabecular, warthin-like variants). FNAB results were compared with histopathological results.
Results
Malignancy rates were 6.3%, 3.2%, 20.7%, 33.3%, 74.2%, and 95.6% in the nodules with ND, benign, AUS/FLUS, FN/SFN, suspicious for malignancy (SUS) and malignant cytologies results, respectively. Preoperative cytology was malignant or SUS in 56.6% of classical, 24.3% of follicular, 92% of aggressive and 41.7% of other variants of histopathologically confirmed PTC. The difference between the groups was significant ($P<0.001$).
Conclusion
Bethesda classification seems to be very effective in predicting the malignancy for the nodules diagnosed with aggressive variant PTC on the final histological examination.

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EP1092

Strain ultrasound elastography in the diagnostic evaluation of thyroid nodules

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Objectives
The aim of the study was to determine different types of thyroid nodules according to their elasticity and to evaluate the diagnostic accuracy of strain elastography in detection of thyroid cancer. 114 thyroid nodules in 84 patients

were examined prospectively with conventional B-mode US, color Doppler, strain elastography (SE) and fine needle aspiration biopsy (FNAB). 72 nodules in 50 patients were submitted to surgery and histologically assessed. For final diagnosis we accepted histology in operated cases and cytology for the rest.
Results
After performing SE, the image was matched to a modified 5 scale scoring system, based on the one of Ueno and Ito. 32.9% of benign and 0% of malignant nodules presented with highly elastic structure - score 1 ($P<0.0001$). Elasticity in a large area of the nodule (score 2) was present in 34.2% of benign and 5.3% of malignant nodules ($P=0.0005$). Indeterminate elasticity (score 3) had 26.3% of benign and 18.4% of malignant lesions ($P=0.4839$). No elasticity (score 4) was determined in 6.6% of benign and in 55.3% of malignant nodules ($P<0.0001$). Stiffness in nodule and surrounding tissue (score 5) was registered in 21.1% of malignant and none of benign lesions ($P<0.0001$). Sensitivity, specificity, PPV, NPV and accuracy were 76.3%; 93.4%; 85.3%; 88.8%; 87.7% for SE; 89.5%; 86.2; 79.1%; 94.4%; 89% for combining B-mode and SE; and 92.1%; 93.4%, 87.5%; 95.9%; 93% for combining B-mode, SE and FNAB, respectively.
Conclusions
The high specificity and NPP of SE alone or as an adjunct to conventional US suggests that high elasticity is a promising criterion for excluding malignancy and that this non-invasive technique may limit the indications for FNAB. Combination of three methods (B-mode, SE and FNAB) has the highest diagnostic accuracy in differentiating malignant from benign nodules and permits the clinician exact selection of patients who would benefit from surgery.

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EP1093

Usefulness of Day 5 sampling in thyroid cancer patients for radioactive iodine therapy with recombinant human thyrotropin

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Background
We evaluated the impact of several anthropometric parameters on serum peak TSH levels after standard two-dose of recombinant human thyrotropin (rhTSH) injection and assessed the usefulness of repeated measurement of TSH and thyroglobulin (Tg) levels at 24 and 72 h after rhTSH injection (Day 3 and 5) to confirm stimulated Tg level.
Methods
We retrospectively reviewed 270 differentiated thyroid carcinoma patients who underwent rhTSH stimulation for radioactive iodine therapy in our clinic between 2013 and 2014. Serum TSH and Tg level were measured twice Day 3 and 5 after rhTSH injection. Univariate and multivariate analyses were performed to elucidate predictive factors of the peak TSH level. The repetitive values of TSH, Tg and TgAb were compared by two-tailed paired *T*-test.
Results
By univariate analysis, peak TSH level (Day 3 TSH) was positively correlated with age and serum creatinine, and negatively correlated with weight, height, body surface area (BSA) and glomerular filtration rate (GFR) ($P<0.01$). GFR and BSA were independently associated with peak TSH level by multivariate analysis (standardized β coefficient $=-0.36$; $P<0.001$ and -0.23; $P<0.01$, respectively). On the subgroup analysis of sixty patients with repetitive measurements, rhTSH-stimulated Tg level on Day 5 was significantly higher than that of Day 3 (0.71 ng/ml vs. 0.54 ng/ml, $P=0.006$).
Conclusions
Body size and renal function influence serum peak TSH levels after rhTSH injection. On this basis, more personalized rhTSH dosage could be used in clinical practice, adjusted for BSA and GFR. The repeated measurement on Day 5 seemed to be necessary to assess stimulated Tg level.

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EP1094

Thyroid nodule ultrasound: which indication for FNA? a prospective study

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Introduction
Thyroid nodules are discovered by ultrasound (US) in a large percentage of population. In most cases they are benign and asymptomatic. When to perform or not a fine-needle-aspiration (FNA) is still matter of debate. Aim of this study was to evaluate the usefulness of a easy-to-use US classification, based on three US classes.
Methods
We prospectively evaluated US features of 1118 thyroid nodules, allocating each nodule in one of three classes, depending on the number of US findings of malignancy: US1 (0-1 finding), US2 (2 findings), US3 (3 or more findings). US evaluation was made using traditional B-Mode and Power-Doppler high-frequency US. We considered the following five US features as finding of malignancy: hypoechogenicity, micro(macro)calcifications, irregular margins, taller-than-wide shape, and intranodular chaotic vascularisation. All nodules were then submitted to FNA, and cytological results were compared to US classification.
Results
Excluding 106 nodules with non diagnostic cytology (Thy1) and 3 nodules with non-thyroidal cytological diagnosis (parathyroid gland or epidermoid cyst), in the remaining 1009 nodules FNA provided the following results:
US1: Thy2 = 563, Thy3 = 39, Thy4 = 2, Thy5 = 0
US2: Thy2 = 182, Thy3 = 90, Thy4 = 6, Thy5 = 3
US3: Thy2 = 27, Thy3 = 47, Thy4 = 20, Thy5 = 30
The distribution of FNA results showed a significant correlation ($r=0.597$) with US classification. Considering thyroid nodules with indeterminate cytology (Thy3), 111 nodules were submitted to thyroidectomy. In this subgroup of patients, the histological result (benign or malignant) showed a significant difference among the three US classes, according to US stratification of suspicion.
Conclusion
Our data confirm the accuracy of traditional US findings in the first diagnostic evaluation of thyroid nodules, proposing a simple, easy-to-use US classification of thyroid nodules. Together with clinical features, this classification might be useful when we have to decide if performing or not a FNA.

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EP1095

Clinical usefulness of dynamic risk stratification in medullary thyroid cancer

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Purpose
To detect persistent/recurrent disease of medullary thyroid carcinoma (MTC) after initial surgery is important. The Tumor-Node-Metastasis (TNM) staging system is useful for predicting disease-specific mortality, but it is static and does not include postoperative serum calcitonin levels. We focused on the clinical usefulness of dynamic risk stratification (DRS) using the best response to initial therapy in patients with MTC.
Methods
A total of 120 MTC patients were classified into 3 DRS groups based on the response to initial therapy. The clinical outcomes were assessed according to the TNM staging and DRS.
Results
In DRS, 70%, 23%, and 7% of patients were classified into excellent, biochemical incomplete, and structural incomplete response group. In TNM staging, 37%, 16%, 13%, and 35% of patients were stage I, II, II, and IV, respectively. There were significant differences in survivals according to the TNM staging ($P=0.03$) and the DRS groups ($P=0.005$). During median 6.2 years of follow-up, 75 patients (63%) were no evidence of disease (NED). About 60% and 17% of patients in stage III and IV were NED, respectively. DRS could predict NED better than TNM staging according to PVE (49.1% vs. 28.7%, respectively).

At final follow-up, 88%, 4%, and 0% attained NED in excellent, biochemical incomplete, and structural incomplete response group, respectively.
Conclusions
DRS based on the best response to the initial therapy could provide useful prognostic information in addition to initial TNM staging for prediction of mortality, as well as the likelihood of NED in patients with MTC.

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EP1096

Sitagliptin use and thyroid cancer risk in patients with type 2 diabetes

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Background
Whether sitagliptin use in patients with type 2 diabetes mellitus may affect the risk of thyroid cancer requires further investigated.
Methods
The reimbursement database of the National Health Insurance in Taiwan was used. Patients with newly diagnosed type 2 diabetes mellitus within 1999–2008 were recruited and followed for at least 6 months for thyroid cancer until December 31, 2011. Patients were divided into those who were newly treated with sitagliptin ($n=50045$, "ever users of sitagliptin") or other antidiabetic drugs ($n=277100$, "never users of sitagliptin"). The treatment effect of sitagliptin (for ever versus never users, and for tertiles of cumulative duration of therapy) was estimated by Cox regression incorporated with the inverse probability of treatment weighting using propensity score.
Results
The respective numbers of incident thyroid cancer in ever users and never users were 25 (0.05%) and 152 (0.05%), with respective incidences of 30.34 and 22.04 per 100 000 person-years. The overall hazard ratios (95% confidence intervals) suggested a significantly higher risk (1.573 (1.025, 2.414)). In tertile analyses, the hazard ratios (95% confidence intervals) for the first (<6.53 months), second (6.53–14.00 months) and third (>14 months) tertile of cumulative duration were 2.098 (1.025, 4.295), 2.476 (1.368, 4.483) and 0.689 (0.283, 1.682), respectively. Sensitivity analyses after excluding patients with benign thyroid disease at baseline showed similar results.
Conclusions
Sitagliptin use is associated with an increased risk of thyroid cancer, especially during the first year of its treatment. The increased risk within a short-term of cumulative duration of exposure probably precludes a mechanism involving de novo development of thyroid cancer. Future studies are required to confirm the findings of the present study.

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EP1097

Immunohistochemistry as alternative to DNA sequencing in detection of BRAF V600E mutation in papillary thyroid carcinomas

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Objective
To compare the results of immunohistochemistry (IHC) and DNA sequencing in detection of BRAF V600E mutation in papillary thyroid carcinomas (PTC). BRAF V600E mutation is the most common genetic alteration in papillary thyroid carcinomas and is associated with worse prognosis. Direct sequencing is usually performed, but less expensive immunohistochemistry can be used instead.
Methods
Study was performed in 54 consecutive PTCs during 2014–2015[A1]. DNA was extracted from formalin-fixed paraffin-embedded tissues by manual-microdissection and BRAF mutation was detected by allele specific PCR with Cobas® 4800 BRAF V600 mutation test (Roche). IHC was performed over tissue fixed for 24-h with 10% neutral formalin using the anti-BRAF V600E (VE-1) mouse monoclonal primary antibody. IHC was scored as positive or negative at pathologist's criteria.
Results
IHC BRAF V600E was positive in 32 PTC and negative in 22. Mutated PTC appeared in older patients (mean: 53.2 vs 50.8 y-o). There were 18 positive tumors by IHC with multifocality (56.2%) whereas only 7 of 22 (31.8%) with negative IHC had two or more foci. Negative IHC PTCs were bigger than positive ones (17.3 vs 12.8 mm). Half of positive IHC cases were classic variants of PTC, but only one in negative IHC neoplasms. Of the 32 cases that were IHC positive for BRAF V600E, 31 were confirmed by sequencing (96.9%) and one case was discordant. Discordance appeared in a 38 year-old woman with an incidental PTC follicular variant of 5 mm, near to a follicular adenoma with suspicious FNA. Pathologist confirmed that tissue had been taken from the tumor.
Conclusions
IHC has an accuracy of 96.9% for BRAF V600E detection and can be used as a cost-effective alternative to DNA sequencing in daily practice.

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EP1098

Sequence defined cMET/HGFR-targeted polymers as gene delivery vehicles for the theranostic sodium iodide symporter (NIS) gene

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The sodium iodide symporter (NIS) in its role as well characterized reporter and therapy gene represents an outstanding tool to target different cancer types allowing non-invasive imaging of functional NIS expression by ^{123}I-scintigraphy and therapeutic application of ^{131}I. Based on its overexpression on the surface of the vast majority of cancer types, the cMET/Hepatocyte growth factor receptor (HGFR) serves as an ideal target for tumor-selective gene delivery.
In the current study, we used sequence defined polymers as non-viral gene delivery vehicles comprising polyethylene glycol (PEG) and cationic (oligoethanoamino) amide cores coupled with a cMET-binding-peptide (cMBP2) to target the cMET/HGF-receptor in a human hepatocellular cancer (HuH7) mouse model. These polymers were complexed with human NIS-DNA (polyplexes) and tested for receptor-specificity, transduction efficiency and therapeutic efficacy.
In vitro iodide uptake studies demonstrated high transduction efficiency and cMET-specificity of NIS encoding DNA polyplexes coupled with cMBP2 (cMBP2-PEG-Stp/NIS) compared to polyplexes without ligand (Ala-PEG-Stp/NIS) and polyplexes containing non-coding DNA (cMBP2-PEG-Stp/Antisense-NIS). Tumor recruitment and vector biodistribution were investigated *in vivo* showing high tumor-selective iodide accumulation in cMBP2-PEG-Stp/NIS-treated mice (6.6 ± 1.6% ID/g ^{123}I, biological half-life 3 h) by ^{123}I-scintigraphy 48 h after intravenous polyplex application, while injection of control vectors did not result in specific iodide uptake. Therapy studies with 3 cycles of polyplexes and ^{131}I applications resulted in a significant delay in tumor growth and prolonged survival of cMBP2-PEG-Stp/NIS-treated mice.
In conclusion, our data demonstrate the enormous potential of cMET-targeted sequence defined polymers combined with the unique theranostic function of NIS allowing for optimized transfection efficiency while eliminating adverse effects as toxicity or high immunogenicity.

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EP1099

Are there any differences between demographic characteristics, preoperative ultrasonographic findings, and cytological results of patients with thyroid tumors of uncertain malignant potential and papillary thyroid carcinoma of classical and non-encapsulated follicular variants?

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Introduction
Thyroid tumors of uncertain malignant potential (TT-UMP) has been accepted as a subgroup of follicular-patterned thyroid tumors for which benignancy or malignancy cannot be assessed exactly. We aimed to evaluate demographic characteristics, ultrasound (US) findings, and cytological results of patients with TT-UMP and compare these findings with the classical variant of papillary thyroid carcinoma (CV-PTC) and non-encapsulated follicular variant of PTC (NEFV-PTC) patients, and also to evaluate the immunohistochemical characteristics of patients with TT-UMP.
Methods
Twenty-four patients with TT-UMP, 672 with CV-PTC, and 132 with NEFV-PTC were included to the study.
Results
Mean longitudinal nodule size and median nodule volume were higher in TT-UMP group compared to CV-PTC and NEFV-PTC groups ($P<0.001$ and $P<0.001$ for CV-PTC; $P<0.001$ and $P=0.008$ for NEFV-PTC). Presence of halo and peripheral vascularization were observed more frequently in TT-UMP group compared to CV-PTC group ($P=0.002$ and $P=0.024$). Nodule localization, texture, echogenicity, presence of microcalcification, and presence of macrocalcification were similar in TT-UMP and CV-PTC groups. US findings and cytological results were similar in TT-UMP and NEFV-PTC groups (all, $P>0.05$). Benign and follicular neoplasm/suspicious for follicular neoplasm cytological results were higher in TT-UMP group compared to CV-PTC group ($P=0.030$ and $P=0.001$). Median tumor size was higher in TT-UMP group than CV-PTC and NEFV-PTC groups (25 mm vs 6 mm, $P<0.001$ and 25 mm vs 14.4 mm, $P=0.006$, respectively). In TT-UMP group, positive expression of HBME-1, CK-19 and Gal-3 was found as 50%, 33.3%, and 25%, respectively.
Conclusion
This study demonstrated that patients with TT- UMP had higher nodule and tumor size compared to CV-PTC and NEFV-PTC patients. Moreover, we found that US features and cytological results were similar in NEFV-PTC and TT-UMP patients.

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EP1100

Comparison of the late effects of ablation therapy with single and fractionated dose of radioiodine in patients with differentiated thyroid carcinoma

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Introduction
According to a limited number of specialized hospital beds for radioiodine therapy in some countries, fractionated dose of radioiodine may be considered as the ablation therapy of differentiated thyroid cancer (DTC). Aim of the study was to compare the late effects of ablation therapy with single and fractionated dose of radioiodine in patients with DTC.
Patients and metods
Patients with DTC treated with one (131)I dose of 2.2 GBq or fractionated dose (1.1 + 1.1 GBq administered in 24-hour intervals) 5–16 weeks after thyroidectomy were retrospectively included.
Results
83 patients treated with single dose and 186 treated with fractionated dose of radioiodine were included. There were no significant differences between the groups in male to female ratio, age at the time of the first (131)I administration, proportion of papillary thyroid cancers ($P>0.05$). Also the mean duration of follow-up did not differ significantly (8.0 vs. 7.8 years respectively, $P=0.68$). There were no significant differences including the course and outcomes of the treatment between the patients treated initially with single and fractionated dose of radioiodine. Cumulated doses were 7.5 vs. 7.0 GBq, second dose of radioiodine was administered in 55.4% and 54.8% of patients, mean number of (131)I administrations during the time of follow-up was 2.0 vs. 2.2 respectively. The overall survival (OS) did not differ significantly between the groups-five years OS was 98.6% for patients treated with single and 99.5% with fractionated dose of 131-I, 10 years – 98.6 and 97.1% respectively.
Conclusions
The outcomes of treatment, expressed by percentage of patients needing second administration of radioiodine, mean number of administrations, cumulative dose of (131)I and probability of overall survival did not differ significantly. Treatment with fractionated doses (1.1 + 1.1 GBq) of (131)I administered in 24 hour intervals can be considered as equivalent alternative to the treatment with single dose of 2.2 GBq.

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EP1101

Papillary thyroid carcinoma in a thyroglossal duct Cyst (TDC) without a thyroid primary

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Introduction
Thyroglossal duct cyst (TDC) is a developmental abnormality of the thyroid gland. Malignancy arising from this duct is very rare. Due to embryological remnants of thyroid tissue located in the TDC, all malignant tumors which develop in the thyroid gland may also develop in the TDC. In case of malignancy, the most probable diagnosis is papillary thyroid carcinoma.
Case report
We present a 27-year-old female patient complaining of a midline neck mass. Ultrasonography revealed cystic lesion of 32×26 mm includes solid zone with the calcifications approximately 15 mm at the midline neck and a 4.5 mm cystic nodule at the right lobe of thyroid gland. Fine needle aspiration biopsy was nondiagnostic. She was operated and histopathologically diagnosed as papillary thyroid carcinoma arising from the thyroglossal canal. With the suspicion of metastasis of the primary thyroid papillary carcinoma total thyroidectomy and central lymph node dissection were performed. Histopathological evaluation revealed colloid goiter and reactive lymph nodes as benign cytology. There was no residual thyroid tissue or any lymph nodes on post-operative neck ultrasonography. Postoperative serum thyroglobulin level was 9.9 ng/ml and anti-thyroglobulin was negative when TSH level was high (>100 mIU/l). Radioactive iodine ablation treatment was planned.
Conclusion
Ectopic papillary thyroid carcinoma may also develop in the TDC due to embryological remnants of thyroid tissue located in the TDC. Therefore the clinician should have a high index of suspicion upon encountering papillary thyroid carcinoma of the TDC to differentiate de novo papillary thyroid carcinoma in the TDC from those originating from the thyroid gland.

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EP1102

Management and transcendence of incidental thyroid 18FDG-PET focal uptake (PEToma)

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Introduction
Incidental focal uptake in the thyroid gland is detected in 1%–2% of 18FDG-PET examinations. FNA is recommended due to an increased risk of malignancy (25–50%), but these figures are extracted from the studied cases (about a half). Moreover there is controversy about the maximum standardized uptake value (Suv_{max}) ability to discriminate between benign or malignant nodules.
Methods
We retrospectively reviewed 4207 FDG-PET scans performed for non-thyroidal reasons from January 2013 to October 2014 at our institution. Patients with focal thyroid uptake were assessed for age, sex, underlying conditions, Suv_{max}, TSH, Ultrasound, FNA cytology and pathological findings.
Results
65 cases (1.54% of PETs) showed focal thyroid uptake, 41 (63%) females, median age (SD) 70 (12) years. Median (SD) SUV_{max} was 7.4 (6), [1.4–32]. In global 49 patients (75.4%) were found to have cancer, most common lung cancer and lymphoma, and currently 19 patients (29.2%) have died. Ultrasound was performed in 36 patients (55.4%): single nodule 16, multinodular 19, normal 1; mean nodular size 16.6 (9.6) mm; in 9 cases the nodule was suspictious. Twenty-five cases (38.5%) underwent FNA. Bethesda score was I: 6 (24%); II: 10 (40%); III: 1 (4%); IV: 3 (12%); V: 1 (4%); VI: 4 (16%). Seven patients were operated on, 5 were thyroid cancer (papillary 4, anaplasic 1). Higher SUV_{max} values prompted FNA exam (P 0.01), however any relation was found between SUV_{max} and cytology (P 0.44) nor nodular size (P 0.07). There was a direct correlation

between TSH levels and SUV_{max} ($P<0.001$), but disappeared when analizing euthyroidal patients (TSH 0.5–4.5, *n* 53) *P* 0.9.
Conclusions
We report similar frequencies and clinical workup of thyroid PEToma compared to previous series. Few cases underwent thyroidectomy, however thyroid cancer was a frequent histological finding. SUV_{max} could not determine risk of malignancy.

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EP1103

The association between Nlo and Mhr in differentiated thyroid cancer

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Purpose
Papillary and follicular cancers are classified as differentiated thyroid cancers. Recently, it has been revealed that Neutrophile/lymphocyte ratio (NLO) and the ratio of monocyte/lipoprotein cholesterol with high density (MHR) are the strong indicators of oxidative stress and systemic inflammation. In this study, we intend the evaluation of all these indicators in our patients diagnosed with differentiated thyroid cancers.
Method
This study included 182 persons which 107 of them were diagnosed with differentiated thyroid cancer in our clinic and 75 of them who were healthy and no significantly different in regard to age and body mass index (BMI) statically were in the control group. The mean age of patients was 45.9 ± 14.7 years and the mean age of control group was 48.2 ± 7.7 years. There was no a significant difference statistically between them ($P=0.1$). The BMI mean of the patients was calculated as 28.0 ± 4.7 kg/kg/m^2 and the BMI mean of the control group was calculated 27.2 ± 3.3 kg/kg/m^2. It was not detected a significant difference between them statistically ($P=0.5$). Cholesterol and hematologic parameters of the patients and the control group after 12 hours fasting were evaluated after studied.
Result
It was detected a significant difference statically between the patients and the control group respectively in NLO mean (3.2 ± 2.8 and 2.4 ± 1.3 $P=0.013$), MHR ratio (0.038 ± 0.05 and 0.1 ± 0.07 $P=0.000$) as the result of the study. In the correlation analysis, there was a positive correlation respectively MHR and Neutrophile($r=0.4$ $P=0.000$), lymphocyte ($r=0.4$ $P=0.000$) and thyroglobuline ($r=0.4$ $P=0.000$), and it was determined a negative correlation between NLO and respectively lymphocyte ($r=-0.2$ $P=0.000$), monocyte ($r=-0.18$ $P=0.01$).
Discussion
It was observed that differentiated thyroid cancers increase systemic inflammation based on the data provided by this study.

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EP1104

Thyroid cancer in hyperthyroid patients treated by surgery

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Introduction
The association of hyperthyroidism and thyroid cancer (TC) is controversial with prevalences in the literature varying from 1.6 to 32.8%. The aim of this work was to evaluate the prevalence of TC in hyperthyroid patients submitted to surgery and to find differences between the tumors according to the type of hyperthyroidism.
Material and methods
retrospective study to evaluate clinical and histopathological data of all hyperthyroid patients older than 18 years that underwent thyroid surgery between 2005 and 2015 at our Hospital. Statistics was done with SPSS 22.0 for windows.
Results
In this period 413 hyperthyroid patients were submitted to surgery, 347 females and 66 males, 108 (26.2%) with Graves Disease (GD), 263(63.7%) with Multinodular Toxic Goiter (MNTG) and 42 (10.2%) with Toxic Adenoma (TA). Concerning sex distribution there was no statistical difference between the 3 groups. The mean age in GD was significantly lower than in TMNG (43.9 ± 13.2 vs 58 ± 13.9 years) and in TA (43.9 ± 13.2 vs 50.5 ± 16.2 years). Histologic examination revealed TC in 89 patients (21.5%) with mean diameter of the tumors of 0.88 cm (0.1–6.5 cm). The majority of the tumors were incidental findings (82%). Concerning the type of surgery performed, total thyroidectomy was more frequent in GD and TMNG compared to TA (97.2% and 94.7% respectively vs 21.4%).The prevalence of TC was 25.1% for TMNG, 16.7% for GD and 11.9% for TA. Histopathology examination revealed Papillary thyroid cancer in the majority of cancer patients, 16/18 (88.9%) in GD, 60/66 (90.9%) in TMNG and 4/5 (80%) in TA. There were no significant differences in tumor size, incidental finding, presence of thyroiditis, extrathyroidal extension, lymphovascular invasion and ganglionar metastasis between the 3 groups.
Conclusion
In our series we found a high prevalence of TC in hyperthyroid patients (21.5%), higher than the majority of the series in the previous literature.

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EP1105

The increased coexistence of autoimmune thyroiditis (AIT) in children and adolescents with thyroid carcinoma (TC) in years 2001–2015 compared to years 1996–2000

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Introduction
In years 1996–2000, the predominance of papillary thyroid carcinoma (PTC) (70.3%) compared to follicular thyroid carcinoma (FTC; 27.0%) and medullary thyroid carcinoma (MTC; 2.7%) was observed in our region. AIT coexisted in 1 PTC (2.7% of all cancers and 3.8% in PTC group).
Aim
The aim of retrospective study was to analyze the coexistence of AIT and TC in years 2001-2015 in relation to years 1996–2000.
Material and methods
Patients aged <18 years with the histopathological diagnosis of TC were analyzed. AIT was confirmed by the presence of antithyroid antibodies in serum or based on cytological result obtained from biopsy.
Results
47 TCs were confirmed in 2001–2015 (41 PTC, 1 FTC and 5 MTC) in 37 girls (78.7%) and 10 boys (22.3%). AIT coexisted only with PTC, in 4/13 (30.7%) 2001–2005, in 2/8 (25.0%) 2006–2010 and in 11/20 (55.0%) 2010–2015. The incidence of PTC/AIT coexistence in 2001–2015 was 41.4% (17/41), i.e. 10-fold more frequent than in 1996–2000.
Conclusions
High risk of the coexistence of PTC and AIT in years 2001–2015 suggests that the careful follow-up of patients with AIT is mandatory.

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EP1106

Biochemical effects of levothyroxine withdrawal in patients with differentiated thyroid cancer

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Background
Many patients with differentiated thyroid cancer (DTC) are treated with radiodine (I-131) after thyroidectomy, while they are hypothyroid and all are submitted to withdrawal of LT4 periodically for the evaluation of their disease. Among the tests used for follow-up is serum thyroglobulin (Tg) as a tumor marker, and occasionally, total body scan with I-131. Maximal sensitivity of the aforementioned tests is established in the hypothyroid state, under elevated thyrotropin (TSH) concentrations, achieved with LT4 withdrawal. The aim of our study was to determine the degree of change in several biochemical parameters due to a short-term but acutely supervening hypothyroidism.
Patients and methods
A total of 345 patients, 60 males (17%) and 285 (83%) females, with a history of DTC were enrolled in the study. Their mean age ($\pm$S.D.) was 54.7$\pm$13.6 years (range = 17–83 years). Their biochemical profile and serum free triiodothyronine (FT3), free thyroxine (FT4) and thyrotropin (TSH) levels were measured during withdrawal of LT4 treatment, and several months after restarting LT4.
Results
During withdrawal, the intra-individual percentage increase in total cholesterol, low density lipoprotein-cholesterol, very low density lipoprotein-cholesterol and triglycerides was of the order of 60–80% and that for high density lipoprotein-cholesterol 30%. Creatinine increased by 30%, whereas Na and K levels decreased by 1%. The increase for creatine phosphate kinase was around 200–300%, for aspartate aminotransferase and alanine aminotransferase 50–80%, for γ-glutamyl transpeptidase 10–20%, and for lactate dehydrogenase 25%. Glucose decreased by 1–4%.
Conclusion
Acute, short- term hypothyroidism has significant impact on many biochemical parameters, reflecting the relative alterations in many organ functions and metabolic pathways. Patients with borderline biochemical parameters, such as creatinine, electrolytes or aminotransferases during euthyroidism, may show significant deterioration of these parameters during hypothyroidism. The presence of other diseases should be considered before submitting these patients to LT4 withdrawal.

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EP1107

Baicalein induces cell apoptosis via the MAPK pathway in FRO anaplastic thyroid cancer cells

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Baicalein induces cell apoptosis via the MAPK pathway in FRO anaplastic thyroid cancer cells.
Anaplastic thyroid cancer is one of the most aggressive forms of malignancies which grow very rapidly. Although several conventional medications have been applied for the treatment of anaplastic thyroid cancer, but current therapies still rather limited and novel therapeutic strategies are required. Baicalein is a flavone, a type of flavonoid, originally isolated from the roots of *Scutellaria baicaiensis* and *S. lateriflora*, and is known various biological properties such as antiinflammation, antioxidation, neuroprotection, antiallergy, and anticancer etc. In this present study, we aimed to investigate the potential effects of baicalein on FRO anaplastic thyroid cancer cells and the underlying mechanisms through which baicalein exerts its action.
Cell viability assay was indicated that baicalein potently suppressed the cell growth in a time- and dose-dependent manner. We also found that baicalein can induce the expression of apoptotic proteins, Bax, cleaved caspase-3, PARP, and Cox-2 and the phosphorylation of ERK, JNK, and p38 MAPK in a dose-dependent manner. Moreover, baicalein decreased the expression levels of E-cadherin and N-cadherin in FRO cells.
In conclusion, these findings suggested that baicalein can induce apoptosis in anaplastic thyroid cancer cells through inhibition of the MAPK pathway.

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EP1108

Ultrasonographical, clinical and histopathological features of 1264 nodules with papillary thyroid carcinoma and microcarcinoma based on tumor size

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Introduction
In recent years, due to the improvements in ultrasonography (US), it has become possible to gain more information about the papillary throid carcinoma (PTC) and papillary tyroid microcarcinoma (PTMC). However, whether PTC and PTMC exhibit the same ultrasonographic features and behave same features is controversial. We aimed to evaluate the patients diagnosed with PTC and PTMC in terms of clinical, ultrasonographical (US) and histopathological features and their relationships with tumor size.
Methods
We retrospectively evaluated 881 patients who underwent thyroid surgery between 2007 and 2014 in our clinic and diagnosed with PTC histopathologically were enrolled the study. Demographic characteristics, US findings and histopathological features were evaluated.
Results
In total, 1264 nodules were identified in the 881 patients. The incidentality rates were higher in the PTMC group and also in the $\leq$5 mm group. In total multifocality rate was 32.9%, and it was significantly higher in PTMC group than the PTC group. PTC and $>$5 mm PTMC groups compared to PTMC and $\leq$5 mm groups respectively, were more aggresive histopathological features
Conclusion
Since the incidentality rates were found significantly more common in our patients with PTMC and those with $\leq$5 mm, ultrasonographic features of the nodules should be evaluated carefully and for cases which are suspicious with US, US-guided fine needle aspiration biopsy (FNAB) should be considered in order to make the correct treatment strategy. Also our study revealed that PTC and $>$5 mm PTMC groups compared to PTMC and $\leq$5 mm groups respectively, have more aggresive histopathological features.

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EP1109

Screening and follow up of an extended Hungarian family with familial medullary thyroid cancer

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Medullary thyroid carcinoma (MTC) originates from the parafollicular or C cells of the thyroid gland and represents approximately 10% of all thyroid malignancies. The operational classification of FMTC is four or more family members with MTC without objective evidence of pheochromocytoma (PC) and parathyroid hyperplasia. In multiple endocrine neoplasia type 2A (MEN 2A) and familial medullary thyroid cancer (FMTC), the majority of germline mutations are restricted to specific positions in exons 10 and 11 of the *RET* gene. Germline mutations may very occasionally occur in other exons, including exon 14 of the *RET* gene. 1n 2000 we reported a large kindred where the V804M mutation and the S836S variant were identified and only the V804M mutation associated with FMTC. That time 80 members of the family were evaluated. In the past 15 years the family has grown to 281 members. In our current study we summarized the follow-up data obtained in patients with *RET* V804M mutation of this family. Molecular screening of the family in the second generation indicated 6 genetically positive patient from 13 that they have germline V804L mutation and a germline S836S polymorphism in separate alleles in exon 14 of the *RET* gene. Five of the six positive members were operated for medullary thyroid cancer, one patient with known high level of calcitonin and nodular thyroid refused the surgery. However, based on the 15 years of follow up data the cancer patients and the other mutation carriers, showed no disease progression. None of the other family members with positive genetic test had clinical or biochemical evidence of MTC This current data confirm that the V804M mutation associates with FMTC presenting as a mild phenotype.

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EP1110

Comparisson between two differnet protocols for the management of patients with differnetiated thyroid cancer

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Introduction
New techniques such as etapification ecotomography (EE) have led to less invasive surgeries in Differentiated Thyroid Cancer (DTC). The trend in recent years has been to a reduction in the doses of radioiodine administered. Our hospital in 2013 incorporated these features to protocolize the administration of radioiodine depending on the characteristics of the tumour and the initial thyroglobulin levels, which may have had an impact in the response to treatment (RT) compared to our previous practice.
Methods
Analysis of clinical records from patients that underwent Total Thyroidectomy for DTC. Protocol 2012: no EE and RI dose between 50-200 mCi. Protocol 2013, with EE and RI dose between 0-150 mCi. Patients were classified according to the ATA risk for recurrence scale. RT was evaluated after one year as excellent, acceptable or incomplete.
Results
84 patients from the 2012 protocol and 93 patients from the 2013 protocol were analyzed. Age, sex and histology were comparable between both groups. The 2013 group underwent more conservative surgeries with a lower percentage of patients undergoing lateral dissections. The ATA risk distribution was comparable between the two groups ($P=0.978$) Radioiodine dosages administered to the 2013 group were significantly lower according to their risk group. The RT distribution at one year follow up was similar between both groups. The percentage of patients with an excellent response was comparable in the Low Risk (2012: 80 vs 2013: 88% ; $P=0.22$) Intermediate Risk (2012: 62.5 vs 2013: 70.2% $P=0.446$) and High Risk (2012: 38 vs 2013: 50% $P=0.546$) ATA categories.
Conclusions
We observed that the 2013 protocol has a RT comparable to the 2012 protocol. This allowed us to perform less invasive surgeries due to the incorporation of EE and it supports the use of lower doses of RI.

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EP1111

Thyroid medullary and papillary carcinoma, a rare combination

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Introduction
Thyroid papillary carcinomas originate from thyroid follicular epithelia and are the most frequent thyroid differentiated carcinomas. Medullary thyroid carcinomas originate from thyroid parafollicular C cells and %25 are a component of Multiple Endocrine Neoplasia (MEN) syndromes. Co-incidence of the two condition on the same patient is so rare.
Case
78 years old female patient who has had simple goiter for 10 years, was investigated about weight loss and palpitation. In the first visit thyroid function tests and ultrasonography (USG) was applied. Thyrotropin level was <0.0025 mIU/ml and there was a 38×35 mm solid nodule on the right thyroid lobe (Picture-1). Thyroid scintigraphy showed increased tracer uptake on the right lobe and extremely decreased uptake on the left lobe (Picture-2). The patient was informed about the treatment choices and decided to be operated. Before the surgery fine needle aspiration biopsy (FNAB) was applied, the result was suspicious for malignancy.
First, right lobectomy was performed and sent to the frozen. The result was follicular lesion. According to this result total thyroidectomy was performed. The pathology result of the left lobe was papillary microcarcinoma 4×3 mm at diameter, no vascular invasion, no capsule invasion and no extra-thyroidal involvement. The pathology of the tissue that had been resulted as follicular lesion on frozen, resulted as medullary microcarcinoma 3×2 mm at diameter. The tumor was surrounded by fibrous band and there were cell groups that belong to the lesion on the adjacent thyroid tissue. There was no vascular and extra-thyroidal involvement. Because of the <5 mm tumor size and low risk factors close follow-up was planned.
Conclusion
Either papillary and medullary carcinoma on the same patient is a very rare condition and on the follow-up need to be evaluated either with serum thyroglobulin and calcitonin levels.

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EP1112

"Modified thyroidectomy difficultly score" for goiters in Iodine deficient population

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Introduction
Thyroid surgery was initially considered as "horrid butchery" due to associated high morbidity and mortality, however with the advent of safe surgical techniques and improved understanding of thyroid physiology, thyroid surgery has become safer. Still there are certain intra-operative factors, as described in Difficulty Thyroidectomy Scale (DTS)which are thought to be associated with adverse outcome. However anatomical parameters also need to be addressed to make it more reliable and effective. So, aim of this study was to use Modified thyroidectomy difficulty scale (MTDS) and to know if anatomical variations also contribute.
Material and Methods
Prospective study on patients who underwent thyroidectomy at Department of Endocrine Surgery, SGPGIMS. We designed a MTDS (4 itemed thyroidectomy difficulty scale with various anatomical parameters like location & branching of recurrent laryngeal nerve, type of external branch of superior laryngeal nerve, parathyroid glands, grade of tubercle of Zuckerkandl (TZ), and retrosternal extension). It was filled by two endocrine surgeons blinded to each other at the end of operation. Analysis was done to look for inter-observer variability and also to compare surgical outcome in terms of operating time and complication rates.
Results
Total 30 patients were assessed on Modified thyroidectomy difficulty score. Cohort included 15 (50%) euthyroid goiters, 12 (40%) toxic goiters, 2 (6.67%) malignant and 1 (3.33%) patient of thyroiditis. Among both trainees, total and individual parametric scores exhibited a high degree of correlation, which rules out any observational bias. DTS correlates significantly with operating time $P<0.01$, hypoparathyroidism $P=0.05$ and nerve palsy $P<0.01$, where MTDS correlates more strongly with operating time <0.01, hypoparathyroidism $P=0.02$ and nerve palsy $P<0.01$. In difficulty score gland size ($P=0.00$) and fibrosis ($P=0.04$) were significant factors. In modified score TZ grading ($P=0.003$) was the only factor.
Conclusion
Modified thyroidectomy score correlates more strongly with the operative time and complication rates.

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EP1113

Role of early ^{18}F-FDG PET/CT in the management of differentiated thyroid cancer patients with negative ^{131}I scan and elevated thyroglobulin levels

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Background
Early detection of residual or recurrent cancer in patients with differentiated thyroid cancer (DTC) is important, especially, when they do not uptake ^{131}I uptake because these tumors do not likely benefit from radioiodine therapy (RAIT). We aimed to evaluate the usefulness of FDG-PET/CT as an early diagnostic work up in DTC patients with negative radioiodine whole body scan (I-WBS) and elevated stimulated Tg (sTg) levels.

Methods
This was a retrospective study. There were 48 consecutive patients with negative I-WBS and elevated sTg level (>5 ng/ml) or positive Tg antibodies (TgAb). FDG-PET/CT was performed within 12 months after first remnant ablation. True positive rate and positive predictive value was calculated according to different sTg levels (ng/ml). [$5 \leq$ sTg <10 ($n=11$), $10 \leq$ sTg <20 ($n=14$), ≥ 20 ($n=19$)] and positive anti-thyroglobulin antibodies ($n=4$).
Results
FDG-PET/CT showed 12 (25%) true positive, 6 (%) false positive, 22 (38%) true negative and 12 (21%) false negative results (sensitivity 60% specificity 79%). True positive FDG-PET/CT leaded to additional surgery in 10 (21%) DTC patients. True positive rate increased as sTg (ng/ml) level increases [9% in sTg between 5–10, 21% in sTg between 10–20, 37% in sTg >20 and 25% in positive TgAb]. Positive predictive value tended to increase with sTg increment [50% in sTg between 5–10, 50% in sTg between 10 and 20, 88% in sTg >20 ng/ml and 50% in positive TgAb].
Conclusions
Early FDG-PET/CT is useful tool for tumor detection in DTC patients with negative I-WBS and increased sTg levels and may change a treatment plan, especially when sTg during I-WBS was greater than 20 ng/ml.

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EP1114

Markers predicting the contralateral lobe involvement in patients with multifocal papillary thyroid carcinoma: An instutional case series of 914 patients

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Background
The characteristics of multifocal PTC remain controversial. Surgical approach to multifocal tumor changes between centers. In cases that the initial procedure was lobectomy, most clinicians would suggest for completion thyroidectomy since the risk of PTC in the contralateral lobe is significant. This study aimed to evaluate the incidence of bilateral involvement, predictive factors for bilaterality and whether or not bilaterality was related with more aggressive histopathologic features in patients with multifocal PTC.
Method
Medical records and pathologic data of 914 patients who underwent total thyroidectomy and diagnosed with PTC were retrospectively reviewed. The patients with multifocal disease were detected and subdivided into two subgroups as unilateral-multifocal PTCs and bilateral multifocal PTCs. These two groups were compared to each other regarding demographic, clinical and histopathological features.
Result
Multifocal disease was detected in 294 patients (32.7%). Of all, 102 patients (36.7%) had unilateral whereas 192 cases (65.3%) had bilateral involvement. As a result of univariate analysis, bilaterality was significantly associated with the number of tumor foci ($P<0.001$), tumor size ($P=0.008$), TSH ($P=0.002$) and capsule invasion ($P=0.018$). Multivariate analysis demonstrated that the number of tumor foci and TSH level were independent risk factors for bilaterality in multifocal PTC ($P<0.001$ and $P=0.006$, respectively).
Conclusion
Incidence of bilateral tumors is high and increases with the number of tumor foci in multifocal PTC. Bilateral involvement in multifocal PTC is not associated with worse histopathological futures.TSH can be taken as a preoperative indicator able to predict multifocal cancers and guide clinical decision making and surgical management.

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EP1115

Abstract withdrawn.

EP1116

Thyroid nodules classified as bethesda 3: final diagnosis

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Introduction
The Bethesda System classifies suspicious thyroid nodules or those with a large size after fine-needle aspiration (FNA) depending on the risk of malignancy through its cytology study. Bethesda category 3 (B3) implies atypia of uncertain significance or follicular lesion of undetermined significance. Objectives: To determine the final diagnosis of category B3 nodules and the number of cases in which a second or third FNA results in a conclusive category (B2, B4, B5 or B6).
Methods
Observational retrospective study of patients with thyroid nodules classified as B3, evaluated between January 2012-December 2015 at "Hospital Universitario Reina Sofía" in Córdoba. Results were analysed with SPSS 19.0. Statistical analysis: Student's t-test to compare means and Chi-squared test/ Fisher's exact test to compare proportions.
Results
88 patients, 83% females. Mean age: 52.8 ± 13.9 years old. 65.9% of nodules were suspicious on ultrasonography. Maximum diameter: 29.9 ± 14.1 mm. 22.8% of patients had symptoms related to their nodules, being dysphagia the most prevalent. 61.4% of patients underwent surgical treatment, 55.6% of which were thyroidectomies. Final diagnosis: 15.9% malignant, 45.5% benign and 38.6% unknown. Final diagnosis after surgery: 42.6% adenoma, 21.1% benign follicular nodule, 18.5% papillary carcinoma, 5.6% nodular Hashimoto and 12.2% others. In the 75 nodules firstly classified as B3, a second FNA (performed in 45 patients) was conclusive in 21 patients (46.6%). A third FNA (7 patients) was determinate in 3 of them (42.9%). We didn't find a statistically significant association between malignant or benign disease with gender, age, symptomatology or size/sonographic features of nodules in our series.
Conclusions
The prevalence of thyroid malignant illness classified as B3 in our study is concordant with the previous published studies, being adenoma the most frequent pathology after thyroidectomy. In nodules firstly categorized as B3, a second or third FNA is determinate in less than half of the cases.

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EP1117

Association of multifocality, tumor number and total tumor diameter with clinicopathological features in papillary thyroid cancer

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Introduction
In this study, we aimed to evaluate impact of multifocality, tumor number and total tumor diameter on clinicopathological features of PTC.
Methods
Medical records of 912 patients who underwent thyroidectomy and diagnosed with PTC were reviewed retrospectively. Patients were grouped into 4 according to number of tumoral foci; N1 (1 focus), N2 (2 foci), N3 (3 foci) and N4 (≥ 4 foci). The diameter of the largest tumor was considered as the primary tumor diameter (PTD) and total tumor diameter (TTD) was calculated as the sum of the maximal diameter of each lesion in multicentric tumors.
Results
Capsular invasion, extrathyroidal extension and lymph node metastasis were significantly higher in patients with multifocal tumors compared to patients with unifocal PTC. As the number of tumor increased, extrathyroidal extension and lymph node metastasis also increased ($P=0.034$ and $P=0.004$, respectively). The risk of lymph node metastasis was 2.287 (OR $=2.287$, $P=0.036$) times higher in N3 and 3.449 (OR $=3.449$, $P=0.001$) times higher in N4 compared to N1. Capsular invasion, extrathyroidal extension and lymph node metastasis were significantly higher in multifocal patients with PTD ≤ 10 mm and TTD >10 mm than unifocal patients with tumor diameter ≤ 10 mm ($P<0.001$, $P<0.001$ and $P=0.001$, respectively). There was no significant difference in terms of these parameters in multifocal patients with PTD ≤ 10 mm and TTD >10 mm and unifocal patients with tumor diameter >10 mm.

Conclusion
In this study, increased tumor number was associated with higher rate of capsular invasion, extrathyroidal extension and lymph node metastasis. In a patient with multifocal papillary microcarcinoma, TTD > 10 mm confers a similar risk of aggressive histopathological behavior with unifocal PTC greater than 10 mm.

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EP1118

Medullary thyroid cancer (MTC): descriptive analysis and prognostic factors in a multicenter study

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Introduction
MTC accounts for 5% of thyroid cancers and can occur sporadically or as part of the multiple endocrine neoplasia type 2 syndrome (MEN 2). The objective of our study is to evaluate the prognostic factors and outcomes of patients with MTC in the community setting.
Methods
Retrospective descriptive multicenter study of patients with histological diagnosis of MTC**.** Descriptive, bivariate analyses (Student t for cuantitative and X^2 test for cualitative variables) and logistic regression with SPSS 19.0 were performed.
Results
102 patients were included (62% females). Median age at diagnosis: 45 ± 16 years. Mean follow-up: 8 years. RET proto-oncogene mutations were found in 52% mainly in codon 634 (24.5%). Average basal calcitonin was 1497 ± 3521 (median 402 pg/ml) and CEA 66 ± 130 ng/ml. All cases underwent total thyroidectomy, with cervical lymphadenectomy in 64 cases (63%). Stage after surgery was I: 39%, II: 13%, III: 14% and IV: 34%. Residual disease was found in 44.5% (40% biochemical evidence of disease, 36% loco-regional metastasis and 24% distant metastasis). They were treated with additional surgery (44%), radiotherapy (11%) and/or tyrosinkinase inhibitors (13%). At the end of the follow up, 48% patients remained free of disease, 9% had calcitonin/CEA levels elevated without disease location, 8% had locorregional disease and 8% distant metastasis; 5 patients died because of MTC. On bivariate analysis, absence of cromogranin A staining, stage, local invasion, male sex, size, presurgery calcitonin levels were statistically significant predictors of residual disease after surgery whereas local invasion, stage, size, pre and postsurgery calcitonin and postsurgery CEA levels predicted persistent disease at the end of follow-up. Stage remained the only statistically significant indicator of both residual disease after surgery and persistent disease at last follow up on logistic regression analysis.
Conclusions
Only staging was significantly associated with persistent disease after surgery and at the end of follow-up.

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EP1119

Visualization of kallikreins in thyroid epithelial and carcinoma cells

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Human tissue kallikreins (KLKs) are serine proteases expressed in various organs including thyroid hormone-generating and target tissues. Besides their involvement in important physiological processes, KLKs are mainly recognized for their association with pathological conditions like cancer. Previously, KLK2 and KLK3 transcripts were detected in normal thyroid and carcinoma tissue, while the levels and subcellular distribution of KLK proteins remained largely elusive. Since the thyroid gland is a hormonally regulated organ, we were interested in investigating possible changes of KLK levels and localization in thyroid epithelial and carcinoma cells upon stimulation with the thyroid stimulating hormone (TSH). The results revealed a redistribution of KLK2 and KLK3 from centrally to peripherally located vesicles upon TSH stimulation of thyroid epithelial cells, indicating TSH-regulated trafficking of KLKs in normal thyrocytes. Moreover, KLK2 and KLK3 were localized to the nuclei of thyroid carcinoma cells, but they were not detectable at this unexpected subcellular localization in thyroid epithelial cells. Thus, KLKs might contribute to thyroid carcinogenesis in different ways, i.e. by their enhanced expression and thus altered protein homeostasis, and by proteolytically processing nuclear substrates which are involved in the regulation of cell cycle progression.

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EP1120

Management of thyroid cancer in outpatient practice

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The incidence of thyroid cancer (TC) is increasing over time. Follow up and adequate treatment of patients with TC is important in everyday routine practice. The aim of the study was to evaluate peculiarities of clinical and pathologic characteristics of patients with TC, and their management after surgery.
Material and methods
We conducted retrospective review of medical records of 116 patients with TC after thyroid surgery followed up in Vilnius Antakalnio out–patient clinic. We recorded demographic, clinical characteristics, TC morphology and extension, treatment and TSH changes.
Results
Mean patients' age was 57.24 ± 16.45 years (87.1% female). Mean age at surgery was 49.04 ± 15.56 years. 44.9% patients were 41–60 years old at the time of surgery. 88.8% of patients had multinodular goitre. 107 patients had papillary TC, 5 medullary, 4 other type. 22.9% patients had capsular invasion, 14.0% – vascular invasion, 19.2% – lymph node metastases. Patients with TC with vascular invasion were older than patients with TC without vascular invasion (37.62 ± 15.08 vs 49.30 ± 15.00, $P = 0.011$). 67.3% patients were diagnosed at stage 1, 9.6% at stage 2, 19.2% at stage 3 and 3.8% had stage 4 disease. Mean TSH before surgery was 2.01 ± 1.87 mUI/l. Neither the presence of extra thyroidal extension, nor vascular invasion, nor cancer stage was associated with TSH levels. Total thyroidectomy was performed in 90.5% of patients and hemithyroidectomy in 9.5%. Radioiodine was administered to 94 patients. Patients have been followed up for 6.50 ± 5.74 year (range 0–26). Mean daily dose of L-thyroxin was 133.81 ± 35.59 mcg (1.85 ± 0.56 mcg/kg) keeping TSH suppression at the level of 0.43 ± 0.65 mUI/l (range 0-3.63). L-thyroxin dose correlated with patient's weight ($P < 0.0001$).
Conclusions
Most frequently thyroid cancer is diagnosed in 41–60 years' women and presents as multinodular goitre, and papillary carcinoma. Long-term TSH suppression after thyroid cancer surgery is kept in conformity with recommendations.

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EP1121

One thyroid, three tumors within: a case of three collision tumors

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Introduction
Collision tumors of the thyroid are neoplasms of distinct histology located within the same gland. Although rare, the most commonly described collision tumors of

thyroid origin are medullary and papillary carcinomas. We describe a case of co-existence of a benign follicular adenoma in a dominant nodule with a micropapillary and a micromedullary carcinoma in a patient carrying a heterozygous germline RET polymorphism.

Case report

A 74-year-old woman presented for follow up at the Endocrine Clinic, with a history of thyroidectomy 10 years previously. Surgery had been recommended because of a growing nodule at the isthmus, despite normal cytology at the preceding FNA, biochemical euthyroidism and negative thyroid antibodies. Histological examination revealed a 2.8 cm encapsulated follicular adenoma at the isthmus, a 0.3 medullary thyroid carcinoma in the right thyroid lobe with evidence of infiltration of surrounding follicles and microscopic lymphatic vessel infiltration and a 0.3 cm classic type papillary thyroid carcinoma in the left thyroid lobe.

The patient's past medical history is notable for rheumatoid arthritis and Sjogren's syndrome with associated pulmonary disease and a non-functioning left adrenal adenoma. There was no evidence of MEN2 features other than MTC in our patient, nor in any family members.

On ultrasound examination, a 1.4 cm vascularized remnant was visible in the left thyroid bed, with no evidence of cervical lymphadenopathy. Biochemical testing showed normal calcitonin at 3.23 pg/ml (<4.8), TSH 0.56 on L- thyroxine 88 μg daily, thyroglobulin <0.2 ng/ml and negative anti-TG.

RET oncogene direct sequencing revealed a germline G691S/S904S polymorphism in heterozygosity.

Conclusion

The RET G691S/S904S polymorphism has been postulated as genetic modifier of MEN2A, although the association of this haplotype with MTC and, moreover, with follicular neoplasia, remains unknown.

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EP1122

A study on age and nodule size in affecting decision for repeat thyroid FNAC after one benign cytology

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Introduction

Fine needle aspiration cytology (FNAC) is a widely adopted pre-operative investigatory tool for thyroid nodules. The British Thyroid Association (BTA) recently updated guidelines recommending that an FNAC that initially yields benign cytology (Thy2) should be repeated if there is any clinical or ultrasound (US) suspicion (1). We postulate that there is a tendency for a more conservative approach in older age groups with smaller thyroid nodules on US studies.

Method

From our multidisciplinary meeting (MDM) database for thyroid nodules under investigation from 2012–2015, we identified 126 cases with a single Thy2 cytology. Cases were recommended for clinical or US surveillance, repeat FNAC or surgery. The mean age and nodule size was compared for the group recommended a more conservative approach (clinical or US surveillance) and the group recommended repeat FNAC or surgery. The mean difference was examined and independent t-test applied.

Results

The group recommended for US (36 cases, 29%) or clinical surveillance (28 cases, 22%) has a mean age of 56.7 ± 16.7 years with a mean nodule size of 25.1 ± 15.2 mm (data are mean $\pm$ standard deviation). The group recommended for surgery (9 cases, 7%) or repeat FNAC (53 cases 42%) has a younger mean age of 47 ± 15.2 years with a larger mean nodule size at 33.7 ± 15.2 mm. Between these groups, there is a mean difference of 9.7 years ($P=0.001$) for age and 8.5 mm for nodule size ($P=0.002$).

Conclusion

After one benign thyroid cytology, there is a tendency for a more conservative approach with US and clinical surveillance in older patients with smaller nodule size. From this study, the thresholds directing such decisions lie at approximately 50 years of age and a nodule size of 30 mm.

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EP1123

Analysis of BRAF and RAS genetic alterations in thyroid cancer in the Greek population

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Introduction

Thyroid cancer is one of the most common malignancies of the endocrine system and displays a variety of histological patterns. The understanding of the molecular pathogenesis and the identification of molecular markers which will be used for diagnosis and prognosis is of high clinical significance. The most common molecular alterations include *BRAF* and *RAS* point mutations and *RET/PTC* and *PAX8/PPARγ* rearrangements. The present study investigated the association of *BRAF* and *RAS* mutations with thyroid cancer in a representative sample of the Greek population.

Methods

The study included 65 patients: 54 with Papillary Thyroid Cancer (PTC), 7 with Follicular, 3 with Medullary and 1 with Low Differentiation Thyroid Cancer. Following the isolation of genomic DNA from tissue biopsies a) real-time Polymerase Chain Reaction (PCR) and b) PCR and sequencing were used for the identification of mutations in codon 600 of the BRAF gene and in codons 12, 13 and 61 of the *HRAS, KRAS* and *NRAS* genes.

Results

BRAF mutations were identified in 8 PTC samples, half of which were of follicular subtype. All mutations include a 1799T→A conversion and a valine to glutamic acid substitution at codon 600. A PTC of follicular subtype was identified harboring a mutation in the *NRAS* gene (181C→A, resulting in a glutamine to lysine change in codon 61). Both mutations result in the activation of the MAP kinase signaling pathway. No mutations were identified in the specific codons of *KRAS* and *HRAS* genes.

Conclusion

Although the sample number is relatively small, the significantly low percentages of *BRAF* and *RAS* mutations point to the conclusion that the molecular alterations leading to thyroid cancer in the Greek Population may differ compared to those previously reported, and this consideration should be taken into account regarding the pathogenesis, progression and treatment of thyroid cancer.

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EP1124

Adjuvant metformin (M) therapy in differentiated thyroid carcinoma (DTC)

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M shows an antiproliferative effect. In vivo, M reduces TSH in type 2 diabetes mellitus (T2DM) and DTC aggressiveness in DTC with T2DM. The aim of the study was to evaluate in DTC diabetic (Gr1, $n=30$ under M 1500 mg/day) and non-diabetic without (Gr2, $n=83$) or under M (gr3, $n=84$; M 1000 mg/day) the adjuvant role of M. Clinical and laboratory examinations were performed up to 24 months. At baseline the DTC groups were similar for age, gender, tumor stage, disease duration, L-T4 dosage and % of subjects under statins. Only BMI was higher in Gr1 and Gr3 respect to the Gr2. The RAI therapy was carried out with lower percentage ($P=0.03$) in the Gr1 than in the other groups. The patients did not have changes in oncological disease, BMI and L-T4 dosage. In DTC patients without T2DM compliance and tolerability towards M fairly. The most frequent adverse events were gastrointestinal. Several Gr3 patients showed weight loss. M adjuvant therapy resulted in a decrease of TSH levels in Gr3, initially higher ($P<0.0001$) compared to the Gr2, with overlapping values assessment at 12–24 months. After the beginning of M the in Gr3, insulin levels were significant ($P=0.05$) lower in Gr3 then in Gr2. In only Gr3 an improvement of the lipid profile was noted. Our data confirm the favorable evolution of the DTC and the high number of DTC with obesity and metabolic disorders. In our T2DM with DTC we have conflicting data (reduction in the use of RAI therapy vs higher number of subjects with detectable thyroglobulin). Difficult is the start of M in DTC patients, but its effects seem to favorable on TSH levels and lipidic status. Our data seem to indicate that *in vivo* M has a partial adjuvant action. More observation time and a wider coverage are needed.

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EP1125

Anaplastic thyroid carcinoma masquerading as subacute thyroiditis

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Anaplastic thyroid carcinoma (ATC) is a rare form of thyroid carcinoma that is associated with an extremely poor prognosis. Ultrasonography (US) and subsequent fine needle aspiration biopsy (FNAB) are the first diagnostic methods in the assessment of a palpable thyroid mass. Nevertheless, some clinical and US features of ATC are not specific. Here, we report on an extremely rare case of ATC masquerading as subacute thyroiditis (SAT).
A 40-year-old woman was admitted to our hospital for an examination of a rapidly growing thyroid mass with slight pain in the neck. Three weeks before admission, the patient noticed the mass on the right side of her neck, with discomfort while swallowing. The woman had a history of antecedent viral symptoms. Physical examination revealed an approximately 3 cm hard and tender mass palpable on the right thyroid lobe. The laboratory inflammation markers, except for the erythrocyte sedimentation rate, were within normal range. Thyroid hormones concentration and antithyroglobulin antibodies were normal. A chest X-ray and the abdominal US didn't show any pathology. Thyroid ultrasound revealed a 3.4×2.6 cm mass with marked hypoechogenicity, ill-defined margins, and no blood supply. Reactive and enlarged neck lymph nodes (level III–IV) were detected. Sonographically, the thyroid lesions were indicative of SAT differentiated from thyroid abscess. FNAB from suspicious thyroid was performed. On cytologic examination, tumor cells with plentiful of neutrophils were assessed, while the direct smear and culture were negative for bacteria. Total thyroidectomy and enlarged neck lymph node dissection were performed. The post-surgical pathologic assessment did not reveal any lymph node metastasis. Histopathologically, ATC was evaluated.
This case demonstrates an extremely rare case of ATC that mimics SAT and thyroid abscess. In the case of atypical clinical and ultrasonographic features of SAT, a careful examination for thyroid malignancy should be proposed.

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EP1126

From thyroidectomy to thyroid cancer: epidemiological data from 2004 to 2014

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Background and aims
To evaluate the evolution of thyroid cancer epidemiological characteristics from 2004 to 2014.
Materials and methods
Retrospective analysis of histological data from thyroidectomies performed in our hospital in the period 2004–2014.
Results
From 2004 to 2014, 2725 thyroidectomies (women 81% vs men 19%) were performed in our hospital. In 1083 of these (40%) histologic examination revealed thyroid cancer.
Thirty-four percent of all cancers were diagnosed from 2004 to 2010, while this percentage arises to 66% during the last four years. Median age at diagnosis was 49.2 years.
In almost half (43.7%) of thyroid cancer patients, Hashimoto's thyroiditis coexisted.
Forty-eight percent of cancers were multifocal, whereas in the remaining 52% there was found a single focus on histologic examination. In the multifocal cancers, median maximum focus was less than 1 cm in 68.7% and >1 cm in 31.3%.
Invasion of thyroid capsule was reported in 36.7% of all cancers.
A total of 26.5% showed extrathyroidal extension, independently of the maximum focus size.
It is interesting to report that frequency of invasive behaviour is increasing from 2008 to 2014. Histologic types: papillary 94%, follicular 2.5%, medullary 2.8%, Hurtle-cell 0.6%, anaplastic 0.1%.
Conclusions
i) The percentage of thyroid cancers is gradually increasing per year in the period studied, which could mean:
– more targeted pre-surgery diagnostic evaluation and referral for thyroidectomy.
– a possible real increase in thyroid cancer frequency.
ii) Maximum frequency of thyroid cancer in middle aged patients, mainly women.
iii) Coexistence of Hashimoto's thyroiditis in almost 50% of cases.
iv) Independently of maximum thyroid cancer focus, increased frequency of invasive behaviour is reported during the last 5 years.

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EP1127

Baseline serum TSH and risk of thyroid microcarcinoma in non-toxic nodular thyroid disease

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Aim
Thyroid cancer comprises the most common endocrine malignancy and a variety of studies have examined the role of TSH as an independent risk factor for the manifestation of differentiated thyroid cancer in otherwise benign thyroid disorders. Objective of the current retrospective study was the assessment of a possible relation between baseline serum TSH and thyroid microcarcinoma in a patient cohort with non-toxic thyroid disorders and without preoperative cytological establishment of thyroid cancer who underwent total thyroidectomy.
Patients and methods
Between 1 January 2005 and 1 March 2010, 186 patients (146 female/40 male) underwent total thyroidectomy because of nodular thyroid disease in our Department. Thyroid specimens were histopathologically examined at the University Pathology Department for the establishment of the final diagnosis of benignity or malignancy. Median values of preoperative serum TSH were estimated in both dignity groups and the results were compared regarding preoperative diagnosis.
Results
Thirty-two patients (17.2%) were diagnosed with microcarcinoma (rate females: males 2.2:1), while 154 patients (82.8%) were free of malignancy. The median value of basal serum TSH was higher in the malignancy group and without statistical significance (1.02 vs 0.80; *P* value 0.293). Regarding patients with solitary thyroid nodule TSH presented higher in the benignity cohort (1.3 vs 0.83; *P* value 0.289), whereas in patients with non-toxic multinodular goiter TSH was higher in the malignancy group but marginally without statistical significance compared to the benignity group (1.16 vs 0.75; *P* value 0.05)
Conclusions
In the present study, basal serum TSH did not feature an independent risk predictor for the development of thyroid microcarcinoma in non-toxic nodular thyroid diseases. A borderline non-significant trend of higher TSH was shown however in non-toxic multinodular goiter harbouring malignancy. Further studies evaluating the role of TSH in thyroid cancer are required.

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EP1128

Nuclear cysteine cathepsins in thyroid carcinomas

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Cysteine cathepsins are endo-lysosomal proteases that play crucial roles in thyroid physiology. However, in thyroid cancer, cathepsin B is overexpressed and secreted into the extracellular space, thus promoting migratory phenotypes of thyroid carcinoma cells through excessive extracellular matrix degradation. In addition, we have shown that N-terminally truncated forms of cathepsins B and V which lack the signal peptide and parts of the pro-peptide are localized to the nuclei of anaplastic thyroid carcinoma cells, while cathepsin L is present within endo-lysosomes as expected.
Cathepsins B, L, and V were also examined in a variety of different human thyroid carcinoma cell lines in comparison to normal thyroid epithelial cells by immunofluorescence and immunoblotting studies, revealing differential protein levels and/or subcellular distribution patterns of the different cathepsins in distinct cell lines. In particular, cathepsin V reached the nuclear compartment of thyroid

carcinoma cells *in vitro*. For correlation of nuclear cysteine cathepsin activities to phenotypic characteristics of thyroid carcinoma cells, over-expression studies were performed with different molecular forms of the cysteine cathepsins B and V which were analysed as chimeric GFP-tagged proteins in synchronized cultures. Here, the results showed again that cathepsin V was trafficked to the nuclei of thyroid carcinoma cells.
In keeping with the hypothesis that nuclear tasks of cysteine cathepsins reside in the processing of nuclear proteins which are relevant for cell cycle progression, thyroid cancer tissue was analysed in addition. Cathepsin V was found prominently in the cellular nuclei of follicular thyroid carcinoma tissue, but not in papillary thyroid carcinoma.
We conclude that cathepsin V rather than cathepsins B and L might serve important functions within the nuclei of certain thyroid carcinoma cells.

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EP1129

The diagnostic value of FNAB for early diagnosis of thyroid cancer: a Greek center experience

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Introduction
Fine needle aspiration biopsy (FNAB) is the initial investigation of choice for thyroid nodules.
Methods
A total of 563 patients (106 males/457 females) underwent FNAB for the same number of thyroid nodules. Their mean age was 56.1 ± 14.1 years. We correlated the demographic profile (age and gender) and sonographic features of these nodules with the FNAB outcome. The Bethesda system for reporting thyroid cytopathology was used.
Results
Out of total 563 cases, 190 (33.7%) cases were diagnosed as non diagnostic (B1), 339 (60.2%) were diagnosed as benign (B2), 17 (3.0%) as B3 (atypia/follicular lesion of undetermined significance), 7 (1.2%) as B4 (follicular neoplasm or suspicious for follicular neoplasm), while 5 (0.9%) cases were categorized as B5 (suspicious for malignancy) and 5 (0.9%) as B6 (malignant). Remarkably, two nodules of category B5 and B6 each had a maximum diameter of 9 mm and 8 mm respectively. When comparing benign result (B2) vs result of category B3–6, irregular shape (7.1% in B2 vs 17.6% in B3–6, $X^2=4.66$, $P=0.043$), ill-defined margins of the nodule (13.3% in B2 nodules vs 29.4% in B3-6 nodules, $X^2=6.4$, $P=0.020$), and the presence of calcifications (34.2% in B2 nodules vs 64.7% in B3-6 nodules, $X^2=12.3$, $P=0.001$) decreased significantly the possibility for benign (B2) result, whereas features such as the size of nodule, the presence of central vascularity, the composition and the hypoechogenity of the nodule did not affect the possibility for B2 vs B3–6 result. Finally, there was no association of gender and age with the Bethesda category result.
Conclusion
Our study supports that the irregular shape of a nodule, ill defined margins, and the presence of calcifications decrease the possibility of a Bethesda benign result. FNAB of nodules <10 mm may reveal suspicious or positive for malignancy cytology.

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EP1130

Diagnostic and prognostic aspects of immunomorphology of post-chernobyl encapsulated follicular thyroid tumours

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Background
An increased incidence of thyroid cancer among young population of contaminated territories of Russia after Chernobyl accident made very important morphological verification of diagnosis. Many epidemiological and molecular studies of post-Chernobyl thyroid cancer conducted by various research teams required an independent review of tumour histology. The International Pathology Panel formed consensus diagnosis for each case of post-Chernobyl thyroid tumours and proposed an appropriate algorithm of morphological diagnosis (E.D.Williams *et al.*, 2000). The main diagnostic problem arose for estimation of malignancy in some encapsulated follicular thyroid tumours. Doubtful features of tumour capsular invasion and focal morphological nuclear changes in tumour cells could be a reason to distinguish among benign thyroid tumours a group of borderline lesions or tumours of uncertain malignant potential. This classification group is not widely accepted, as the malignancy of encapsulated follicular thyroid tumours should be more precisely determined.
Aim
To analyse diagnostic and prognostic significance of immunoexpression of markers of malignancy in encapsulated thyroid tumours.
Material and methods
We studied an immunoexpression of markers of malignancy: Galectin-3, Cytokeratin-19, HBME-1, Fibronectin and Cyclin D1 in 51 benign, 87 malignant and 53 tumours of uncertain malignant potential.
Results
We revealed that 3.9% benign and 41.5% tumours of uncertain malignant potential express the markers of malignancy with a level of diagnostic specificity of 98–100%. Follow up during the period of 1–10 years after surgical thyroid lobectomy for borderline tumours showed no progression of tumour growth.
Conclusion
We concluded that some of benign and borderline thyroid tumours are represent malignant neoplasms with low grade and favourite prognosis.
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EP1131

Fine needle thyroid biopsy – time to change of indications?

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Introduction
After a period of enthusiasm for the early detection of cancer, apparently we are entering a period of skepticism, questions and side effects in the form of unnecessary operations and their complications and costs. This also applies to thyroid cancer, and actually nodules and lesions visible only in ultrasound-Method. Prospective observation of consecutive patients in one centre.
Results
In Years 2013 and 2014 we have performed 2189 ultrasound guided fine needle biopsy of thyroid gland. Indication were determined in accordance with the recommendations of the National Society of Endocrinology. Ambulatory patients (1702) were referred by family doctors and specialists, hospital patients (487) only by endocrinologists. Based on biopsy were diagnosed 6 cases of thyroid cancer (0.3%) but only 1 (0.06%) in outpatients and 5 by inpatients (1%). The results "suspicion" about the cancer as follicular or oxyphilic lesions was by 29 (1.3%) patients. We must point out that patients referred for biopsy by endocrinologists with palpable changes have a much larger risk of finding pathological changes than be referred only based on ultrasound image.
All patients except one with an established tumor of the thyroid have clear clinical symptoms, in the form of compression and/or rapid tumor growth. The risk of cancer is found in the thyroid biopsy, if there are no clinical symptoms seem very small in our region. However, the decision to take or omission of such diagnosis in patients with incidentally detected changes in the ultrasound must be taken together with the patient, because the patient will bear the consequences for delayed treatment of cancer or complications of unnecessary surgery.
Conclusion
The decision on whether to carry out a biopsy the thyroid gland and its possible therapeutic consequences should be taken jointly with the conscious patient, especially in areas with low incidence of thyroid cancer.

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EP1132

Ultrasonographic scoring index can be useful in the prediction of thyroid malignancy in subcentimeter and supracentimeter thyroid nodules

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Introduction
The increased rate of thyroid malignancy as well as incidental and subcentimeter thyroid nodules have been attributed to increasing use of high-resolution US which can detect the non-palpabl or subcentimeter (maximum diameter ≤ 1 cm) thyroid nodules. We aimed to evaluate the sonographic features of the tyroid nodules between ≤ 1 cm and > 1 cm according the histopathology results and to determine the ultrasonographical predictive factors for malignancy and an ultrasonographic score according the sonographic features to avoid unnecessary fine-needle aspiration biopsy (FNAB).
Methods
We retrospectively evaluated 2233 nodules of 1118 patients who underwent thyroidectomy. Predictive factors for distinguishing between malignant and benign histopathologic results according the ultrasonographic features were evaluated by multivariate logistic regression analysis. Multiple binary logistic regression with the forward logistic regression method was used to develop the formula for recommending sonographically guided biopsy.
Results
Among the 2233 nodules 337 nodules were in the ≤ 1 cm (group 1), 1896 were in the > 1 cm (group 2). According the histopathological results, in group 1; 173 nodules were in the benign, 164 nodule were in the malignant group. Whereas in group 2; 1423 nodules were in the benign, 473 nodules were in the malignant group. In group 1, AP/T ≥ 1, the presence of microcalcification, macrocalcification and hypoechoic pattern were significantly higher in the malignant group and in group 2, the presence of microcalcification, macrocalcification, hypoechoic and iso-hypoechoic pattern, solid texture, peripheral and intranodular vascularization pattern were significantly higher in the malignant group. In group 1, the best ultrasonographic index score was found > 2, whereas in group 2 the it was found > 4.
Conclusion
Our US scoring may lead to clinicians and surgeons to diagnose thyroid malignancy more accurately and to select the nodules for FNAB especially in subcentimeter nodules.

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EP1133

Thyroglobulin (Tg) levels post initial treatment predict the recurrence risk in differentiated thyroid carcinoma (DTC)

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Aim
To know if Tg levels after treatment (total thyroidectomy and radioiodine ablation) in the DTC can predict their prognosis in the long term.
Material and methods
Basal Tg and Tg after rh-TSH were measured in 229 patients with DTC without any evidence of residual tumour (negative neck ultrasonography) after treatment. The group was followed until tumour recurrence or, if recurrence was not found, a minimum of 12 month (mean $\pm$ SD $= 63 \pm 37$ months).
Test response was classified in three categories: Excellent response: Tg stimulated < 1 ng/ml; indeterminate response: 1–10 ng/ml and incomplete response: > 10 ng/ml. All selected cases had negative Tg-antibodies.
Results
The relationship between Tg level and recurrence is described in the following table.

	Tg stimulated < 1 ng/ml	1–10 ng/ml	> 10 ng/ml	Total
Recurrence YES	1 (0.5%)	8 (21.6%)	7 (70%)	16
Recurrence NO	181	29	3	213
Total	182	37	10	229

Tumour recurrence was localized: 14 lymphadenopathy, 1 lung metastasis, 2 local. Time recurrence: 3–104 months (mean: 41, median 34).

When initial Tg levels were positive, but tumour recurrence was not detected at the end of the follow up ($n = 32$), the evolution of Tg stimulated levels was studied. Eight out of 32 patients showed an increase of Tg levels, in 3 cases Tg levels were stable, in 8 patients Tg decreased and in other 6 cases Tg became indetectable (without any additional treatment). In 7 patients Tg stimulated was no measured.
Conclusions
1. When Tg stimulated levels post-treatment are undetectable the possibility of recurrence is minimal.
2. The probability of recurrence increases according to Tg levels.
3. However, it has to be considered that a positive Tg level can decrease and even become negative during the follow-up.

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EP1134

Cerebellar metastasis from follicular thyroid carcinoma

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Differentiated thyroid carcinoma (DTC) is the most frequent endocrine neoplasm. Follicular thyroid carcinoma (FTC) is the second histological variant in frequency after papillary thyroid carcinoma (PTC). Cerebellar metastases from DTC are extremely rare, corresponding about 1% of all cerebellar metastases, and being the majority metastases from PTC. To the best of our knowledge there have been no reported cerebellar metastases from CFT so far. We present here the first clinical case of cerebellar metastasis from FTC. She was a 78 year-old woman who underwent total thyroidectomy 23 years ago showing an atypical thyroid adenoma in the left thyroid lobe in the pathological study. She received radioiodine therapy in several occasions (total accumulated dose 704 mCi). A chest computed tomography (CT) performed 15 years later identified two lung nodules with cervical lymphadenopathies. Cervical ultrasound and fine-needle aspiration (FNA) was performed, showing reactive lymphadenitis. Serum thyroglobulin levels were increasing in subsequent medical visits (4.8 to 57.9 ng/ml). Thyroglobulin antibody levels were always negative. In the follow-up localizing study a whole body CT scan revealed stable pulmonary metastases and an image at the left cerebellar hemisphere level compatible with metastasis of 2×1.6 cm. The patient underwent surgery of the cerebellar lesion. Inmunohistochemical findings showed a thyroid origin of the metastatic lesion, with tumor cells with diffuse and intense positivity for cytokeratin 7 (CK7), thyroid transcription factor-1 (TTF-1) and thyroglobulin, focal and weak positivity for CK19, and negativity for PGAF, Galectin-3 and CK20. The analysis of V600K V600E BRAF gene mutations was negative. These findings support histological metastasis from FTC. In conclusion, we report the by first time a patient with cerebellar metastasis from FTC, who was successfully treated by surgical resection.

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EP1135

Can ratio of primary tumor diameter to total tumor diameter be a new parameter in the differential diagnosis of agressive and favorable multifocal papillary thyroid microcarcinoma?

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Introduction
In this study, we aimed to evaluate the usefulness of ratio of primary tumor diameter to total tumor diameter as a new parameter for the differentiation of agressive and favorable papillary thyroid microcarcinomas (PTMC).

Methods
The diameter of the largest tumor focus was taken as the primary tumour diameter (PTD). For multifocal tumors, total tumor diameter (TTD) was calculated as the sum of the maximal diameter of each lesion. A ratio was obtained by dividing PTD to TTD and defined as tumor diameter ratio (TDR) (PTD/TTD = TDR). Positive (PPV) and negative predictive values (NPV) and sensitivity and specifity of TDR to predict capsular invasion, extrathyroidal extension (ETE) and lymph node metastasis (LNM) were determined.
Results
Mean TDR significantly decreased as number of tumor foci increased. In multifocal PTMCs, the sensitivities of TDR for the detection of LNM, ETE and capsular invasion were 100%, 100% and 94.2%, respectively, the specifities were 86.2%, 88% and 94.7%, respectively. TDR had a PPV of 99.3% and NPV of 100% for LNM; PPV of 58.5% and NPV of 100% for ETE; and PPV of 89.1% and NPV of 97.3% for capsular invasion. In patients with multifocal PTC > 10 mm, mean TDR was signficantly lower in patients with LNM compared to ones without LNM (0.76 ± 0.12 vs 0.44 ± 0.10; $P < 0.001$).
Conclusion
Decreased TDR was associated with capsular invasion, ETE and LNM in patients with multifocal PTMC. It was also predictive for LNM even in patients without capsular invasion or ETE. This new parameter might be particularly helpful for the detection of aggressive behavior in multifocal PTMCs.

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EP1136

Overview of differentiated thyroid cancer in a tertiary health care center in the Canary Islands

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Introduction
Our objective is to determine the profile of patients with differentiated thyroid cancer (DTC) attended in our center and the therapeutic approach employed.
Methods
Retrospective review of medical records from patients treated for DTC during the years 2013 and 2014.
Results
Data from 387 patients, 84% female, 96% Caucasian, mean follow up of 10.82 years. The average age at diagnosis was 44.24 years, 77% had normal thyroid function, and 42% positive thyroid autoimmunity. The fine needle aspiration (FNA) results prior to surgery (Bethesda criteria) were: Category (C) 1 0.9% of cases C2 28.2%, C5 39.9%, C6 20.2%, while the remaining 10.8% were shared between C3 and C4. 27.5% had more than one loci, with certain predilection for the right lobe (42.3%, 32% for left lobe, 5% in isthmus and 20.7% bilateral). Regarding the histological type, papillary carcinoma predominated, with 70% of cases, 27.3% were follicular carcinomas (including Hürthle cell carcinoma); the remaining 2.7% were shared between poorly differentiated, mixed forms and insular carcinoma. The surgical approach consisted in total or near-total thyroidectomy in 93.9% of cases, with only 6.1% being hemithyroidectomies; 87.1% of patients received an ablative dose of I-131 after surgery. 153 cases had enough data available for staging, stage I being predominant with 74.5% of cases (stages II, III and IV, 11.1%, 13.1% and 1.3% respectively). Only 2.1% had recurrent nerve paralysis, and 5.9% suffered persistent hypoparathyroidism.
Conclusions
In our series the percentage of follicular neoplasms is higher than reported in the literature. Taking into account the recommendations from the 2015 guidelines of the American Thyroid Association, the therapeutic approach was overly aggressive, both for the extent of surgery and the subsequent use of I-131. However, the rate of severe complications resulting from surgery is not high.

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EP1137

Fine-needle aspiration of thyroid nodules: our experience before and after Bethesda

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Introduction
Thyroid nodules are common. Fine-needle aspiration cytology (FNAC) has an essential role in the evaluation of thyroid nodules, but results may be nondiagnostic. A standardised (FNAC) reporting system: Bethesda system for reporting thyroid cytology (BSRTC) is widely used.
Purpose
The aim of this study was to assess the diagnostic accuracy of (FNAC) of thyroid nodules performed at our Hospital before and after the introduction of (BSRTC).
Methods
We studied records of all patients who had undergone (FNAC) in the period between 2005 and 2015. We identified two methods of (FNAC) reporting: Traditional and (BSRTC) reporting. The 'traditional' reporting system was as follow: nondiagnostic; benign; suspicious or malignant. The (BSRTC) used the 'thy' classification. We used SPSS v 15 statistical package for Analysis.
Results
The total number studied was 156. Mean age for the traditional group was 56.93 ± 14.87 vs. 59.39 ± 13.57 in the (BSRTC) group ($P = 0.34$). Overall diagnostic adequacy was 95/156 (60.9%). In the 'traditional group', the diagnostic accuracy was 62/118 (52.54%) vs. 33/38 (86.84%) in the (BSRTC) group ($P = 0.001$). We re-evaluated all non-diagnostic cytology reported with the 'traditional method' now using (BSRTC) system. Cytology reports were assigned a group (Thy 1–5). Of the 56 non- diagnostic cytology: 17/56 (30.4%) were reassigned to thy2; 1/56 (1.8%) to thy3; 38/56 (67.8%) remained as thy1 (non-diagnostic). Reclassification improved the overall diagnostic accuracy to 113/156 (72.43%) ($P = 0.015$) with an improvement in the traditional group diagnostic yield to 80/118 (67.8%) ($P = 0.008$).
Conclusion
The use of the (BSRTC) reporting system improved our (FNAC) diagnostic yield significantly.

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EP1138

The prevalence of thyroid malignancy incidentally detected by ultrasound in patients with non-thyroidal head and neck cancer

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Thyroid cancer is one of the common head and neck malignancies and may be found incidentally with other head and neck cancers. The purpose is to evaluate the prevalence and risk of malignancy in incidental thyroid lesions identified by ultrasound (US) in patients with head and neck cancer. We retrospectively reviewed medical records of all patients with head and neck cancer other than of thyroid origin between January 2004 and January 2012. A total of 697 patients (542 men and 155 women; mean age, 59.1 ± 12.7 years) underwent US of the neck for the evaluation of cervical lymph node status (including thyroid gland). We evaluated the prevalence of patients with incidental thyroid lesions identified by US and the risk of malignancy in these patients. Of the 697 patients with head and neck cancer, 236 (33.9%) had incidental thyroid lesions on US. Based on US findings, 61 patients underwent fine-needle aspiration, with 39 eventually undergoing thyroidectomy. Among these thyroid lesions, 24 incidental thyroid lesions of 22 patients were histologically proven to be malignant (23 papillary and 1 follicular carcinomas). The risk of malignancy was 9.3% on a patient-by-patient basis. We propose that screening of the thyroid gland should be included in the preoperative US examination for cervical lymph node metastases in patients with non-thyroidal head and neck cancer.

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EP1139

Our experience with low doses of radioactive iodine (30 mCi) in patients with differentiated thyroid cancer

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Background
The management of patients with differentiated thyroid cancer (DTC) has been changing in recent years and aggressiveness of treatment depends on the risk of persistent or recurrent disease.
Objective
The aim of this study was to assess the efficacy of low doses of Radioactive Iodine (RAI;^{131}I) therapy in patients with DTC.
Methods
We retrospectively evaluated all patients who were diagnosed with DTC ($n=213$) at a tertiary hospital center in Cordoba (Spain), between January 2000 and December 2013. In all patients included, initial treatment consisted of total or subsequent completion thyroidectomy, with or without lymphadenectomy, RAI ablation therapy at a dose of 30 mCi ($n=17$) or $\geq$100 mCi: 100 mCi ($n=143$), 150 mCi ($n=5$), 200 mCi ($n=4$). Demographic and clinical variables were compared between both groups of RAI therapy.
Results
Seventeen patients received a low dose of ^{131}I (10♀; 7♂; 100% papillary). All subjects were classified as low risk of recurrence according to the revised ATA guidelines. Differences were found in the main prognostic factor as aggressive histological criteria ($P=0.014$), pTNM Stage ($P=0.045$), stimulated thyroglobulin (Stim-Tg) measured at 6–12 months ($P=0.007$). Statistically significant differences were not found in age (<45 or ≥45 years), sex, histology, total thyroidectomy or subsequent completion, neck lymphadenectomy, and the number of adverse effects. The hospitalization time was lower in the group of patients who received 30 mCi (6 hours us $\geq$48 hours; $P<0.001$). All of 17 patients had no evidence of disease after an average follow-up of 3.59 years. Up to now, recurrence has been detected in none of them.
Conclusions
Therapy with low doses of 131I (30 mCi) is an effective treatment in patients with low-risk of recurrence with de advantage of having a lower hospitalization time.

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EP1140

A giant lung metastasis of thyroid papillary carcinoma

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Introduction
Papillary thyroid carcinoma (PTC) patients with distant metastasis (DM) have variable clinical forms. PTC mostly metastasizes to the regional cervical lymph node. Metastasis rate is approximately 20–90% available when diagnosed. In addition, the overall incidence of DM is approximately 10%. DM are usually to the lungs, bone and brain. Furthermore rarely liver, pancreas, skeletal muscle, adrenal gland, ovaries, sphenoid sinuses and submandibular gland metastases can be occurred. Lung metastases of PTC can manifest as local mass, nodular, multiple miliary metastases, generalized lymphadenopathy and pleural effusion.
Case report
A 61-year-old woman presented to the outpatient clinic with complaints of dry hacking cough and chest pain. Chest x-ray revealed major pulmonary lesions (90×131 mm) which was confirmed on computed tomography analysis (3D Measurement 99×102×126 mm). Transthoracic lung biopsy was performed and PTC metastasis was diagnosed in histological examination. Since the histological diagnosis was PTC, we checked the thyroid gland. Ultrasound examination of thyroid gland showed 30×34 mm and 20×15 mm hypoechoic solid nodules with micro calcification in the left lobe. Malign sitology was verified with fine needle aspiration biopsy. Because of these findings total thyroidectomy was performed. Microscopically, PTC was diagnosed without capsular, perineural and lenfovascular invasion. The surgical board of tumor was negative. Lung metastases of PTC was considered inoperable by thoracic surgery because the invasion of third and fourth rib. The patient was discharged after treatment of iodine 131 therapy.
Conclusion
The incidence of DM related with PTC is %4–6. However, we did not find giant lung metastases as our case when we did literature review. It was also interesting that the local invasion in thyroidectomy materials was absent. As a result, the PTC associated metastasis must be thought when we find giant mass in the lung.

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EP1141

Relation of F-18 FDG PET/CT positivity with tumor cytopathology and molecular markers in malignant and benign thyroid tumors

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Introduction
The role of F-18 FDG PET/CT in follow-up of differentiated thyroid cancer (DTC) is well established. Molecular markers were shown to be related with malignancy risk of thyroid nodules and prognosis of DTC. The goal of this study was to assess the relation of molecular markers such as NIS, Galectin-3, PTEN, Ki-67, p53 with PET positivity and malignancy of thyroid.
Methods/design
We evaluated patients who had 18-FDG uptake in thyroid gland at F-18 FDG PET/CT and subsequently underwent total thyroidectomy. Pathology and PET-CT reports were investigated retrospectively. Fifteen patients with 27 nodules who had FDG uptake in thyroid were included. Twenty-one nodules were PET positive. Thirteen nodules were malignant and eight were benign. Six malignant nodules of these patients without 18-FDG uptake were also included. Immunohistochemical staining with Galectin-3, NIS, PTEN, p53 andKi67 in surgical specimens was performed.
Results
Six out of eight benign nodules (75%) were not stained with Galectin-3 and seven (36.8%) of malignant nodules had negative Galectin-3 staining. Twelve nodules stained moderately intense or intense with Galectin-3. NIS expression was frequent and intense in elder people. Loss of PTEN expression was frequent in malignant nodules. PTEN staining was not seen in 42.1% (n:8) of malignant and 12.5% (n:1) of benign nodules. Nodules were not stained for p53.F-18 FDG positivity in malignant and benign nodules was not associated with Galectin-3, NIS, Ki67 or PTEN expression.
Conclusion
FDG-PET positivity and malignancy risk were not associated with Galectin-3, NIS, Ki67, PTEN and p53 expression. New studies are necessary for explaining pathogenesis and role of molecular markers in development of FDG-PET positive thyroid nodules.

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EP1142

Accuracy of fine-needle aspiration biopsy in Albanian experience

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Background
Fine-needle aspiration biopsy (FNAB) is the gold standard in detecting thyroid cancer. The overall incidence of thyroid cancer is 9–13% in patients with thyroid nodule that are eligible for FNAB. If the sample taken is sufficient, a negative FNA-B response eliminates the carcinoma risk in 98–99% of cases.
The aim of the study
To access the role of FNAB in the early diagnosis of thyroid cancer in Albania.
Materials and methods
This is a retrospective study involving 65 patients with thyroid cancer from 2008–2015. All patient performed FNAB under ultrasonography, before surgery. Age, gender, ultrasound characteristics, FNAB and post-surgery biopsy were studied.
Results
FNAB results: 42% was positive, 35% was indeterminate and 23% was negative. The study revealed that 15 of 65 patients with thyroid cancer had a negative response to cytoponction. In cases with negative FNAB, post-surgery biopsy revealed 13 cases with papillary carcinoma, 2 cases with follicular carcinoma, no cases with anaplastic or medullar carcinoma.
Conclusion
The study showed that, suspicious or positive cytology should be evaluated for surgery. According to our results, since a negative FNAB response does not exclude the possibility of cancer, an attentive evaluation of the FNAB result and ultrasound pattern in very important before a pre operatory diagnosis.

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EP1143

Medullary and papillary carcinoma of the thyroid gland occurring as a collision tumour: a case report

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Introduction
Medullary thyroid carcinoma (MTC) is a relatively uncommon tumour of the thyroid as compared with papillary thyroid carcinoma (PTC). Concurrent of medullary thyroid carcinoma (MTC) and papillary thyroid carcinoma (PTC) in a single patient is a rare.
Case
Forty-nine year-old male patient was referred to endocrinology for multinodular goiter evaluation. He had no palpable nodules. There was no apparent family history of endocrine disorders or external radiation therapy. The thyroid ultrasound showed an isoechoic nodüle 9 mm in size, in the left lobe and two hypoechoic nodes on the right lobe 4.4 and 7 mm in size, with accompanying linear calcification. The patient was euthyroid, serum calcium level and antithyroid autoantibodies were normal. Fine needle aspirations cytology demonstrated a suspicious for PTC. The patient underwent total thyroidectomy. The histology and immunohistochemistry showed multifocal papillary microcarcinoma (5mm- in the right lobe/7mm in the left lobe) and medullary microcarcinoma (3 mm-in the right lobe). Postoperatively calcitonin level < 0.2 pg/ml, and thyroglobulin level <0.1 ng/ml. Radioiodine treatment was not performed. Urinary metanephrines levels were in normal ranges. RET protooncogene was found to be negative.
Discussion
The simultaneous occurrence of MTC and DTC in thyroid gland can be observed in two main settings: a mixed tumor showing dual differentiation or a collision tumor showing two separate different carcinomas. The latter category nodules with MTC and PTC were detected distinct locations, seperated by normal thyroid area. Pathogenesis of these tumors is unclear. The collision theory is suggested that two independent tumors are located in the gland by coincidental. Other possible explanations for these tumors the presence of RET protooncogene mutation in both type thyroid cells. Recent studies and our case suggested that MTC and PTC are usually coincidental and independent. Endocrinologist and pathologist should to be alert in this condition.

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EP1144

Clinical evaluation and outcome of indeterminate (Thy 3) thyroid nodules

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In thyroid nodules with indeterminate cytology, presurgical evaluations for risk management comprise biochemical tests, ultrasonography (US), elastography-US (USE), contrast-enhanced US (CEUS) and mutation analysis. The cytology of 130 Thy 3 nodules was reviewed according to the BTA 2014 classification. Nodules were divided into Thy 3a and Thy 3f categories. Histology was available in 97 nodules. Malignancy was the final diagnosis in 19% of surgically treated nodules. No significant difference in the risk of malignancy was found between Thy 3a (26%) and Thy 3f (14%) nodules. Post-surgical histologic examination of the Thy 3a and Thy 3f nodules showed a higher incidence of Hurtle cell adenomas in Thy 3f (29%) than in Thy 3a (3%) nodules ($P=0.01$). BRAF V600E mutation was positive in some Thy 3a but not in any Thy 3f nodules ($P=0.04$). Cut-off values by ROC analysis from US (score), USE (ELX 2/1 strain index) and CEUS (time-to-peak index and peak index) were similar in Thy 3a and Thy 3f nodules. Data showed that malignancy can be suspected if the US score is >2, ELX 1/2 strain index >1, time–to-peak index >1 and peak index <1. In a group of 24 revised nodules (12 Thy 3a and 12 Thy 3f) the diagnostic power of cumulative pre-surgical analysis by means of US, USE and CEUS showed high positive and negative predictive values (83% and100%, respectively) for the presence of malignancy in Thy 3a and Thy 3f nodules. In our series of revised Thy 3 nodules, malignancy was low and displayed no significant differences between Thy 3a and Thy 3f categories. The use of cut-offs based on histology as a reference, in both Thy 3a and Thy 3f nodules, could reduce surgery. In mutation-negative Thy 3 nodules, observation should be the first choice when not all instrumental results are suspect.

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EP1145

Brain metastasis from follicular thyroid carcinoma as first manifestation of the disease

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Introduction
The prevalence of brain metastasis from differentiated thyroid carcinoma is 1%. Brain metastasis as the first manifestation of the disease is extremely uncommon.
Case report
We present a case of 44-year-old woman with headache and a tumor in right parietal zone. The patient has had multinodular goiter for 15 years, with two dominant nodules in left thyroid lobe. Both of them were isoechoic with hypoechoic halo and measured 2 cm. Fine-needle aspiration was benign and without changes over time. Computed tomography scan (CT) and magnetic resonance (MR) brain demonstrated a $6.2\times6.5\times5$ cm right parietal lesion with bone erosion (intracranial and extracranial component) mimicking a meningioma. Laboratory tests were as followed: TSH 1.83 mcU/ml [0.3–5], T4L 0.94 ng/dl [0.9–2.1], thyroglobulin 3207 ng/ml [0–80] and antithyroid antibodies were negative.
Surgery of brain tumor was performed and histopathology revealed a $6\times5.7\times2$ cm dural metastasis and a 4×2.8 cm skull metastasis of follicular thyroid carcinoma. Later, total thyroidectomy detected a 2 cm well differentiated follicular thyroid carcinoma in left thyroid lobe, with a small capsular infiltration and without vascular and lymph node invasion.
After that, radiotherapy and radioactive iodine therapy was administered to the patient with an initial good response.
Conclusions
Brain metastasis from differentiated thyroid carcinoma are rare and dural metastasis from follicular thyroid carcinoma are exceptional, with only a few published cases in the literature. In these cases the prognosis is poor, with a one year survival rate. Although, the treatment is controversial, nowadays brain surgery and radiotherapy are the best options.

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EP1146

Coexisting papillary thyroid carcinoma and renal cell carcinoma: 4 cases

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Papillary thyroid cancer (PTC) constitutes 85% of all differentiated thyroid cancers. PTC is usually sporadic, but may occur in a familial form. Familial cancer syndromes such as Cowden's syndrome and familial adenomatous polyposis are associated with PTC. Lal et al. recently published a study in which subsequent thyroid cancer was most common among the patients with renal cell cancer (RCC). RCC is a common malignancy of uroepithelial region, which constitutes about 3% of all adult malignancies. We presented 4 cases consecutively diagnosed with PTC and RCC within 12 months (Table). 3 cases with BRAF positivity had lymph node metastasis. The BRAF gene is located on chromosome 7. BRAF is a signaling protein downstream of Ras that activates the MAP-kinase pathway and implicated in cell differentiation and proliferation. Mutations of this gene have been found in cancers, including non-Hodgkin

lymphoma, colorectal cancer, malignant melanoma, PTC and lung carcinoma, while few studies reported RCC cases with BRAF mutation. In 2016, Natasha Banerjee et al. reported a case with metastatic RCC and BRAF mutation, in whom a good clinical outcome was achieved following BRAF inhibition. BRAF positivity observed in 3 of our cases suggests that further studies are required on a common mutation that exists in RCC and PTC.

	CASE 1	CASE 2	CASE 3	CASE 4
Age	64	48	56	67
Gender	Male	Male	Male	Male
Clinic	Euthyroid	Euthyroid	Hyperthyroid	Hyperthyroid
PTC-variant	Classic and follicular	Classic and follicular	Classic and oncocytic	Classic, follicular and oncocytic
PTC-grade	pT1a –pN1	pT1a –pNx	pT3a –pN1	pT4a –pN1
Focality	Multifocal	Multifocal	Multifocal	Multifocal
Metastasis	+	−	+	+
BRAF mutation	V600E (+)	Not analyzed	V600E (+)	V600E (+)
RAI (I-131)	+	−	+	+

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EP1147

Multi-directional approach for mean platelet volume in differentiated thyroid cancer

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Background
Differential thyroid cancer (DTC) is classified into papillary, follicular and papillary micro thyroid cancer. Also, mean platelet volume (MPV) is an independent risk factor for cardiovascular disease. The aim of the present study was to investigate MPV values in DTC patients.
Materials and methods
The levels of MPV were assessed in 183 patients with DTC 44 papillary thyroid cancer (mean age 43.$\pm$13.9) 34 papillary micro thyroid cancer (mean age 43.1$\pm$10.6), 28 follicular cancer (mean age 46.9$\pm$12.5) and 77 control subjects (mean age 47.5$\pm$5.9). Patient group and the control group were matched for age, BMI. None of the study subject had hypertension, radiotherapy and dyslipidemia. All the study subjects were investigated by platelet and biochemical parameters.
Results
Serum MPV levels were found to be increased in papillary thyroid cancer (PTC) (8.87$\pm$0.99), papillary micro thyroid cancer (PmTC) (8.82$\pm$1.39) and follicular thyroid cancer (FTC) (8.69$\pm$0.76) patients than in the control group ($P=0.000$, $P=0.000$ and $P=0.001$, respectively). It was similar between the three groups. The MPV levels were significantly positively correlated with C-reactive protein ($r=0.247$; $P=0.043$), waist circumference ($r=0.195$; $P=0.261$), thyroglobuline ($r=0.246$; $P=0.03$), gamma glutamyl transferase ($r=0.024$; $P=0.762$), tumor size ($r=0.209$; $P=0.047$) and RDW ($r=0.207$; $P=0.005$) which cardiac risk factors. The multiple regression analysis of MPV and other risk factors was performed. Age, CRP, gender, total cholesterol, were independent predictive factors of MPV. Adjustment for other these factors did not alter these relative risks.
Conclusions
Our results suggest that patients with DTC have higher MPV levels even than healty controls. As higher MPV levels are close related with cardiovasculer diseases DTC patients have greater risk of atherothrombotic complications than controls. Furthermore our study suggest that MPV might be a good follow criterium in DTC patients because of its positive correlation with the tumor size and thyroglobulin

Keywords: mean platelet volume, papillary micro thyroid cancer, papillary thyroid carcinoma, follicular thyroid cancer, cardiovascular risk
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EP1148

Preoperative predictors of malignancy in lesions classified as BETHESDA IV

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Background
Differential diagnosis of a thyroid nodule is difficult if it is a follicular lesion. Follicular lesions include follicular adenoma (FA) or a malign neoplasm (follicular cancer (FC) or follicular variant of papillary thyroid carcinoma (FVPTC)). Cytology can't separate benign from malignant condition in follicular lesions. Differential diagnosis is important because patients often undergo less than ideal interventions, such as a total thyroidectomy for a benign lesion or require completion thyroidectomy after a lobectomy for a malignant nodule. Herein we aimed to search whether there is a clinical or ultrasonographic marker discriminating malign lesions from benign ones.
Method
Eighty consecutive patients with an operated follicular thyroid neoplasm at a tertiary hospital from 2007 to 2014 were reviewed. Age, gender, symptoms, history, physical findings, nodule size, sonographic, cytologic, and final pathologic results were recorded. Malignant and benign groups were compared according to preoperative clinical and imaging features.
Results
34 of 102 nodules were malignant where as 68 were benign. Gender distribution, baseline thyroid function tests and thyroid autoantibody positivity were similar between the benign and malignant groups. Family history of differentiated thyroid cancer (DTC) was significantly higher in the malignant group ($P=0.002$). Regarding to ultrasonographic parameters, nodule volume and vascularity were significantly greater in the malignant nodules ($P=0.04$ and 0.008, respectively) Presence of microcalcification/irregular macrocalcification was also higher in the malignant group compared to benign group ($P=0.017$). When we subdivided malignant nodules as FVPTC (18 lesions) and FC (16 lesions), microcalfication was significantly more common in FVPTC ($P=0.022$).
Conclusion
Family history and certain ultrasonographic parameters might be helpful in preoperative differentiation of benign and malignant follicular neoplasms. A combination ofthose with both FNA and molecular results may help us to decide management of patients with follicular thyroid lesion.

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EP1149

Burkitt lymphoma of the thyroid (A rapidly growing painless thyroid mass during pregnancy)

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Introduction
Primary thyroid lymphomas (PTL) are rare tumors, accounting for 2.5% of all non-Hodgkin's lymphomas and fewer than 2% of all malignant thyroid tumors. Primary thyroid's Burkitt lymphoma represents a very unusual type of PTL. Only very few cases of primary thyroid's Burkitt lymphoma have been reported during pregnancy.
Observation
We present a 30 years old female patient who developed a rapidly enlarging painless neck mass. This mass was noticed by the patient few days after a severe

flue at 20th week of pregnancy. We received our patient at 29th week and 4 days of her first pregnancy. She had no other diseases or family history of thyroid disease. Physical examination revealed an enlarged thyroid gland. Compressive signs were limited to respiratory distress. Ultrasound of the neck showed increased dimensions of thyroid gland. Her thyroid function tests were normal. Anti-thyroid peroxidase antibodies were positive. Fine needle aspiration biopsy within the thyroid gland was compatible with thyroiditis. Compression was objected on MRI cervical examination which revealed a voluminous goiter with discreet lamination of the trachea. So she had a prophylactic ceasarean delivery of a healthy, premature male infant at 32 weeks of gestation. Urgent thyroidectomy was performed and the diagnosis of thyroid's Burkitt lymphoma was made on pathology. Subsequent staging procedures included CT imaging of the neck, chest and abdomen which revealed nodes enlargement in the chest. Chemotherapy was initiated six weeks after surgery.
Conclusion
Thyroid's Burkitt lymphoma is rare; its occurrence during pregnancy is even rarer. Its diagnosis and management is difficult. A multidisciplinary team is tremendously important in order to take the right decisions to save both the baby and the mother.

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EP1150

Can we predict malignancy in AUS/FLUS by measuring TSH?

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Background
Fine-needle aspiration (FNA) is an important test for triaging patients with thyroid nodules and differentiating benign from malignant disease. According to Bethesda System Classification, the rate of AUS/FLUS is between 3–6% of all FNA. The malignancy risk is of 5–15%. TSH levels might be associated to the likelihood of malignancy in thyroid nodules according to some studies. Our aim was to establish a possible correlation between TSH level and malignancy of AUS/FLUS.
Methods
Retrospective study using SPSS.
Results
The authors reviewed a total of 2891 patients from January 2012 to December 2014. There were 564 (15.9%) AUS/FLUS in 3557 thyroid FNAs performed. The malignancy risk was 9.6%. The rate of carcinomas on operated patients was 30%. From a total of 180 performed surgeries, there were 54 carcinomas. TSH value was determined in carcinomas. 11 were excluded because of missing data or because of patients under thyroid hormonal replacement before surgery. On the 43 remaining patients correlation between AUS/FLUS and TSH values was established. The mean value for TSH in carcinomas versus control group (benign lesions) was 1.74 vs 1.45 (P value $=0.117$).
Conclusion
We could not establish a correlation between TSH level and the likelihood of carcinomas in AUS/FLUS in our series. A bigger data may be necessary to get statistically significant results.

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EP1151

Neutrophil-Lymphocyte Ratio (Nlr) and Platelet -Lymphocyte Ratio (Plr) may be superior to C-Reactive Protein (Crp) for predicting the occurrence of differentiated thyroid cancer

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Aim
Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are prognostic markers of differentiated thyroid cancers. In our study we evaluated NLR, PLR and C-reactive protein for predicting the occurence of differentiated thyroid cancer. This is the first study that compares NLR and PLR to C-reactive protein indifferantiated thyroid cancer not only papillary cancer but also folliculer cancer.
Materials and Method
This study includes 51 papillary carcinoma, 42 papillary microcarcinoma and 31 folliculer carcinoma patients attending to our outpatient Endocrinology Clinic at Erzurum Region Training and Research Hospital between 2009 and 2014. The control group include 50 age, sex and body mass index matched healty subjects. Blood counts and CRP were measured at the day before surgery. Thyroglobulin was measured after 6 months of operation.
Results
There were positive correlations between tumor diameter, age, white blood cell (WBC) and thyroglobulin levels. There were also positive correlation between NLR, PLR and CRP levels.
Conclusion
In our study we found out that higher NLR and PLR was associated with higher levels of thyroglobulin which indicates worse survival. CRP levels were also associated with poorer tumor profile but the determining rate was lower according to ROC analysis.

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EP1152

Local classification of differentiated thyroid cancer: does it help to discriminate the response to treatment?

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Introduction
The prediction of the risk of recurrence in differentiated thyroid cancer (dtc) in chile is different from ata. The use of the stimulated thyroglobulin (tg) post-surgery in the prediction of the risk is controversial. We present a cohort applying a new local protocol that includes the tg for supporting the discrimination of the patients for offer low doses or radio iodine.
Objective
Asses if the local risk classification (lc) allow us to discriminate the response to the treatment (rt).
Method
Analysis of medical records from the patients with total thyroidectomy for dtc during 2013. Compared the lc with de ata risk stratification scale. We evaluated the response to the treatment after a year of evolution according with the levels of suppressed and stimulated tg and images. The results were divided in excellent or acceptable/incomplete.
Results
96 patients were analysed. The thyroidectomy was total in a 100%. Histological type: 92.7% papillary. 68.7% received radio iodine in doses from 30 to 150 mci; in the group of very low risk lc no one went to ablation. Rt was excellent in 74%, acceptable in 20% and incomplete in 6.2%. Using the cohort value of the tg lower than 2 ng/dl, we get un lr of 0.22 for predicting a good response.
Conclutions
In the local classification all the patients with very low risk presented excellent response to the treatment, allowing discriminate better this group.

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EP1153

Thyroid cancer in a patient with neurofibromatosis type 1: von recklinghausen disease

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Introduction
Neurofibromatosis type 1 or von Recklinghausen disease is a systemic hereditary disease characterized by disorders regarding the skin, neural and skeletal systems. Osteoporosis is one of the skeletal manifestations of neurofibromatosis type 1, being associated with increased fracture risk. Neurofibromatosis type 1 is associated with a propensity for the development of cancer, breast cancer in particular being associated with neurofibromatosis type 1.
Aim
The aim was to present the case of a patient with neurofibromatosis type 1 who developed breast and thyroid cancer and was diagnosed with osteoporosis.
Case report
A female patient, aged 47, with neurofibromatosis type 1 developed breast cancer at the age of 45 and had surgery and radiotherapy. The patient had a mother with neurofibromatosis type 1, who had breast cancer and had died from metastatic generalized breast cancer. A year later the patient presented with a nodule in the thyroid gland. Fine needle aspiration biopsy was performed and revealed the presence of papillary thyroid cancer. Near total thyroidectomy was performed and histology was positive for a papillary thyroid cancer. The patient complained for diffuse musculoskeletal pain, $25(OH)D_3$ levels and bone mineral density were measured. $25(OH)D_3$ levels were 20 ng/ml, T score was -2.9. Ibandronate was administered at a dose of 150 mg once monthly along with calcium and vitamin D orally. A year later bone mineral density was measured, T score being -2.7, compatible with improvement in bone mineral density.
Conclusions
Neurofibromatosis type 1 is a systemic hereditary disease characterized by a tendency for the development of cancer. Recently, osteoporosis has been described as one of the features of the disease. The case of a patient has been described with neurofibromatosis type 1 and osteoporosis who improved after treatment with risedronate (Benlidayi *et al*. 2015). The patient described herein was also given bisphosphonates with a good therapeutic response.

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EP1154

Collision thyroid tumors among patients diagnosed with thyroid carcinomas

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Introduction
Collision thyroid tumors are defined as independent and histologically distinct tumors that coexist within the thyroid gland. Collision thyroid tumors are rare and their prevalence is unknown.
Methods
A retrospective, registry-based study was performed by reviewing the electronic medical records of the Department of Endocrinology, Ippokratio General Hospital of Thessaloniki, Greece. All patients with thyroidectomy and thyroid cancer diagnosis were assessed to detect the prevalence of collision thyroid tumors.
Results
In total, 305 patients ($n=305$) were diagnosed with thyroid cancer. Two hundred sixteen ($n=216$) patients were diagnosed with papillary thyroid carcinoma, 35 patients ($n=35$) were diagnosed with follicular thyroid carcinoma, 41 patients ($n=41$) were diagnosed with medullary thyroid cancer and 13 patients ($n=13$) were diagnosed with anaplastic thyroid carcinoma. From the 305, collition thyroid tumors were only found in 3 patients (0.98%). The first patient presented with multinodular goiter with calcifications. The initial FNA showed Hurthle Cell Carcinoma, whereas pathology findings revealed co-existence of myeloid and papillary (2-focal) thyroid cancer. RET testing was negative. The second patient presented with primary hyperparathyroidism and it was unilateral lobectomy that revealed micro-papillary thyroid cancer co-existing with micro-myeloid thyroid cancer. RET testing was negative. The third patient underwent thyreoidectomy due to rapid increase of the nodule's size although the initial FNA was negative for malignancy. Pathology findings revealed co-existence of myeloid and papillary (2-focal) thyroid cancer and genetic testing for RET was positive for the polymorphisms G691S in exon 11 and S904S in exon 15. Of note, the first patient was also diagnosed with bilateral adrenal incidentalomas whereas the second with bilateral adrenal hyperplasia and the third with unilateral adrenal incidentaloma.
Conclusion
Collision thyroid tumors are a rare finding in patients diagnosed with thyroid carcinomas. It has been suggested that activation of a common tumorigenic pathway takes place, however existing evidence is limited.

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EP1155

Second primary malignancies in patients with differentiated thyroid carcinoma

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Introduction
It has been shown that thyroid cancer has a significant correlation with cancers originated from other organs. The aim of this study was to investigate the association between synchronous primary cancers in patients with thyroid cancer.
Material and Method
A retrospective analysis of medical records of 560 thyroid cancer patients treated in the years 2007–2013 and followed up over 2–8 years, was performed. In 38 patients (6.7%), 5 male patients, 33 females (mean age 65.4 ± 13.5 years,) of the analyzed group other primary malignant neoplasms were observed. Among these 30 patients follicular thyroid cancer was stated in 7 and papillary cancer – in 31 patients. Within the TNM system, thyroid cancer classification of these patients varied between in pT1aN0M0 and pT3mN1M1. Two female patients with pT1aN0M0 papillary cancer did not receive complementary radioiodine treatment.
Results
In 36 patients concurrently two malignant neoplasms occurred. In two female patients multiple concurrent primary neoplasms were stated: thyroid cancer with breast and ovary cancers, and thyroid cancer with kidneyand uterus cancers and pituitary adenoma. In the studied group breast cancer was the most frequent (14 patients), uterus cancer (4 patients), brain tumour (3 patients), blood malignancies and lung cancer (4 patients), kidney cancer (3), NET and melanoma (2 patients). Six patients were diagnosed first with thyroid cancer and next with breast cancer and in six patients breast cancer preceded thyroid cancer diagnosis and treatment. In two patients synchronous cancers were stated. During follow up one female patient died of NET of unknown origin with liver metastases.
Conclusions
It appears that female patients with thyroid cancer are more susceptible to breast cancer than the general population, therefore particular attention should be paid to diagnosing breast and thyroid nodules in these patients. The genetic background of concurrent malignant neoplasms requires further investigation.

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EP1156

A case of thyroid cancer followed by metachronous cancers and a pituitary tumour

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Introduction
Based on cancer registries, the risk of second primary malignancies in patients with DTC increases by 30%. In our case report we aimed at understanding the patomechanism of metachronous primary tumours in patients with thyroid cancer.
Case
In a 71-year old female surgery of nodular goitre (1988), followed by papillary thyroid cancer (pT3NxMx) surgery (2008) and complementary 131-I treatment (2009), were performed. In diagnostic WBS (2010) no pathologic 131-I uptake and no enlargement of lymph nodes were stated. Tg concentration after rhTSH stimulation was 10.7 ng/ml. Consecutive 131-I therapy followed (2010). Endometrial cancer, pT1cNxMx, was surgically removed (2011), followed by tele- and brachytherapy. In 2012 a small left kidney tumour and a tumour in the lower left lung were seen in her chest CT. Following nephrectomy, clear cell cancer infiltrating the capsula was established. Resection of lower lobe of left lung

followed (2013) and found to be endometrial cancer metastasis. The patient underwent chemotherapy (6 paclitaxel and carboplatin cycles, 2013). Due to increase in thyroglobulin concentration, WBS was performed (2014), with no pathologic 131-I uptake, rhTSH-stimulated TSH (351.9 uU/ml) and Tg (13.8 ng/ml). PET/CT showed 18F-FDG accumulation in a pituitary tumour (SUVmax 21.7). A large (40×30×45 mm) intra- and extrasellar tumour was confirmed in brain CT, with penetration of cavernous sinuses and compression of optic chiasm and inferior frontal gyri. A wait-and-watch strategy was suggested by consulting neurosurgeon due to multiple malignancy, with emergency neurosurgery if necessary. No pathologic mutations were found in AIP, MEN1, p53, PTEN and CHEK2 genes. Diagnostic follow up for pituitary tumour is under way.
Conclusions
To elucidate the genetic background of metachronous neoplasms, molecular screening is necessary. Due to possible concurrence of melanoma, breast, prostate or kidney cancer with thyroid cancer, careful screening of the neck of patients with such tumours is recommended.

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EP1157

Benign and malignant thyroid gland diseases in the patients with primary hyperparathyroidism

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Aim
This study aimed to evaluate concurrently detected thyroid pathologies in the patients who underwent surgery for primary hyperparathyroidism.
Materials and Methods
In this study, we retrospectively analyzed the files of the patients who underwent surgery for primary hyperparathyroidism between 2012–2015. Pre-operative and post-operative laboratory examination results and the results of pre-operative radiological and nuclear medicine studies of the patients were retrospectively recorded.
Findings
A total number of 41 patients with primary hyperparathyroidism were divided into two groups as the group with primary hyperparathyroidism and benign thyroid pathology (21 patients) and the group with primary hyperparathyroidism and malignant thyroid pathology (20 patients). In the group 1, 18 and 3 of 21 subjects were females and males, respectively. The patient group 2 included 15 male and 5 female patients. The mean age of the subjects were found to be 55.6 and 53.9 years in group 1 and group 2, respectively. Both groups were matched fora ge and gender. In terms of thyroid pathology, 20 of 41 patients (48.7%) who underwent total thyroidectomy for primary hyperparathyroidism were found to have thyroid papillary carcinoma, while benign pathologic conditions were detected in 21 (51.3%) individuals.
Conclusion
Co-occurrence of thyroid diseases and primary hyperparathyroidism is common. Therefore, all patients should be pre-operatively evaluated for the presence of thyroid pathology to determine the technique of parathyroid surgery.

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EP1158

Hyalinizing trabecular tumor of thyroid in a patient with suspicious for papillary cancer in fine needle aspiration biopsy: a case report

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Introduction
Hyalinizing trabecular tumor is a very rare neoplasm of thyroid and can be misinterpreted as papillary or medullary cancer in fine needle aspiration biopsy (FNAB).
Case report
Multinodular goiter was detected in a 65 years old woman using metformin and L-thyroxine for impaired blood glucose and Hashimoto thyroiditis, respectively. FNAB was performed in two nodules and reported as suspicious for malignancy and benign. She underwent total thyroidectomy and a lesion with fragmented thin fibrous capsule was detected. The lesion was not including colloid and was characterized by eosinophilic, polygonal and elongated cells with wide cytoplasm and oval, elongated and irregular nucleus. There was also straight nuclear notchs and pseudoinclusions. Narrow hyalinized stroma including thin vascular structure was present between trabecules. There was no capsular or vascular invasion. Cytokeratin 19, HBME-1 and calcitonin were negative and TTF-1 was highly positive with immunocytochemical staining. Ki 67 proliferation index was 1–2%. No staining with BRAF VE-1 antibody was observed. The lesion was diagnosed as hyalinizing trabecular tumor depending on morphological and immunocyto-chemical findings.
Conclusion
It is difficult to differentiate hyalinizing trabecular tumor of thyroid and papillary thyroid cancer due to similarities in morphology and origin of two tumors, and FNAB may be misinterpreted as papillary thyroid cancer. Diagnosing hyalinizing trabecular tumor of thyroid which is benign or has low malignant potential and which can be treated by lobectomy will certainly prevent patient from overtreatment.

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EP1159

Case of papillary carcinoma occasionally found in young patient and the importance of immediate radical therapy

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Introduction
The number of thyroid cancer is progressively increasing and the majority of those diagnosis are papillary thyroid cancer- the most common type of thyroid cancer. Females are more likely to have thyroid cancer. Thyroid cancer can occur in any age group, although it is most common after age 30, and its aggressiveness increases significantly in older patients. Thyroid cancer does not always cause symptoms. Often the first sign of thyroid cancer is a thyroid nodule.
Case report
27 years old woman attended our clinic with the complains of fatigue, tachycardia especially at night time. She had no other complains. The patient was sent from cardiologist to check thyroid function. 1 year ago, during pregnancy her thyroid function and thyroid ultrasonography was normal. We performed laboratory studies: TSH 1.57(0.4–4.0) FT4 1.14(0.89–1.76) antiTPO 126.23(0–60) antiTG 126.23(0–60.0); Thyroid ultrasonography was performed: in the right lobe hypoechogenic solid nodule 5×5×6mm was found. As the nodule had fibrotic areas Fine Needle Aspiration (FNA) was performed. The conclusion was TIR3A: low–risk indeterminate lesion (we use classification provided by Italian society of anatomic pathology and diagnostic cytology) We suggested chirurgical intervention, but she was against. We aimed to recheck her hormonal status and ultrasonography after 3 months. So she attended our clinic once again after 3 months, hormonal status was within normal range, the size of nodule was 5×5×8 mm and enlarged lymph nodes were found. Once again FNA was performed and the conclusion was TIR5- Papillary carcinoma. So she was immediately sent to radical treatment. Total thyroidectomy, lymph dissection was performed.
Conclusion
With this case we want to say that when TIR3 is diagnosed it is necessary to perform immediately chirurgical intervention in order to prevent metastatic lesion and the progression of disease.

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EP1160

Three siblings with familial nonmedullary thyroid carcinoma

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Introduction
Nonmedullary carcinoma of thyroid is most common of thyroid carcinoma with familial predisposition and very low incidence.We describe cases of three

brothers with familial nonmedullary thyroid carcinoma diagnosed over a span of six years clinical follow up.
Case
58 years male with swelling in neck for 5 days. On examination he had left thyroid nodule. Ultrasound thyroid showed multinodular goiter while fine needle aspiration cytology (FNAC) left lobe revealed follicular lesion. Patient was planned for left lobectomy but perioperative frozen section of left lobe showed follicular carcinoma with capsular invasion so total thyroidectomy was perfomed. Histopathology of right lobe thyroid showed papillary carcinoma of thyroid. As disease has familial tendency, his three years younger brother asymptomatic underwent ultrasound thyroid for screening purpose. His ultrasound showed multinodular goiter, FNAC revealed features suspicious of papillary carcinoma thyroid. Patient underwent total thyroidectomy with central neck dissection and histopathology showed classical papillary thyroid carcinoma with lymph node metastasis. Patients youngest brother had complains of chronic urticaria with elevated thyroid antibodies (Anti TPO of 695.10 normal less than 35 and Anti Thyroglobulin of 29.50 normal less than 40) with TSH 1.80, T4 8.80 (4.6–10.5). In view of strong family history he was advised ultrasound thyroid which showed multinodular goitre and FNAC revealed papillary carcinoma thyroid. He underwent Total thyroidectomy with bilateral selective neck dissection and histopathology confirmed papillary carcinoma classic variant with lymph node metastasis. None of the brothers had exposure to radiations or other malignancies.
Conclusion
In conclusion our cases describes the importance of high index of suspicion and a detailed family history when evaluating patients with nonmedullary thyroid cancers.
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EP1161

Differentiated thyroid papillary carcinoma with cerebellar metastasis, case report

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Introduction
Differentiated thyroid cancer has usually good prognosis and long-term survival. Distant metastasis ratio is 5–15%. Metastasis to cerebrum, breast, liver, kidney, muscle, and skin is relatively rare. The study of molecular mechanisms of PTC has demonstrated that BRAFV600E gene mutation is a significant event in the process of this disease.
Case
55-year-old-male patient who had multinodular goiter showed malignant cytology in fine-needle-biopsy. Total thyroidectomy, neck dissection were performed. Pathology was consistent with PTC, diameter was 4.5 cm with vascular and perineural invasion, 11/13 lymph nodes had PTC infiltration. Bilateral cervical, mediastinal lymph node, bilateral multiple areas in lung, C4-C5 vertebrae had increased FDG uptake in PET/CT after surgery. Second-look neck dissection was performed. 33/46 lymph nodes had PTC infiltration. 200 mCi of RAI ablation therapy was given [TSH: 82 μIU/ml (0.34–5.6), thyroglobulin: 38 817 ng/ml (1.15-35), *anti*-thyroglobulin:107 IU/ml (0-115)]. On whole body scanning (WBS), radioactivity was detected in neck, mediastinum and both lungs. Because of high thyroglobulin levels, RAI ablation treatment with the dose of 250 mCi was planned after one year of first ablation. On WBS, radioactivity was detected in region of mediastinal, axillary, hemithoraxes and liver. Patient did not come to follow up for one year, then he admitted to emergency department with headache and vomiting. 37×47 mm mass with solid-cystic components in right side of cerebellum was detected in cranial-MRI. Patient was referred to neurosurgery clinic. There were multiple lymph nodes with pathological dimension in both axillary and mediastinal areas and multiple metastatic foci existed in bilateral lower lungs, in liver and 8×5 cm in left, 3.5×2.5 cm in right adrenal glands were consistent with metastases in CT. Cerebellar mass was excised. PTC infiltration was reported and BRAF V600E mutation was analyzed in cerebellar metastatic mass.
Conclusion
BRAFV600E mutations in PTC are associated with extrathyroidal spread, lymph node metastasis, tumor recurrence and mortality.
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EP1162

The efficacy and safety of sorafenib treatment on iodide refractory metastatic differentiated thyroid carcinomas

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Introduction
Differentiated thyroid carcinomas (DTC) are originated from thyroid follicular epithelial cells and comprises %90 of all thyroid carcinomas. Researches indicate that sorafenib is more efficacious than other chemotherapeutic agents on metastatic iodide refractory DTCs.
Material and methods
In our center, between 2013 and 2015, sorafenib was applied to six patients who had iodide refractory metastatic DTC. Five of the patients were female. The mean age at diagnosis was 68.6. Minimum 150, maximum 800 mCi RAI treatment were administered to the patients were applied after total thyroidectomy.
Results
After sorafenib treatment, on the follow-up skin rashes were the most frequent adverse effect and followed by hypertension, high ventricular rate atrial fibrillation and esophagitis. Skin lesions were mild and occurred on the first month of the treatment, after dose reduction symptoms resolved by 1 month. One patient had died of pericardial effusion. The response rates were evaluated according to 'response evaluation criteria in solid tumors RECIST'. Progressive disease, stable disease, and partial response were observed in three patients, one patient and one patient, respectively. One patient has not been assessed by imaging.
Discussion
Literature indicates that the adverse effects occur at the early phase, after reducing the dose or quitting, symptoms resolve and by the time patients' drug tolerance increase. Younger patients' drug compliance is higher. In our patients, adverse effects occurred in the first month consistent with literature. After dose reduction and treatment of the adverse effects, all of the symptoms resolved. However, low drug tolerance was observed in our patients and attributed to the advanced ages of the patients.
Conclusion
The efficacy of sorafenib is higher than the conventional chemotherapeutics, but management of side effects is crucial. Therefore, the patients should be informed about side effects before treatment and it should be used in experienced centers.
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Biphasic synovial sarcoma: an exceptional rare cervical mass

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Introduction
Synovial sarcoma represents a type of cancer derived from soft tissues; young males are more affected.
Material and methods
This is a case report of a male with a cervical mass confirmed as sarcoma. Later on the investigations lead to the discovery of a thyroid nodule challenging the differential diagnosis. We assessed thyroid ultrasound, computed tomography (CT) at the cervical, thorax, mediastinum and abdomen; TSH (Thyroid Stimulating Hormone), TPO antibodies (anti-thyreoperoxidase); pathological and immune-hysto-chemistry (IHC) reports.
Results
A 31-year patient accidentally discovered by self-palpation a right cervical mass which required investigations including CT. An oval, well shaped, encapsulated tumor of 4.7/3.5 cm (axial plane) was found with inhomogeneous structure (and some areas of necrosis) at the level of right lateral wall of oro-pharynx. Cranio-caudally, the mass was situated between cervical vertebras C2–C6. The lesion was removed and a biphasic synovial sarcoma was confirmed: highly cellular structure with oval cells and reduced eosinophilic cytoplasm, small amorphic

cysts, multiple vascular elements of hemangioperycitoma- like pattern, and an epithelial component with glandular elements. IHC revealed: positive VIM, TLE-1, EMA, MIC2 in tumor cells, negative SOX10, S100, positive ACT and CD34 reaction for vessels. After surgery, CT did not find any secondary lesions (neither local or at distance) except for a small thyroid nodule. The thyroid ultrasound identified a hypo-echoic, inhomogeneous nodule of 1.44/0.78 cm at inferior right lobe. Endocrine profile revealed: TSH = 1.27 μUI/ml (N: 0.5–4.5 μUI/ml), TPO = 10 UI/ml (N: 0–35 UI/ml), parathormon of 43.54 pg/ml (N: 15–65 pg/ml). Neuroendocrine markers were: chromogranin A of 42 mg/ml (N: 20–125 ng/ml), neuron specific enolase of 4.2 ng/ml (N: 0–12 ng/ml), circulating serotonin of 95.4 ng/ml (N: 40–400 ng/ml), calcitonin of 1 ng/ml (1–11.8 ng/ml). Fine needle aspiration pointed benign features. Close follow-up is recommended knowing the general oncologic and particular thyroid context.
Conclusion
Biphasic synovial sarcoma of cervical origin is extremely rare and thyroid may be involved as a spreading site.

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Bone metastatsis from differentiated thyroid cancer treated successfully with I^{131}: case report

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Differentiated thyroid cancer (DTC) in general has a good prognosis when ist diagnosed early. Late stage disease with bone metastasis may cause severe complications, increases mortality rate, decreases the quality of life, and shortens the patients' survival. The treatment is still controversial. Surgery or radioiodine therapy alone is usually unsatisfactory.
Case presentation
We report a case of a 40-year-old female presented, in August 2012, with a complaint of the progressive swelling of her neck for the last year on left side. Her past history was right thyroid lobectomy for multiple nodules at the age of 28, biopsy was microfollicular adenoma. thyroid ultrasound showed hypoechoic nodule 1.58 × 1.73 × 2.15 cm with increased flow on color Doppler. Thyroid-stimulating hormone (TSH) was 1.45 and thyroglobulin (Tg) was 948.9 μg/l (range: 1–100 μg/l). Thyroid scan showed a cold nodule left lobe. FNA-cytology was negative for malignancy. The patient was elected to proceed with completion thyroidectomy. Surgical pathology showed Multifocal papillary thyroid cancer no vascular or capsular invasion. On September 2012 she received 100 mCi and post treatment whole body scan revealed uptake on thyroid bed and intense activity in the region of the pelvis. Pelvic CT showed litic lesion in sacral bone. She started treatment with Levothyroxine 175 μg/day. On April 2013 without treatment TSH was132.4 Thyroglobulin 0.1 and the thyroglobulin antibodies (anti-TG) were negative. Diagnostic whole body scan showed resolution of the previously seen areas of uptake within the thyroid bed and pelvic area. On October 2015 she is on treatment with LT4 175 μg/day Tg 0.01, TSH 0.05 and negative Anti TG. Pelvic CT showed decreased litic lesion with peripheral sclerotic pattern.
Conclusion
This case demonstrates the benefits of RAI therapy even in patients with metastatic thyroid cancer treated successfully only with I^{131}.

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EP1165

An unusual case in endocrinology practice: suture granuloma

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Background
Suture granuloma, the rare complication of thyroidectomy, results from use of nonabsorbable suture materials. Despite its typical ultrasound images and benign course, it carries utmost importance in differential diagnosis of lymph nodes, recurrent nodules, and recurrence in case of thyroid cancers.
Case report
A 54-year-old female patient, who underwent bilateral thyroidectomy in July 2010, was diagnosed with multinodular goiter and incidentally discovered micropapillary carcinoma (2 mm). Four years later she was readmitted to hospital due to painless swelling in the right and left anterior neck region. Ultrasonography revealed nodules with irregular boundaries, containing micro and macrocalcifications and hyperechoic lines in both sides of thyroid bed and isthmus. Fine needle aspiration biopsy was performed in the right and left sided mass and cytologic examination was compatible with the diagnosis of suture granuloma.
Conclusion
Suture granuloma should be considered in differential diagnosis of local recurrence of thyroid disease and lymph node metastasis in patients who undergo thyroidectomy.

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Sonographic findings that can be mistaken for thyroid cancer

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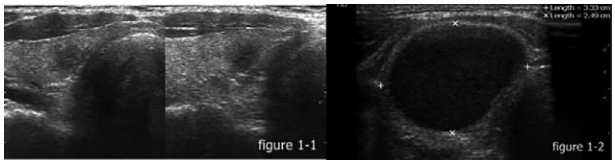
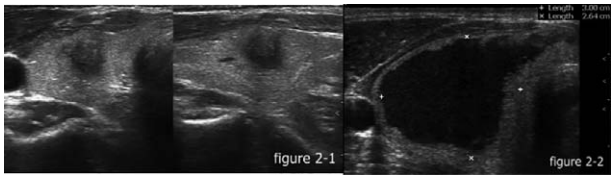
Introduction
Thyroid nodule is a common disease that is found in 50% of the adult population; of total, 5% of thyroid nodule cases are diagnosed as thyroid cancers. Thyroid ultrasonography is the most sensitive diagnostic imaging method for the diagnosis of thyroid cancer. The ultrasonographic findings that indicate malignancy are taller than wider, speculate margins, marked hypoechoic lesion, microcalcification, and macrocalcification. In contrast to findings indicating pure cyst, sponge form is benign. Hence, knowledge of these ultrasonographic findings is helpful in determining whether FNA (fine needle aspiration) is required to determine malignancy of the thyroid nodule. In the cases presented herein, ultrasonographic findings indicated malignancy. However, nodules were benign.
Case1
Sonographic findings after fluid drainage. Patient: aged 38 years, male. Figure (1-1) Ultrasonography findings show irregular margins. Figure (1-2) Fluid drainage the palpable neck nodule that the patient presented with 3 years ago.



Case 2
Sonographic findings after percutaneous ethanol injection therapy (PEIT).
Patient: aged 52 years, male. Figure (2-1) Ultrasonography findings show taller than wider speculate margins. The findings also show microcalcification in the middle. Figure (2-2) Percutaneous ethanol injection therapy performed for the palpable neck nodule that the patient presented with 5 years ago.



Conclusion
When performing thyroid ultrasonography, it is important to consider the previous ultrasonographic findings and procedure history to avoid unnecessary FNA.

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